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Te Tohu Waihonga- Aotearoa New Zealand Clinical Practice Guideline for Neonatal Hypoglycaemia

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Authorship
This guideline was developed by the Te Tohu Waihonga Guideline Group. For membership and terms of reference see Appendix B & C.

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Revision of the guideline
The guideline is intended to be a living document; therefore, the Liggins Institute will continue to monitor new publications, reports and resources and identify those relevant to the current guideline. Available evidence will be reviewed on a 3-yearly basis, commencing in 2028, to determine if the entire guideline, or selected topics only, need to be updated. New topics will be addressed in future versions of the guideline where appropriate.

Publication Approval

The recommendations contained in this guideline were reviewed by ????? and approval granted on XX/XX/2024 for a period of XXX years. This approval signifies that the guideline recommendations meet the XXXX standard for clinical guidelines.

Foreword

Tē tōia, tē haumatia

Nothing can be achieved without a plan and way of doing things

+ Endorsements

Acknowledgements

We would like to thank the many people who have contributed to these Guidelines, including the Governance Group who helped steer the project, the Panel members who have generously contributed their time, experience and insights, and the hard working evidence synthesis team. Thanks particularly to our methodological advisor, Sue Brennan, and team at the Melbourne GRADE Centre for their patience and sage advice.

Summary of recommendations for practice

[Placeholder for flow chart]

a. Wording of Recommendations

Recommendations in this Guideline are worded according to the guidance provided in the GRADE handbook (1). These can be summarised as:

Strong recommendation: The panel is very confident that the desirable consequences of the proposed course of action clearly outweigh the undesirable consequences or vice versa;

Conditional recommendation: There is

- a close balance between benefits and down sides (including adverse effects and burden of treatment), or

- uncertainty regarding magnitude of benefits and down sides, or

- uncertainty or important variability in the value consumers place on the treatment outcomes, or

- the cost or burden of the proposed intervention may not be justified;

Conditional recommendation for either option: The panel feels strongly that

- the pros and cons of the intervention and the comparison are very closely balanced, or

- there is so much uncertainty that a recommendation for or against the intervention would be speculative

b. Antenatal

Recommendation 1. Expression of breastmilk may be considered after 36 weeks' gestation in pregnant women whose baby is likely to be at risk of neonatal hypoglycaemia and who have no contraindications. [Conditional recommendation]

Recommendation 2. Tighter glycaemic control during pregnancy is recommended for women with diabetes. Follow recommendations of the national guideline – "Testing for, diagnosing and managing gestational diabetes (diabetes of pregnancy) Te whakamātau, te tautohu me te whakahaere i te mate huka hapūtanga". [Conditional recommendation]

Recommendation 3. For intrapartum glycaemic control, follow recommendations of the national guideline "Testing for, diagnosing and managing gestational diabetes (diabetes of

pregnancy) Te whakamātau, te tautohu me te whakahaere i te mate huka hapūtanga". [Conditional recommendation for either option]

c. Prevention

Recommendation 4. Umbilical cord clamping should occur not earlier than 1 minute after birth if the baby's condition allows. [Conditional recommendation]

Recommendation 5. Encourage skin-to-skin contact between mother and baby as early as possible after birth. [Conditional recommendation]

Recommendation 6. Keep the baby dry and warm after birth. Prioritise skin-to-skin contact with the mother. [Conditional recommendation]

Recommendation 7. Feeding should be initiated in the first hour after birth. [Conditional recommendation]

Recommendation 8. Mother's own expressed breastmilk is NOT helpful for preventing or treating neonatal hypoglycaemia in the first 48 hours after birth. Encourage breastfeeding rather than postnatal expression. [Conditional recommendation]

Recommendation 9. Oral dextrose gel should NOT be given routinely to at-risk babies to prevent neonatal hypoglycaemia. Consider offering prophylactic dextrose if risk of hypoglycaemia is considered to be high by practitioner or family and they are well-informed about available evidence. [Conditional recommendation]

Recommendation 10. Formula should NOT be given to at-risk babies to prevent neonatal hypoglycaemia. [Conditional recommendation]

d. Diagnosis

Recommendation 11. Blood glucose measurements should be offered for all babies at risk of neonatal hypoglycaemia (see recommendation 12). [Conditional recommendation]

Recommendation 12. Screening is recommended for babies with the following risk factors:

- Maternal diabetes (any type);
- Preterm birth (<37 weeks' gestation);
- Small for gestational age (<10th percentile using customised or population growth charts);
- Large for gestational age (>90th percentile using customised or population growth charts);
- If gestation unknown: low birthweight (<2500 g) or macrosomia (>4500 g);

- Unwell (e.g. respiratory distress, hypothermia (<36.5 °C), delayed or poor feeding >1 hour after birth);
- Maternal use of antidepressant medications, alpha or beta blocker medications, amphetamines (both prescribed and not prescribed), anti-psychotic medications.

Screening is also recommended for babies with any clinical signs potentially related to hypoglycaemia including: jitteriness, seizures, poor feeding, lethargy, irritability, cyanosis, hypotonia, apnoea, tachypnoea, hypothermia, respiratory distress, asphyxia, abnormal cry, pallor, and vomiting. [Conditional recommendation]

Recommendation 13. Test the blood glucose concentration of babies at risk of neonatal hypoglycaemia at 1-2 hours after birth, (preferably after the first feed but before 2 hours) then at intervals of 3-4 hours, independent of feeding schedule.

Stop testing after glucose concentrations have remained ≥2.6 mmol/L for 12 hours from birth or from the first normal test (≥2.6 mmol/L) after any low glucose concentrations (<2.6 mmol/L) provided the baby is feeding adequately. [Conditional recommendation]

Recommendation 14. Pain management strategies should be used during blood sampling for neonatal hypoglycaemia. Effective pain management strategies include skin-to-skin contact, breastfeeding, and oral sucrose. [Conditional recommendation]

Recommendation 15. Testing should use a validated and reliable point-of-care device using a glucose oxidase, glucose dehydrogenase or hexokinase method with electrochemical or amperometric detection. [Strong recommendation]

Recommendation 16. A blood glucose concentration of <2.6 mmol/L should be used as the definition (operational threshold) for neonatal hypoglycaemia. [Conditional recommendation]

Recommendation 17. Clinical observations are recommended for monitoring all babies at risk of or with neonatal hypoglycaemia. Any signs that are associated with neonatal hypoglycaemia should result in prompt measurement of blood glucose concentrations (see recommendation 11). [Conditional recommendation]

Recommendation 18. Continuous glucose monitoring should NOT be used routinely for the diagnosis and monitoring of neonatal hypoglycaemia. [Conditional recommendation]

Recommendation 19. Ketones, lactate, and insulin concentrations should NOT be measured routinely in addition to glucose for the diagnosis and monitoring of neonatal hypoglycaemia

in the first 72 hours. Consider measuring glucose, beta-hydroxybutyrate, and insulin concentrations in babies with hypoglycaemia that persists beyond 72 hours to help distinguish between those with congenital hyperinsulinemia and those with other causes. [Conditional recommendation]

Recommendation 20. Neurological monitoring and brain imaging should NOT be used routinely for monitoring babies with neonatal hypoglycaemia. Consider using early MRI (within 6 days of onset of hypoglycaemia) for babies with severe (<1.0 mmol/L) or persistent hypoglycaemia to assist with counselling and prognosis. [Conditional recommendation]

e. Treatment

Recommendation 21. A target blood glucose of ≥2.6 mmol/L should be used for treating neonatal hypoglycaemia within the first 72 hours after birth. A target blood glucose of ≥3.4 mmol/L should be used for treating neonatal hypoglycaemia after the first 72 hours after birth. [Conditional recommendation]

Recommendation 22. Babies diagnosed with neonatal hypoglycaemia should be treated with 40% oral dextrose gel. [Conditional recommendation]

Recommendation 23. Formula may be considered as a treatment option for babies diagnosed with neonatal hypoglycaemia. [Conditional recommendation]

Recommendation 24. Intravenous (IV) dextrose should be given if blood glucose concentration remains <2.6 mmol/L despite treatment with increased feeding and buccal dextrose gel. Do NOT give an initial bolus of IV dextrose routinely. [Conditional recommendation]

Recommendation 25. Consider use of diazoxide if hypoglycaemia persists despite treatment with intravenous dextrose and is severe (<1.5 mmol/L) or unstable. [Conditional recommendation]

Recommendation 26. Consider use of intramuscular glucagon for short-term management of neonatal hypoglycaemia until IV access can be established. [Conditional recommendation]

Recommendation 27. Consider caring for babies who require monitoring for neonatal hypoglycaemia at a primary care setting if timely and accurate blood glucose monitoring is possible, treatment can be initiated if required, e.g. with buccal dextrose gel, and the baby

can be transferred promptly to a secondary/ tertiary facility if necessary. [Conditional recommendation for either option]

f. Subsequent Care

Recommendation 28. No recommendations have been made about which babies are at a higher risk of experiencing adverse long-term outcomes because of neonatal hypoglycaemia.

Recommendation 29. Whānau of all babies born at risk, whether or not they develop neonatal hypoglycaemia, should be well informed before discharge about clinical signs that may indicate hypoglycaemia and how to seek help if these occur. General practitioners and Well Child/ Tamariki Ora providers should be made aware of a history of neonatal hypoglycaemia and its relevance for later developmental surveillance. [Conditional recommendation]

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1.1 Introduction

Neonatal hypoglycaemia (low blood glucose concentration) is common in the first few days after birth, with approximately 30% of Aotearoa New Zealand babies born at increased risk (2). Rates of neonatal hypoglycaemia in Māori are unknown. Newborn babies at increased risk include babies of mothers with diabetes, with low or high birthweight, or born preterm (3). Approximately half of these babies will develop hypoglycaemia (4).

Glucose is the primary source of energy for the brain (5). Newborn babies have relatively large brains and few alternative sources of energy for the brain, so are particularly vulnerable to brain injury if blood glucose concentrations are low. Severe or prolonged hypoglycaemia can lead to brain injury, seizures, and developmental delay (6, 7). Therefore, early detection and treatment is recommended to reduce the risk of brain damage (8, 9).

Currently there is wide variation in management of neonatal hypoglycaemia throughout Aotearoa New Zealand (10). Up-to-date guidelines based on the best available current evidence will provide important guidance for practitioners and whānau to help increase the likelihood of preventing the neonatal hypoglycaemia where possible, detecting and treating episodes of neonatal hypoglycaemia in a timely manner, and providing the most appropriate treatments. Implementation of national guidelines will help to promote the best possible health outcomes for babies and their whānau (family).

Te Tiriti o Waitangi (The Treaty of Waitangi), is our foundational document that holds the health system accountable to ensure whānau Māori experience equitable and culturally safe health outcomes (11, 12). The Waitangi Tribunal has heard the Health Services and Outcomes enquiry (WAI2575) and made recommendations to address the health inequities caused through the ongoing act of colonisation (13). In addition to Te T iriti o Waitangi, Pae Tū: Hauora Māori Strategy (Pae Tū), the Manatū Hauora (New Zealand Ministry of Health) interim strategy for maximising health and well-being outcomes with and for Māori informed development of this Guideline. Additionally, guidance and input was sought from Māori parents of pēpi at risk of or experiencing neonatal hypoglycaemia, and Māori health practitioners (14). Equitable health outcomes for Māori was considered at all stages of Guideline development. Hence, this Guideline is intended to be appropriate to the Aotearoa

New Zealand context, and responsive to the needs of Māori accessing health for their pēpi at risk of, or experiencing, neonatal hypoglycaemia.

The name of this guideline Te Tohu Waihonga draws inspiration from an old whakataukī, "Ko te hā i pēnei me te waihonga," which refers to the sweetness of the nectar from Aotearoa's native flora. This whakataukī symbolises anything sweet, much like the nectar, and forms a connection to hypoglycaemia. Te tohu means "guidance" or "directions," making the name Te Tohu Waihonga a symbol of the guidance provided by the clinical guideline. By using this name, we align the guideline with traditional Māori perspectives (te ao Māori), reminding us of our responsibility to ensure that it contributes to achieving health equity for Māori.

1.2 Making a difference for Māori

[Some of the content of this section has been submitted for publication, and the references and quotations may be updated in due course.]

There are opportunities to contribute to achieving equitable health outcomes for Māori, by screening pēpi at risk of hypoglycaemia, treating those who need it, and providing follow-up. Providing a good standard of care has the potential for improving health outcomes that have an impact on the life course for pēpi, and the whānau who care for them.

Research led by Rogers et al (2024) highlighted the experience of whānau Māori having a pēpi at risk of neonatal hypoglycaemia as three key themes: whānau, shifting the narrative, and health system. Whānau want the very best health outcomes for pēpi and want to be involved in decision making as a collective.

" that grief when you get told that you have to birth in a hospital, because you just feel at times that it's such a sterile non space where things could happen, whereas in a birthing centre, because I've… you know my sister's five pēpi have all been in a birthing centre, and as a whānau we've been there, we've been able to, you know yeah you know like yeah and manaaki her right through. And you know, even have my Dad as her really strong pou through her pregnancies."

"I can't do this alone, because pēpi is not just mine –pēpi is my whānau's."

To make a difference for Māori, health professionals need to include whānau as part of the health care team and ask whānau who they would like be present when discussing the health of pēpi. During these conversations, listening to whānau led solutions in balance with the evidence-informed treatment recommendations is important, as is allowing time for the whanau to process the information and ask questions to enable them to make fully informed decisions about care for their pepi.

" I think it's really just making sure there are lots of questions asked and reading whether the person feels comfortable or not because if they don't seem to be feeling comfortable then they're not going to really have the ability to listen and take in everything they need to, and feel comfortable enough to question."

"Whenever I look at medical intervention or medical experiences, it's that's very much about um a perceived power imbalance. One would always think that the person that's communicating to you has all the knowledge and because of that generally holds the power, so it's often not um, It might not feel appropriate to question or to or you might feel like, it's not… like it wouldn't be right to question some of the things they were saying or, or be inquisitive about it."

Underpinning this is the importance of whakapapa, whom pēpi carry the legacy for, upholding the mana of the whānau and pēpi, and tikanga. Whānau Māori experience interpersonal, institutional, and structural racism and a colonial health system structure which holds power and hierarchy. Actions health professionals can take todismantle racism and colonial privileges, are to uphold mana, empower whānau, and facilitate tikanga as business as usual. An example of this would be ensuring whānau are fully informed of treatment options and are enabled to make collective decisions.

"They are the newest part to your whakapapa, how do we nurture that conversation in ways that makes cultural embedded sense to us, as well as the practical stuff like I think it's always a balance but if there's a tikanga led process then we totally understand the practical need to do the heel prick tests because we know that oh that's just about protecting your whakapapa, all good, let's do it. They won't remember this, all good. But we need to be nurtured through that distress. And I think that's a huge factor in building clinically competent and culturally competent you know health professionals and clinicians, that they

understand that there's a nuance to that, not just on the surface of this is a process that we've gotta do."

The lived experiences of Māori who have pēpi at risk of developing hypoglycaemia offers solutions to optimise care and outcomes. These solutions can be used to influence future health care service provision for whānau Māori for the benefit of pēpi and their whānau. It is important to acknowledge the rights of Māori to access evidence-based healthcare and the obligations to improve health and wellbeing through transformative and reflective healthcare.

These are examples of personal experiences of whānau Māori, which are deeply connected with the health system which is described in the Social Determinants of Health section.

Social Determinants of Health for Māori

As tangata whenua (Indigenous people) of Aotearoa, Māori have unique rights in accordance with He Whakaputanga o te Rangatiratanga o Nu Tireni (The Declaration of the Independence of New Zealand, 1835) and Te Tiriti o Waitangi (The Treaty of Waitangi, 1840). Through Te Tiriti o Waitangi, a legally binding agreement was made between Māori and The Crown, however, there have been ongoing breaches of this agreement since signing.

The Treaty of Waitangi Act 1975 established the Waitangi Tribunal, a commission of inquiry to hear breaches by the Crown of the Treaty (15). The Tribunal's report on The Napier Hospital and Health Services Report in 2001 clearly defined the Crown's role in actively protecting the health of the Māori community

"Combating ill health amongst Māori, whether by medical or other means, was therefore part of the agenda of active protection that the British rulers took on under the Treaty of Waitangi… the Crown was duty bound to provide resources or programmes delivering appropriate health services to Māori." (15)

At the Tribunal's Hauora Health Services Inquiry (2018) both Crown and claimants accepted that

"Māori health inequities are not only caused by health issues but influenced by a wide range of factors, including income and poverty, employment, education, and housing – termed the social determinants of

health. The parties also accepted that Māori health inequities are influenced by the cumulative effects of colonisation." (16)

The colonisation of Māori manifested itself partly as institutional racism which was defined in the report as

"A pattern of differential access to material resources, cultural capital, social legitimation and political power that disadvantages one group, while advantaging another." (16)

Social determinants of health are non-medical factors that influence health outcomes, and they are social, economic, political, and cultural factors. These factors are "the conditions in which people are born, grow, work, live, and age, and are the wider set of forces and systems shaping the conditions of daily life." (17) The Director General of Health, Dr Bloomfield, when giving evidence in the Tribunal's Hauora Health Services Inquiry in 2018 stated

"Socio-economic deprivation for Māori impacts on their ability to access good health but it is compounded by other factors including racism. The impact of personal and institutional racism is significant on both the determinants of health and on access to and outcome from health care itself. Racism is associated with poorer health, including poorer mental health" and "the state of health for Māori is unacceptable and it is the core business of the New Zealand health and disability system to respond effectively" and "there is still considerable work needed to achieve equitable health outcomes between Māori and non-Māori. This has been an ongoing issue for the primary health care system and one that is not acceptable or tolerable." (16)

Māori inequities in comparison to non-Māori within the Health sector are very well documented with the Ministry of Heath's own Tatau Kahukura report documenting a plethora of areas where Māori experience negative health outcomes (18). In fact, in the Wai 2576 Hauora hearings the Crown acknowledged

"There is no need for this Tribunal panel to inquire into the question of whether Māori health status is significantly worse than for non-Māori at a population level; this is well established and not disputed." (16)

What is needed now is collective action on addressing these inequities.

The United Nations Declaration on the Rights of Indigenous Peoples (19), an international convention, further supports Māori rights in Aotearoa. A breach of these rights with the

power and resource distribution being in the hands of Pākeha are key influencing factors for the drivers of social determinants of health and resulting in health inequities.

Data describing rates of hypoglycaemia for pepi Maori are invisible reflecting an absence of explicit inclusion, and therefore a deficit within the published literature. Given the higher rates of gestational diabetes in hapū Māori, it is reasonable to speculate that pēpi Māori would also have higher rates of hypoglycaemia (20). Neonatal hypoglycaemia can result in increased morbidity and mortality, however rates for pēpi Māori have not been described. In general, pēpi Māori experience higher rates of early neonatal death compared to non-Māori, and every avenue should be pursued in a pro-equity approach (21).

Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism (13, 22, 23). This was also heard from whānau Māori when interviewed about their experiences of neonatal hypoglycaemia screening, testing, and diagnosis.

"So maybe we get written off a little bit like they wouldn't understand, or they didn't ask so we won't tell them…"(24) "Or before that nurse has walked on the ward nurse said big mum, Māori, big baby, it's got to be something wrong. That's that." (24)

"They took blood and they thinged it on the card so it might have been different, they might have been checking other things as well. But that wasn't actually explained. And it's the translation of information and knowledge is really important for whānau because we don't know that we can ask. You know like our agency around her mana as a baby and ours too. And like why? Why is it happening like that? what is happening? And I think if we can answer the why it's so much more empowering that we're doing something (24)

"And, like, let's just book in a date and get it done, like an induction. And, yeah, and then it was framed further in the discussion as, you'd be totally negligent if you chose to do anything else but what I want you to do." (24)

A systematic literature review by Graham et al, provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system (25). Although data in this review was not specific to pēpi, the key findings relating to barriers and facilitators could be easily translated into the pēpi population. Key barriers identified were how aware whānau Māori were to perceived racism and discrimination, and this was interpreted as the healthcare professionals being uninterested in their (whānau Māori) health and wellbeing.

"They interrogate you because you're brown." (25)

Māori also self-silenced to avoid causing additional stress and pressure on staff because they didn't want to "be a nuisance", and this meant that some whānau had a lack of information, which was distressing for them:

"I was too frightened to ask." (25)

Whānau often sacrifice time, money, and their own wellbeing to support whānau needing health support:

"You won't survive if you don't have the support of your whānau." (25)

For those who didn't have support, they felt isolated and alone. Whānau Māori like having one key hospital person:

"It makes you more relaxed and calm knowing you've got that one person instead of four or five different people looking at you." (25)

Positive experiences, engagement, and health outcomes is linked with having a trusting and positive relationship with a healthcare professional (25). Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "*just so welcoming*."(25)

For the realisation of equitable Māori health outcomes in pēpi Māori, acknowledgement of Indigenous rights needs to occur alongside redistribution of power and resources. The Government in power in 2022, following the Wai2575 claim to the Waitangi Tribunal, passed legislation to address these claims, resulting in health reforms under the Pae Oral Act (2022). Manatū Hauora (Ministry of Health) has an approach to achieving goals of mana whakahaere (stewardship), mana motuhake (self-determination), mana tangata (equity across lifecourse), and mana Māori (rights), by applying principles of tino rangatiratanga (leadership), equity, active protection, options, and partnership. This is something that was expressed by whānau Māori participant in the hypoglycaemia experience research.

"But certainly, for me, whenever I look at medical intervention or medical experiences, it's that's very much about a perceived power imbalance. One would always think that the person that's communicating to you has all the knowledge and because of that generally holds the power, so it's often not, it might not feel appropriate to question or to or you might feel like,

it's not… like it wouldn't be right to question some of the things they were saying or be inquisitive about it. So, I guess being aware that when you're communicating … that there might be a perceived power imbalance well that you might not feel your dominance. like dominance in that relationship for most receivers, but fear you are." (24)

1.3 Application of the Guideline

Purpose

Clinical recommendations are courses of action that have been judged as more likely to maximise desirable health outcomes for the population in question, in specific settings, when compared to other alternatives, after the evidence has been evaluated using a structured, transparent process (26, 27). The literature suggests that when practitioners consider clinical guidelines in their decision-making when treating patients, health outcomes improve (28). The purpose of the Te Tohu Waihonga - Aotearoa New Zealand Clinical Practice Guideline for Neonatal Hypoglycaemia (the Guideline) is to provide evidence-based, actionable, clinical recommendations for the prevention, diagnosis, and management of neonatal hypoglycaemia, and to assist health professionals and whānau in caring for, and contributing to, equitable health outcomes for newborn babies. This national Guideline is also intended to support consistency in the management of neonatal hypoglycaemia across the country, and thus promote equitable health outcomes for all babies and their whānau.

The questions addressed in this Guideline were identified by the Guideline Panel as having the highest clinical importance for health professionals caring for babies at risk of or diagnosed with hypoglycaemia, and their whānau. The full set of key clinical questions identified by the Guideline Panel and addressed in developing these Guidelines is provided in Appendix A. The Guideline is intended to be a living document, so that the questions addressed in this document will continue to be reviewed as new evidence becomes available.

Scope

The target population that this Guideline applies to is newborn babies in all birth settings in Aotearoa New Zealand who are at risk of or who have been diagnosed with neonatal

hypoglycaemia. The Guideline is intended to support health practitioners and whānau of affected babies in choosing the best course of action regarding prevention, diagnosis and treatment, and should be considered in conjunction with clinical judgement and whānau preferences. “Implementation considerations” are addressed wherever possible, that is, supporting information that will assist the health practitioner in putting the recommendation into practice (29).

Target Audience

This Guideline is intended for use by all health professionals involved in the care of women, whānau, and their newborn babies during pregnancy, childbirth, and the postnatal period. Although the Guideline may be most relevant to Lead Maternity Carers and health professionals involved in the care of mothers and newborn babies in hospital settings, the Guideline is also relevant to specialists, general practitioners, pharmacists and any other health professional involved in the care of mother or baby during the antenatal or postnatal periods.

This Guideline is also intended for use by consumers (pregnant women, mothers of newborn babies, their partners and whānau). It may also be used by policy makers in maternity and neonatal care.

Terminology

We acknowledge and respect gender diversity within the birthing population of Aotearoa New Zealand, including trans and non-binary people. However, in this guideline, we use the terms ‘mother’ and ‘women’ due to their prevalence in the literature reviewed to ensure clarity about the specific individuals to whom the health practitioner is providing clinical care, and to ensure clarity about the biological benefits of breastfeeding and skin to skin contact between the mother and baby. Using alternative terms may introduce confusion about the meaning of the findings and conclusions being communicated (30).

Similarly, the term “baby” rather than “neonate” is used as this term is more parent-centred, and parents are also an intended audience for these guidelines. Note that, unless otherwise stated, the term “baby” refers to an infant up to four weeks of age (the neonatal period).

Culturally safe practice includes health practitioners respecting and engaging with each individual receiving care and adapting their use of language accordingly in practice.

Appendix H provides definitions of Māori kupu (words) used in the guideline; Appendix I provides a glossary of clinical and technical terms, and Appendix J provides a list of abbreviations and their meanings.

1.4 Methods and Development of Guidelines

Framework for Meeting Te Tiriti o Waitangi Obligations

The development of Te Tohu Waihonga - Aotearoa New Zealand Clinical Practice Guideline for Neonatal Hypoglycaemia was informed by the National Health and Medical Research Council (NHMRC) Standards for Guidelines (31) and responsibilities under Te Tiriti o Waitangi. As Aotearoa New Zealand is a bicultural nation under Te Tiriti o Waitangi, the expertise and views of Māori health practitioners and consumers have played a central role in informing the development of this Guideline.

A framework was developed and endorsed by the Governance Group at initiation of the project to ensure the principles of Te Tiriti o Waitangi were applied in all stages of Guideline development:

1. Tino rangatiratanga: Māori representation occurs in the Governance and the Panel membership, where Māori are able to exert tino rangatiratanga (cultural and social responsibility) and mana motuhake (justice and equity, reflected through power and authority) and have their voices heard within this structure to influence design, delivery, and monitoring for this guideline. Both the Governance and Panel members will ensure that an equity statement is included in all sections of the guideline.
2. Equity: All members of this group must commit to achieving equitable health outcomes for Māori infants who this guideline will apply to and will do this by ensuring that all aspects of this guideline will be viewed with an equity lens for Māori by and with Māori.
3. Active protection: All members will be active in their commitment to achieving equitable health outcomes for Māori infants and will be accountable to ensuring an equity lens has been applied to the entirety of this guideline.

4. Options: All members will ensure that Māori models of health care (including and not limited to Kaupapa Māori services) are considered in this guideline.
5. Partnership & Participation: Membership of the Governance and Panel Groups include Māori representation across multiple health care professional groups. Both the Governance and Panel Groups are to purposely work in partnership to create this guideline.

Inclusion of Diverse Ethnic Perspectives

In addition to people of European and Māori ethnicities, people of Pacific and Asian ethnicity form the largest ethnic groups in Aotearoa New Zealand (32). Therefore, the focus on equity was also further upheld by seeking the views, experiences and input of consumers and practitioners from these ethnic groups during the development of the Guideline.

Contributors to the Guideline

The Governance Group

The Governance Group comprised seven individuals with expertise in paediatrics, neonatology, maternal-fetal medicine, neonatal pharmacy, and research synthesis and guideline development (Appendix B). This group provided advice, expertise, and direction on the development of the Guidelines and oversaw every aspect of its development, including review of the evidence, drafting the Guideline including recommendations, consulting with stakeholders, publication and dissemination.

Other responsibilities of the Governance Group included:

- Ensuring the Guideline was developed in line with best practice, include the AGREE II standards (33).
- Identifying and inviting members to join the Guideline Panel.
- Providing administrative support for the Guideline Panel.
- Ensuring wide consultation to develop an evidence-based guideline that will function as a useful resource for health professionals and will be of interest and relevance to pregnant women and their whānau in all Aotearoa New Zealand health care contexts.
- Ensuring that the Governance Group and the Guideline Panel uphold the principles in Te Tiriti o Waitangi and work towards achieving health equity for Māori (14).

- Ensuring that the Guideline recommendations will help meet the health needs for Māori.
- Producing a plan for the dissemination, implementation and ongoing monitoring of clinical uptake of the Guideline recommendations.

The Governance Group met on a quarterly basis and a subgroup of the Governance Group met monthly. The Governance group also met regularly with guideline methodologists Sue Brennan and Max Murano from the Melbourne GRADE Centre during the later phases of Guideline development.

The Guideline Panel

The Guideline Panel were recruited by seeking nominations from a wide range of relevant professional and consumer groups in Aotearoa New Zealand (Appendix B). Their role included ensuring the proper evaluation and interpretation of the evidence, that consumer perspectives and preferences were taken into account, and that final recommendations were relevant to clinical practice.

The responsibilities of the Guideline Panel included:

- Upholding Te Tiriti o Waitangi and addressing health equity for Māori (Appendix C).
- Providing advice, expertise and direction in relation to the Guideline.
- Confirming key clinical questions and outcomes.
- Confirming thresholds of the minimum effect size or threshold for decision making (Appendix D).
- Reviewing evidence and formulating recommendations.
- Signing off recommendations and disseminating the recommendations amongst their organisation for feedback, comments and endorsements.
- Disseminating the finalised Guideline to help ensure clinical uptake.

Members of the Guideline Panel participated in four meetings. The objective of the first meeting was to confirm the key clinical questions and critical outcomes; the second meeting to review evidence and formulate recommendations; the third meeting to review evidence and formulate recommendations for two additional questions that had emerged during the second meeting; and the fourth to review feedback on the clinical recommendations following a period of consultation and finalise the Guidelines. The second meeting was held

in person over two days. The other meetings were held online, with panel members attending one of the two or three offered timings for each. There were also a number of e-mail communications amongst the Governance Group and Guideline Panel, particularly to finalise the draft clinical recommendations and the draft Guidelines for consultation.

Research Evidence Synthesis Team

An evidence synthesis team led by a specialist in research synthesis provided most of the evidence for the development of the Guideline (Appendix B). The team searched for evidence relevant to each of the guideline questions, identified existing systematic reviews, and conducted new systematic reviews as required. Evidence to Decision documents (EtDs) were prepared by the evidence synthesis team and the Governance Group for each key clinical question based on the synthesised evidence using the GradePro GDT guideline development tool.

Methodology Expertise

The Governance Team contracted guideline methodologists from the Melbourne GRADE Centre to assist with technical advice, including training the Governance Group and Guideline Panel members. Prior to the second panel meeting, the methodologists conducted an online training session for the Governance Group and Guideline Panel members on the GRADEPro GDT tool and GRADE approach to evaluating data. The lead methodologist also attended the second panel meeting to assist with application of the process during the meeting. The methodologists also provided specialist advice on consideration of Equity issues in the development of Guideline using the GRADE approach, and adjudicated conflicts of interest.

Declaration of Interests

All Panel members were asked to declare all relevant interests using forms which included specific questions under the headings of financial, organisational and intellectual interests. The time period of disclosure was the last five years. These declarations were independently adjudicated by the lead methodologist according to WHO guidance and are summarised in Appendix K. For details of the original declarations contact the Guidelines team.

Stages in Development of Recommendations

Identifying Priority Questions and Outcomes

The key clinical questions were drafted during the scoping phase by the Governance Group and the Guideline Panel, and the importance of outcomes were rated as a) critical for making a decision, b) important but not critical, or c) of limited importance. The key clinical questions and the associated ratings were finalised at the first Panel meeting (Appendix A).

For each outcome, consensus was reached on the minimum size of effect that would support recommending using or not using a particular intervention. The standard way of presenting an effect size is in numbers of babies who would benefit or be harmed per thousand babies receiving the intervention, also known as the absolute risk difference (aRD). Draft thresholds for each of the outcomes were provided to all panel members and feedback solicited via an online survey to reach a final consensus on the most appropriate thresholds for each outcome (Appendix D).

Evidence Search and Synthesis

Systematic Reviews

Multiple systematic searches were undertaken by the Research Evidence Synthesis Team to address the key clinical questions, each of which was reframed into one or more questions in PICO format (Population, Intervention, Comparison, Outcome) (Appendix A). Databases consulted included Ovid MEDLINE, Ovid Embase, Web of Science, Cumulated Index in Nursing and Allied Health Literature (CINAHL), Cochrane Cochrane Central Register of Controlled Trials, Epistemonikos, Scopus, International Clinical Trials Registry Platform (ICTRP), Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov, International Standard Randomised Controlled Trial Number (ISRCTN). The search strategies were published as an appendix with each systematic review publication. Selection of database and search terms varied according to the key clinical questions being addressed.

When up-to-date systematic reviews were available to address a question, data were extracted from that review. Where necessary, more recent data were added to those included in a systematic review and the findings were re-analysed. Where no relevant systematic review was identified but suitable data were available, the Evidence Synthesis team conducted a new systematic review. Where the available evidence was not in a

format amenable to systematic review, the evidence identified by systematic search was summarised in narrative form with summary tables.

Systematic literature searches were also undertaken to collect evidence about other factors to be taken into account when formulating recommendations, including consumer preferences and values, equity considerations, resources required and associated costs, acceptability of interventions to stakeholders and feasibility of implementing interventions in Aotearoa New Zealand.

Overall equity considerations were specifically addressed in the development of the section on “Making a difference for Māori”, written by Māori members of the Governance Group and Guideline Panel (Section 1.2).

Evidence to Decision Frameworks

GRADEPro GDT (34) is an online tool used to prepare Evidence to Decision Frameworks (EtD) and facilitate the process of developing clinical recommendations. Using GradePro GDT, EtDs were prepared for each of the key clinical questions by the Research Evidence Synthesis Team and members of the Governance Group. The EtD provides a framework for summarising the evidence for review by the Guideline Panel, organised by topics including Desirable Effects, Undesirable Effects, Certainty of the Evidence of Effects, Values, Balance of Effects, Resources Required, Certainty of Required Resources, Cost Effectiveness of Required Resources, Equity, Acceptability, and Feasibility sections. A short summary of equity issues was included in the Equity section in every EtD (Appendix G) and two additional subsections; Considerations for Māori and Considerations for Pacific, were included in the Desirable Effects, Undesirable Effects, Balance of Effects, Equity, Acceptability and Feasibility sections of every EtD. Considerations for Asian people were also included where relevant data were available.

Review of Evidence

After the EtDs were finalised and the training session held, members of the Governance Group and the Guideline Panel were each asked to enter their judgements for each section of each EtD online in GRADEPro. This was intended to help the Panel members to become familiar with the EtDs, and the Governance Group to assess the degree of consensus

amongst the group before the second Panel meeting, to help guide time allocation at the meeting.

At the second and third Panel meetings, each EtD was presented to the group. After discussion of the evidence relating to each recommendation, each panel member entered their judgements for the EtD into an anonymous online survey. The survey findings were then used to identify a consensus judgement or where further discussion was required to reach a consensus, and a final recommendation. An attempt was made to reach consensus on all judgements, but where this was not possible, differing views were recorded in the EtD.

The Panel discussions also identified research recommendations and implementation considerations (29).

Drafting of Recommendations

The draft recommendations addressing each of the key clinical questions were prepared by the Governance Group based on the decisions in the second and third Panel meetings and revised after feedback from the Guideline Panel. The draft recommendations and Guideline were then circulated again for final feedback and sign-off by the Governance Group and Guideline Panel.

Stakeholder Consultation

Draft Guidelines were circulated to relevant stakeholders for feedback (Appendix X). All feedback was collated and a summary document prepared listing responses to each item. A fourth Panel meeting was held to revise the draft Guidelines in response to the feedback and sign off on the final recommendations.

Dissemination and Implementation

An implementation project will be developed to help facilitate rapid uptake of the Guideline recommendations. Key steps in this will include:

Pre-Implementation Needs Assessment

A pre-implementation needs assessment will be conducted to identify gaps between current practice and the Guideline recommendations. The audit will be repeated post-implementation to assess change in practice.

Development of Implementation Toolkit

A structured set of resources and tools will be developed to facilitate the implementation of the recommendations outlined in the Guideline. This toolkit will include a summary of the Guideline recommendations, training materials, checklists, and other resources to support the implementation of the Guideline. Specific resources to be developed include a flow chart to summarise the recommendations for screening for neonatal hypoglycaemia, and short videos and information pamphlets about neonatal hypoglycaemia and neonatal blood testing. These will be made freely available online in several languages including te reo Māori.

Pilot Implementation

The recommendations of Te Tohu Waihonga will be piloted in several different hospitals using the Implementation toolkit. Healthcare providers will receive training and support on using the implementation toolkit and incorporating the recommended practices into their daily workflows. Data will be collected on the practices themselves (quantitative data) as well as practitioners' personal experiences of implementing the Te Tohu Waihonga (qualitative data). This information will help to identify and address barriers to implementation in a "real-life" clinical context, and adjustments to the Implementation Toolkit will be made where necessary.

Dissemination

Resources will be prepared for dissemination of the Guideline to hospitals and clinicians to raise awareness of, and provide key information about, Te Tohu Waihonga. These resources will include this complete version of the guideline and recommendations, a succinct summary of key recommendations, and a summary version for whānau, available in te reo Māori, English, and other languages. All resources will be made available online and freely available for downloading.

2. Recommendations

Health equity

These general points apply to all recommendations so are summarised here rather than repeated for each recommendation. Additional points are listed under specific recommendations where relevant.

Health equity for Māori

Health professionals must apply this guideline equitably to prevent harm and ensure accountability in implementing recommendations for Māori as part of a pro-equity approach. Pākehā benefit from health system privileges, while Māori face systemic racism, leading to reduced health benefits. Health equity can be improved if Māori receive effective interventions.

Ensure Māori whānau are fully informed about their healthcare options as a part of a mana Motuhake (self-determination), including prevention, monitoring and treatment options, health benefits and potential risks. Detailed explanations of all interventions, their necessity, and results should also be provided to help achieve equitable health outcomes. Ensure whānau are provided with information in multiple formats (oral, written, online, video) that align with cultural values.

Whānau living in rural areas may face additional financial costs and barriers to accessing specialist services. Proactively support these whānau by informing and supporting them to access available financial assistance and resources to access specialist services.

Health equity for other groups

Health professionals must apply this guideline equitably to prevent harm. Health equity can be improved if all whānau receive effective interventions.

Many groups, including Pacific, Asian, migrant and rural communities, also face significant health inequities. These groups often encounter barriers such as language difficulties, lower health literacy, and challenges in understanding their healthcare options. It is important that all whānau are fully informed about their healthcare options, including prevention, monitoring and treatment options, health benefits and potential risks. Detailed explanations of all interventions, their necessity, and results should also be provided to help

achieve equitable health outcomes. Culturally appropriate communication, use of interpreter services where required, along with the use of multiple formats (oral, written, online, video), can help improve engagement with health services.

Rural communities may also experience additional challenges, such as increased travel costs and limited access to specialist care. Providing proactive support, including information about and assistance to access financial and other resources to help access specialist services, is crucial to reducing these inequities and improving health outcomes.Specific additional issues are addressed under the recommendations and EtDs where relevant.

Question1. Does antenatal expression of breastmilk reduce the risk of neonatal hypoglycaemia?

PICO (Population, Intervention, Comparison, Outcome): Should antenatal expression of breastmilk vs. no expression of breast milk be used for preventing neonatal hypoglycaemia?

Recommendation 1:

Expression of breastmilk may be considered after 36 weeks' gestation in pregnant women whose baby is likely to be at risk of neonatal hypoglycaemia and who have no contraindications. [Conditional recommendation]

Justification: Moderate to very low certainty of evidence suggests that antenatal expression of breastmilk may lead to a small reduction in neonatal hypoglycaemia, a moderate increase in fully breastfeeding at hospital discharge, and a moderate decrease in the duration of the initial hospital stay.

The acceptability of this practice varies due to some women experiencing difficulties and discomfort with antenatal expression.

Antenatal expression of breast milk may encourage mothers to breastfeed, and have an additional positive effect on their hinengaro (mental health) through providing nutrition for their baby.

Implementation considerations: Breast pumps are not appropriate for antenatal expression; hand expression suffices for this purpose.

Expression of breastmilk should not be considered in at risk pregnancies. For contraindications consult local guidelines, LMC, diabetes specialist, obstetrician or lactation consultant.

Advise all mothers that they may experience Braxton Hicks contractions, but to stop expressing if contractions become regular and painful, and contact their LMC (35).

Monitoring and evaluation: Nil.

Research priorities:

Studies are needed on:

The effects of expressing milk on maternal well-being, including factors such as stress from the inability to express colostrum.

Health equity: Provide whānau with resources and support for antenatal expression of breastmilk that align with their cultural values. Ensure whānau have access to reliable refrigeration or freezer for storing expressed breastmilk.

Evidence to decision table: refer to Appendix G

Question 2. Does tight maternal glycaemic control reduce the risk of neonatal hypoglycaemia?

PICO: Should tighter maternal glycaemic control during pregnancy in women with diabetes vs. less-tight maternal glycaemic control during pregnancy be used for preventing neonatal hypoglycaemia?

Recommendation 2:

Tighter glycaemic control during pregnancy is recommended for women with diabetes. Follow recommendations of the national guideline – "Testing for, diagnosing and managing gestational diabetes (diabetes of pregnancy) Te whakamātau, te tautohu me te whakahaere i te mate huka hapūtanga"(36). [Conditional recommendation]

Justification: Low certainty evidence showed that tight maternal glycaemic control during pregnancy compared to less tight had little to no effect on neonatal hypoglycaemia, but resulted in a small reduction in mortality and morbidity, and admissions to NICU. However, adverse effects for mothers when using tight targets should be considered. Women may have difficulty in adhering to tighter glycaemic targets.

Implementation considerations: See the national guideline "Testing for, diagnosing and managing gestational diabetes (diabetes of pregnancy) Te whakamātau, te tautohu me te whakahaere i te mate huka hapūtanga"(36).

Monitoring and evaluation: The the national guideline "Testing for, diagnosing and managing gestational diabetes (diabetes of pregnancy) Te whakamātau, te tautohu me te whakahaere i te mate huka hapūtanga"(36) suggests that tight targets are frequently harder to achieve, which may explain poor adherence to tight targets (36). Monitoring of adherence is recommended.

Research priorities:

Studies are needed on:

1. The effect of tight maternal glycaemic control on neonatal hypoglycaemia and long-term childhood outcomes.
2. Factors influencing adherence to tight glycaemic control targets in pregnancy and how whānau can be supported to achieve these, particularly in specific populations.
3. Patient values and preferences surrounding tight glycaemic control in pregnancy.
4. The cost-effectiveness of employing tight glycaemic control in pregnancy.

Health Equity: Gestational diabetes occurs at higher rates in Māori, Pacific, Asian, and Indian populations. Health professionals working alongside these population groups need to work towards tight glycaemic control in a pro-equity approach to improve outcomes. Health professionals should ensure that glycaemic targets are based on clinical guidelines and individual patient needs prioiritising those who are most affected by issues such as access and systemic privilege, to avoid potential harm and ensure equitable care.

Evidence to decision table: refer to Appendix G

Question 3. Does tight intrapartum glycaemic control reduce the risk of neonatal hypoglycaemia?

PICO: Should tight intrapartum glycaemic control vs. less tight or no intrapartum glycaemic control be used for neonatal hypoglycaemia?

Recommendation 3:

For intrapartum glycaemic control, follow recommendations of the national guideline "Testing for, diagnosing and managing gestational diabetes (diabetes of pregnancy) Te whakamātau, te tautohu me te whakahaere i te mate huka hapūtanga"(36). [Conditional recommendation for either opition]

Justification: Very low certainty of evidence showed potential benefit in reducing neonatal hypoglycaemia and admission to NICU, but also potential harm including increased caesarean section and reduction in exclusive breastfeeding.

Implementation considerations: Tighter glycaemic control during labour may be more relevant for women with type I and type II diabetes than women with GDM. Clinical decision-making should determine the appropriate level of intrapartum control and monitoring on an individualised basis.

Monitoring and evaluation: Nil.

Research priorities:

Studies are needed on:

The effects of tight glycaemic control during labour for women with Type I and Type II diabetes, and GDM, including short-term and long-term maternal and neonatal/childhood outcomes. Given the potential iatrogenic harms associated with this treatment approach, separate recommendations may be necessary for each group.

Health Equity: People living in rural areas face challenges in accessing specialised care. Although women with diabetes often give birth at specialist centres, some may not have received a timely diagnosis during pregnancy, potentially leading to inequitable access to appropriate care and interventions. The responsibility lies with the system to facilitate equitable access, removing barriers rather than placing the burden on whānau.

Ensure that appropriate glucose analysers and dextrose gel for treatment of neonatal hypoglycaemia are available in all settings where newborn babies are cared for, including in primary units, to avoid potentially widening health inequities.

Evidence to decision table: refer to Appendix G

Question 4. Are babies who had delayed cord clamping less likely to develop neonatal hypoglycaemia?

PICO: Should delayed cord clamping vs. early cord clamping be used for the prevention of neonatal hypoglycaemia?

Recommendation 4:

Umbilical cord clamping should occur not earlier than 1 minute after birth if the baby's condition allows. [**Conditional recommendation**]

Justification: Low certainty evidence shows that delayed cord clamping may result in small reduction in neonatal hypoglycaemia, moderate reduction in neurodevelopmental impairment at 12 to 24 months, moderate reduction in neonatal mortality, and small increase in fully breastfeeding at hospital discharge.

The NZ College of Midwives (2024) guidelines suggest delaying cord clamping for 3 minutes or until the umbilical cord stops pulsating (whichever occurs later) for term and pre-term babies who do not require resuscitation at birth, as this is associated with improved neonatal outcomes.(37) WHO (2023) also recommends delayed umbilical cord clamping (not earlier than 1 minute after birth) for improving maternal and infant health and nutrition outcomes (38).

Implementation considerations: Delayed cord clamping needs to be done well, in a warm environment with appropriate support for the baby. If the baby becomes hypothermic, this could increase the chances of hypoglycaemia. Place the baby directly on the mother's chest immediately after birth, cover both with a warm blanket. If baby is unwell and needs resuscitation, cord clamping before one minute after birth might be required.

Monitoring and evaluation: Evaluate the integrity of the umbilical cord, checking for any abnormalities or issues such as excessive bleeding or structural damage. If any concerns are identified, do not delay cord clamping (39). Monitor the baby's heart rate and if it is lower than 60 beats per minute and not improving, do not delay cord clamping (39).

Research priorities: Nil.

Health Equity: Refer to health equity summary on Page 30.

Evidence to decision table: refer to Appendix G

Question 5. Does skin-to-skin contact reduce the risk of neonatal hypoglycaemia?

PICO: Should skin-to-skin contact vs. no skin-to-skin contact be used for the prevention of neonatal hypoglycaemia?

Recommendation 5:

Encourage skin-to-skin contact between mother and baby as early as possible after birth.

[Conditional recommendation]

Justification: Low certainty of evidence shows skin-to-skin contact may result in a large reduction in neonatal hypoglycaemia and duration of hospital stay, a small reduction in admission to NICU, less separation from the mother for treatment of hypoglycaemia before discharge home and a large increase in breastfeeding.

Skin-to-skin is largely acceptable and feasible as it is already standard practice in Aotearoa New Zealand. Cost is negligible.

WHO also recommends that early and uninterrupted skin-to-skin contact between mothers and babies should be facilitated and encouraged as soon as possible after birth (40).

Implementation considerations: Place the baby directly on the mother's chest immediately after birth, and cover both with a warm blanket. UNICEF recommends that babies should have skin-to-skin contact at least until after their first feed (41).

Skin-to-skin contact might not be appropriate for all babies, depending on the clinical condition of the mother and baby.

Monitoring and evaluation: All babies should be routinely monitored whilst in skin-to-skin contact. Observations should include checking of airway and breathing, colour, tone and temperature (42).

If there are any concerns about the baby's oxygen saturation, it should be monitored closely, but it may be feasible to do this during skin-to-skin contact

Research priorities:

Studies are needed on:

Effect of skin-to-skin contact with adults other than the mother on neonatal hypoglycaemia.

Health Equity: Refer to health equity summary on Page 30.

Evidence to decision table: refer to Appendix G

Question 6. Are babies given thermal care (measures to reduce heat loss) less likely to develop neonatal hypoglycaemia?

PICO: Should thermal care vs. routine care be used for prevention of neonatal hypoglycaemia?

Recommendation 6:

Keep the baby dry and warm after birth. Prioritise skin-to-skin contact with the mother. [Conditional recommendation]

Justification: Low certainty evidence in VLBW babies shows plastic wrap/bag results in moderate reduction in hypoglycaemia, large reduction in the duration of initial hospital stay, large reduction in hypothermia on admission to NICU and small increase in hyperthermia on admission to NICU.

Plastic wrap is readily available and commonly used for keeping preterm babies warm.

Very low certainty of evidence shows use of a thermal mattress or thermal blanket had little to no effect on hypoglycaemia, and a large reduction in moderate hypothermia on admission to NICU. Thermal mattresses are expensive and lack of evidence of effectiveness means they are not a routine option.

A study on delayed bathing was considered by the Panel to not be relevant to this recommendation.

Implementation considerations: Consider use of plastic wraps to keep the baby warm when skin-to-skin is not practicable. If a specific neonatal plastic wrap is not available, clingfilm can be used and is widely available.

Monitoring and evaluation: Monitor baby's temperature to avoid hyperthermia.

Research priorities:

Studies are needed on:

The most effective strategies for preventing hypothermia and consequent hypoglycaemia, particularly in term babies and those at risk of hypoglycaemia, and when skin-to-skin is not feasible.

Health Equity: Refer to health equity summary on Page 30.

Evidence to decision table: refer to Appendix G

Question 7. Does early feeding reduce the risk of neonatal hypoglycaemia?

PICO: Should early feeding vs. delayed feeding be used for the prevention of neonatal hypoglycaemia?

Recommendation 7:

Feeding should be initiated in the first hour after birth. [Conditional recommendation]

Justification: Low certainty of evidence shows early feeding may be associated with a large reduction in hypoglycaemia, a small to moderate reduction in neonatal mortality, and a large increase in fully breastfeeding at hospital discharge.

Early feeding is widely acceptable and feasible in Aotearoa New Zealand.

Early breastfeeding is associated with higher rates of exclusive breastfeeding, with the associated benefits.

WHO also recommends all mothers should be supported to initiate breastfeeding as soon as possible after birth, within the first hour (40).

Implementation considerations: If the mother wants to breastfeed but is unable to in the first hour, consider expression of breastmilk at this time to support establishment of lactation and encourage breastfeeding.

It is important to ensure that the baby whose mother plans not to breastfeed is fed a formula that is safe, suitable and properly prepared.

Monitoring and evaluation: Nil.

Research priorities: Nil.

Health Equity: Ensure whānau are fully informed and supported about the benefits of pēpi's first feed being from the breast. Discuss with whānau if they have cultural practices that are important to carry out following the birth, and support this to be woven into care together with clinician activities. Harm occurs when health professionals do not engage with whānau about their cultural preferences.

Evidence to decision table: refer to Appendix G

Question 8. Are babies given expressed breast milk (mother's own or donor human milk) less likely to develop neonatal hypoglycaemia?

PICO: Should expressed breastmilk vs. other or no intervention be used for preventing or treating neonatal hypoglycaemia?

Recommendation 8:

Mother's own expressed breastmilk is NOT helpful for preventing or treating neonatal hypoglycaemia in the first 48 hours after birth. Encourage breastfeeding rather than postnatal expression. [**Conditional recommendation**]

Justification: Very low certainty evidence from one RCT suggests that supplementation of breastfeeding with donor breastmilk or formula, but not mother's own breastmilk, may increase blood glucose concentrations in hypoglycaemic babies in the first 48 hours after birth.

However, breastfeeding hypoglycaemic babies in the first 48 hours reduced the likelihood of hypoglycaemia recurring. Thus, mothers should be encouraged to breastfeed rather than to express breastmilk to feed to their baby.

Implementation considerations: The increase in blood glucose concentration after breastfeeding is greater after longer feeds (>30 minutes) and after feeding from both breasts, so encouraging these practices may be helpful for babies at risk of or experiencing neonatal hypoglycaemia.

Many mothers face challenges and negative experiences when trying to express breastmilk, but some mothers of unwell or preterm babies may find it empowering to contribute to their baby's well-being through expressing milk.

Monitoring and evaluation: Nil.

Research priorities:

Studies are needed on:

1. The effectiveness of donor milk for preventing and treating hypoglycaemia.
2. The effectiveness of expressed breastmilk for treating neonatal hypoglycaemia beyond 48 hours after birth.

Health Equity: The acceptability of donor milk is individual for whānau Māori, so each whānau group should be asked what their preference is, including acceptability of donor milk before giving to pēpi. Harm occurs when health professionals do not engage with whānau about their cultural preferences.

Accessibility of donor milk is a concern, especially outside major centres where NICUs and milk banks are scarce. In Aotearoa New Zealand, systemic inequities impact access to lactation consultants and the establishment of donor milk banks.

Evidence to decision table: refer to Appendix G

Question 9. Are babies given prophylactic oral dextrose gel less likely to develop neonatal hypoglycaemia?

PICO: Should oral dextrose gel vs. placebo be used for preventing neonatal hypoglycaemia?

Recommendation 9:

Oral dextrose gel should NOT be given routinely to at-risk babies to prevent neonatal hypoglycaemia. [Conditional recommendation]

Consider offering prophylactic dextrose if risk of hypoglycaemia is considered to be high by practitioner or family and they are well-informed about available evidence.

Justification: Prophylactic oral dextrose gel reduces the risk of neonatal hypoglycaemia in at-risk babies but does not reduce NICU admission or need for intravenous treatment. It may make little to no difference to the risk of neurodevelopmental impairment at two years, but the confidence intervals include the possibility of substantial benefit or harm. Evidence at six to seven years is limited to a single small study.

In view of its limited short-term benefits, and potential applicability to a very large proportion of all newborn babies (approximately 30%), prophylactic oral dextrose gel should not be incorporated into routine practice until additional information is available about the balance of risks and harms for later neurological disability.

Implementation considerations: Whānau need to be fully informed about the benefits and risks.

Draw up the prescribed dose (0.5ml/kg or 200 mg/kg 40% dextrose gel) into an enteral syringe and administer at 1 hour of age, using the procedures as for dextrose gel treatment (see recommendation 22).

Prophylactic dextrose gel can be given to a baby while having skin-to-skin care.

Monitoring and evaluation: All babies at risk of hypoglycaemia require clinical monitoring and testing for hypoglycaemia, whether or not they have received prophylactic dextrose gel.

Research priorities:

Studies are needed on:

1. Effect of prophylactic oral dextrose gel for neonatal hypoglycaemia on later neurological disability.
2. The effectiveness of prophylactic oral dextrose gel compared to other preventative interventions such as harvested colostrum, donor milk or infant formula.

Health Equity: Māori, Pacific, and Asian whānau are likely to accept oral dextrose gel treatment, especially if the mother has experienced diabetes. Discuss with whānau if they have cultural practices that are important to carry out following the birth, and support this to be woven into care together with clinician activities. Harm occurs when health professionals do not engage with whānau about their cultural preferences.

Evidence to decision table: refer to Appendix G

Question 10. Are babies given formula less likely to develop neonatal hypoglycaemia?

PICO: Should formula vs. control be used for preventing neonatal hypoglycaemia?

Recommendation 10:

Formula should NOT be given to at-risk babies to prevent neonatal hypoglycaemia. [Conditional recommendation]

Justification: Very low certainty of evidence shows uncertain effect on of formula on the prevention of neonatal hypoglycaemia, fully breastfeeding at hospital discharge or length of hospital stay, and uncertain effects on blood glucose concentrations.

Implementation considerations: Whānau should be provided with breastfeeding support, particularly for at-risk babies, ensuring that breastfeeding is promoted as the first line of prevention for neonatal hypoglycaemia. Implementation should account for cultural preferences and the importance of breastfeeding in different communities.

Monitoring and evaluation: Nil.

Research priorities: Nil.

Health Equity: Refer to health equity summary on Page 30.

Evidence to decision table: refer to Appendix G

Question 11. What are the benefits and risks of testing?

PICO: Should testing for neonatal hypoglycaemia vs. not testing be used for babies at risk of neonatal hypoglycaemia?

Recommendation 11:

Blood glucose measurements should be offered for all babies at risk of neonatal hypoglycaemia (see recommendation 12). [Conditional recommendation]

Justification: Most babies with hypoglycaemia have no clinical signs, so blood testing is the only way to detect low glucose concentrations.

It is current practice to test babies considered at risk of neonatal hypoglycaemia and there is no evidence to support changing this approach.

There is no robust evidence of benefit for at-risk babies and some evidence of harm, primarily from painful procedures and a reduction in breastfeeding. Nevertheless, the

potential for death and brain damage from undiagnosed hypoglycaemia was considered to outweigh the pain and distress caused by testing.

Although resource requirements are substantial, with current screening criteria applicable to 26-28% of all babies, it is feasible as it is currently being done.

Implementation considerations: Whānau should be fully informed about the reasons for testing and encouraged to participate in decisions about pain relief (see recommendation 13). Provide easily understandable information in a range of formats, including videos and apps. Address how babies can be supported during tests, and how the test can be made less painful for the baby (see recommendation 14).

Monitoring and evaluation: Nil.

Research priorities:

Studies are needed on:

Outcomes in children whose whānau declined screening for neonatal hypoglycaemia and the reasons for declining.

Health Equity: Screening rates for babies delivered rurally or from underrepresented groups are not known. However, if testing is implemented equitably, this is likely to increase health equity. Ask whānau what their preferences are for painful procedures. Some whānau may wish to use rongoā Māori (traditional Māori medicine that takes a holistic approach) e.g. waiata, karakia, oriori to support pēpi during a painful procedure.

Evidence to decision table: refer to Appendix G

Question 12. Who to test?

i) Which babies are at increased risk of neonatal hypoglycaemia?

ii) Which babies should be tested for neonatal hypoglycaemia?

iii) Which signs and symptoms are indications for testing?

PICO: Should expanded or restricted criteria vs. current criteria be used for screening for neonatal hypoglycaemia?

Recommendation 12:

Screening is recommended for babies with the following risk factors:

- Maternal diabetes (any type);
- Preterm birth (<37 weeks' gestation);

- Small for gestational age (<10th percentile using customised or population growth charts);
- Large for gestational age (>90th percentile using customised or population growth charts);
- If gestation unknown: low birthweight (<2500 g) or macrosomia (>4500 g);
- Unwell (e.g. respiratory distress, hypothermia (<36.5°C), delayed or poor feeding >1 hour after birth);
- Maternal use of antidepressant medications, alpha or beta blocker medications, amphetamines (both prescribed and not prescribed), anti-psychotic medications.

Screening is recommended for babies with any clinical signs potentially related to hypoglycaemia including: jitteriness, seizures, poor feeding, lethargy, irritability, cyanosis, hypotonia, apnoea, tachypnoea, hypothermia, respiratory distress, asphyxia, abnormal cry, pallor, and vomiting. **[Conditional recommendation]**

Justification: These criteria are similar to those already in use around Aotearoa New Zealand.

The cost of testing is likely to be small compared to the cost of brain injury from undetected hypoglycaemia for the individual, although the evidence that prompt detection and treatment of hypoglycaemia alters neurodevelopmental outcomes is very uncertain.

Implementation considerations: Testing should be undertaken using a reliable analyser (see recommendation 14).

Address how babies can be supported during tests, and how the test can be made less painful for the baby (see recommendation 13).

Consider prompt referral to a paediatricians if a baby is unwell or shows clinical signs associated with neonatal hypoglycaemia. However, testing and treatment if required should not be delayed pending such referral (see recommendation 21).

Monitoring and evaluation: Nil

Research priorities:

Studies are needed on:

Outcomes of screening versus not screening large-for-gestational age babies.

Health Equity: The frequency of risk factors for hypoglycaemia varies with ethnicity.

Ensure whānau are fully informed of the reasons for testing, health benefits and potential adverse effects of blood glucose testing, and the results of any tests. Refer to health equity summary on Page 30.

Evidence to decision table: refer to Appendix G

Question 13. When to test?

i) At what age should testing start?

ii) How often should testing be performed?

iii) When should testing stop?

PICO: Should other timings vs. start at 1-2 hours, intervals of 3-4 hours, finish after 12 hours of glucose concentrations above the threshold be used for testing neonatal hypoglycaemia?

Recommendation 13:

Test the blood glucose concentration of babies at risk of neonatal hypoglycaemia at 1-2 hours after birth, (preferably after the first feed but before 2 hours) then at intervals of 3-4 hours, independent of feeding schedule. [**Conditional recommendation**]

Stop testing after glucose concentrations have remained ≥ 2.6 mmol/L for 12 hours from birth or from the first normal test (≥ 2.6 mmol/L) after any low glucose concentrations (< 2.6 mmol/L) provided the baby is feeding adequately.

Justification: There is a physiological nadir in blood glucose concentrations at approximately 30-90 minutes after birth. In many babies, low glucose concentrations during this period will resolve spontaneously. Limited evidence suggests that low glucose concentrations are more common at 1 hour than at 2 hours and become less common thereafter.

A relatively small proportion (0.3-1.1%) of cases of neonatal hypoglycaemia may be missed if screening ends at 12 hours.

Severe hypoglycaemia is most common within the first 12 hours after birth.

Limited evidence suggests that 10 – 17% of episodes occur between the initial test at 1–2 hours and the second test, approximately 3–4 hours later, so repeated testing is required.

There is very little change in blood glucose concentrations with feeding in the first 48 hours, so timing of testing can be independent of feeding.

Implementation considerations: The criteria for stopping testing should be 12 hours of blood glucose concentrations ≥2.6 mmol/L with adequate feeding, not the number of tests conducted.

Monitoring and evaluation: Babies who have required intravenous dextrose or supplemental feeds for the treatment of neonatal hypoglycaemia should have 12 hours of blood glucose concentrations ≥2.6 mmol/L after these additional measures have ended before testing is stopped.

Research priorities: The correct time to stop testing is not known. The GLOW study showed that healthy term babies continued to have episodes of glucose concentrations <2.6 mmol/L up to 5 days after birth, although few occurred after 3 days.

Studies are needed on:

1. whether extending screening beyond 12 hours improves outcomes.
2. the frequency and clinical significance of glucose concentrations <2.6 mmol/L after 12 hours in babies who previously had glucose concentrations ≥2.6 mmol/L.

Health Equity: Refer to health equity summary on Page 30.

Evidence to decision table: refer to Appendix G

Question14. What is the best care for babies while being tested?

PICO: Should specific pain management strategies vs. control/ placebo/ no intervention be used for pain management during blood sampling for neonatal hypoglycaemia?

Recommendation 14:

Pain management strategies should be used during blood sampling for neonatal hypoglycaemia. [Conditional recommendation]

Effective pain management strategies include skin-to-skin contact, breastfeeding, and oral sucrose.

Justification: Skin-to-skin contact, breastfeeding, and oral sucrose each result in medium to large reductions in pain scores related to heel-prick testing with minimal or no apparent adverse effects. Expressed breastmilk may also result in a small reduction in pain scores but there are few studies and the evidence is very uncertain.

Implementation considerations: Whānau should be given the opportunity to be involved in the choice of and provision of pain management related to blood testing.

Monitoring and evaluation: Nil.

Research priorities: Nil.

Health Equity: Ask whānau what their preferences are for painful procedures. Some whānau Māori may wish to use rongoā Māori (traditional Māori medicine that takes a holistic approach) e.g. waiata, karakia, oriori to support pēpi during a painful procedure.

Evidence to decision table: refer to Appendix G

Question 15. Which type of device should be used for testing?

PICO: Should a point-of-care testing method be used to screen for hypoglycaemia in neonates?

Recommendation 15:

Testing should use a validated and reliable point-of-care device using a glucose oxidase, glucose dehydrogenase or hexokinase method with electrochemical or amperometric detection. [Strong recommendation]

Justification: Using more reliable testing methods is essential for accurate diagnosis and treatment. It can also reduce the number of heel pricks and is cost saving.

The common practice of using a less accurate device, with confirmation of low glucose concentrations using a more accurate device, is NOT appropriate as it does not address the problem of false negative tests (13-30%), potentially delays treatment, and increases costs.

The panel considered that recommending more reliable devices was essential to drive improvements in equity and resource allocation, leading to long-term cost savings despite potentially initial higher costs.

Implementation considerations: Examples of currently available devices meeting these requirements include Elite XL, iSTAT, Freestyle, and ABL 800.

Monitoring and evaluation: A list of currently available devices that are appropriate for neonatal blood glucose testing should be made widely available and updated regularly.

Research priorities: Nil.

Health Equity: It is essential that appropriate analysers are available in all settings where newborn babies are cared for, including in primary units, to avoid potentially widening health inequities.

Evidence to decision table: refer to Appendix G

Question 16. What is the best working definition (operational threshold) of neonatal hypoglycaemia?

PICO: Should higher or lower blood glucose concentrations vs. blood glucose concentration of 2.6 mmol/L be used for defining of neonatal hypoglycaemia?

Recommendation 16:

A blood glucose concentration of <2.6 mmol/L should be used as the definition (operational threshold) for neonatal hypoglycaemia. [Conditional recommendation]

Justification: There is some evidence for supporting the current operational threshold of <2.6mmol/L, and a lack of evidence to justify changing it.

Low certainty evidence from a single RCT shows that using a threshold of <2.0mmol/L has little to no effect on neurodevelopmental outcomes at 18 months but results in a large increase in moderate hypoglycaemia (2.0 – 2.6 mmol/L), and a moderate increase in severe hypoglycaemia (<2.0 mmol/L). The effect on serious adverse effects was uncertain.The panel noted that babies with initial blood glucose concentrations <1.9 mmol/L were excluded from this trial, and that 18 months was likely too early to detect any effects of hypoglycaemia on neurodevelopmental outcomes of interest.

The operational threshold of blood glucose concentrations <2.6 mmol/L is consistent with WHO guidelines (43).

Implementation considerations: Consider additional investigations (see recommendation 18) and consultation with an paediatric endocrinologist if hypoglycaemia persists after 72 hours of age.

Monitoring and evaluation: Blood glucose concentrations should continue to be monitored while babies are being treated for hypoglycaemia and for at least 12 hours after treatment stops and baby is feeding adequately.

Research priorities:

Studies are needed on:

Benefits and harm of changing to a lower or higher glucose threshold, particularly on later neurodevelopmental outcomes at least through to school age.

Health Equity: The impact on health equity is not clear.

Evidence to decision table: refer to Appendix G

Question 17. What clinical observations are needed?

PICO: Should clinical observations vs. other/no clinical observations be used for monitoring babies with neonatal hypoglycaemia?

Recommendation 17:

Clinical observations are recommended for monitoring all babies at risk of or with neonatal hypoglycaemia. [Condiaitonal recommendation]

All newborn babies require clinical observation in the first hours and days after birth. Any signs that are associated with neonatal hypoglycaemia should result in prompt measurement of blood glucose concentrations (see recommendation 11).

Justification: Clear evidence supports the benefits of monitoring, as babies showing clinical signs of hypoglycaemia tend to have poorer outcomes than those who do not.

Some babies who develop severe and potentially brain-threatening hypoglycaemia do not have risk factors or have a recurrence of hypoglycaemia after hospital discharge. These babies will only be identified by clinical signs.

Implementation considerations: It is important to educate whānau of all babies about clinical signs that may indicate hypoglycaemia and how to seek help if these occur. This includes at risk babies who have normal blood glucose concentrations in the first 12 hours and those whose hypoglycaemia appears to have resolved.

Monitoring and evaluation: Nil.

Research priorities

Studies are needed on:

Optimal protocols for clinical observations in babies at risk of hypoglycaemia, including the best predictors of hypoglycaemia and duration of monitoring.

Health Equity: Refer to health equity summary on Page 30.

Evidence to decision table: refer to Appendix G

Question 18. What is the role of interstitial or transcutaneous glucose measurement?

PICO: Should continuous glucose monitoring vs. intermittent blood glucose testing be used for babies at risk of or diagnosed with neonatal hypoglycaemia?

Recommendation 18:

Continuous glucose monitoring should NOT be used routinely for the diagnosis and monitoring of neonatal hypoglycaemia. [Conditional recommendation]

Justification: In two RCTs in VLBW babies, those with continuous glucose monitoring (CGM) spent more time with blood glucose concentrations in the normal range and underwent fewer blood tests. However, there was little to no effect on the number of hypoglycaemia events.

Current devices are not sufficiently accurate for use in babies (approximately ±1 mmol/L accuracy) and technical difficulties can be time consuming to remedy.

CGM is well tolerated in babies, and insertion may be less painful that heel-prick blood tests.

CGM is cost-effective in adults with diabetes, but its cost-effectiveness in babies is uncertain.

Implementation considerations: Nil.

Monitoring and evaluation: This technology is evolving rapidly, so this recommendation should be reviewed frequently.

Research priorities:

Studies are needed on:

1. The potential utility of CGM when a baby is transitioning from intravenous dextrose to breastfeeding.
2. The utlity of CGM in late preterm and term babies at risk of hypoglycaemia.
3. The clinical significance of episodes of low glucose concentrations that would not have been detected without CGM, including their association with neurodevelopmental outcomes, and the effect of treatment on these outcomes.
4. The cost-effectiveness of using CGM in babies whose glucose concentrations are very unstable.
5. Whānau perspectives on use of CGM in babies.

Health Equity: The effect on health equity is not known but is likely to depend on access to the devices and the specialist expertise required to use them. Refer to health equity summary on Page 30.

Evidence to decision table: refer to Appendix G

Question 19. Should metabolites other than glucose be measured?

PICO: Should measurement of other metabolites in addition to glucose vs. measurement of glucose alone be used for diagnosing and monitoring of neonatal hypoglycaemia?

Recommendation 19:

Ketones, lactate, and insulin concentrations should NOT be measured routinely in addition to glucose for the diagnosis and monitoring of neonatal hypoglycaemia in the first 72 hours. [Conditional recommendation]

Consider measuring glucose, beta-hydroxybutyrate, and insulin concentrations in babies with hypoglycaemia that persists beyond 72 hours to help distinguish between those with congenital hyperinsulinemia and those with other causes.

Consider measuring insulin before 72 hours if hypoglycaemia is severe (<1.5 mmol/L) and the baby does not have risk factors for hypoglycaemia or has other concerning clinical features.

Justification: Measuring ketones, lactate or insulin may help uncover uncommon causes of hypoglycaemia but requires additional blood tests, thus causing additional distress to the baby and whānau and incurring additional costs.

Since most neonatal hypoglycaemia is transitional, testing before 72 hours may show concerning findings (e.g. detectable insulin concentrations at the time of low glucose concentrations) that will resolve spontaneously and therefore should not alter management for most babies.

Preliminary evidence suggests that measuring ketones at approximately 72 hours may help distinguish the cause of the hypoglycaemia (44).

If hyperinsulinism is suspected and there are no risk factors for hypoglycaemia, insulin concentrations might be measured earlier. However, there was uncertainty about whether testing before 72 hours makes a difference even for congenital hyperinsulinism.

The overall consensus was that 72 hours is an appropriate time to consider measuring other metabolites, as testing earlier is unlikely to be useful.

Implementation considerations: Consider measuring insulin before 72 hours if hypoglycaemia is severe (<1.5 mmol/L) and the baby does not have risk factors for hypoglycaemia or has other concerning clinical features. Additionally, consider paediatric endocrinology/metabolic referral for severe hypoglycaemia (<1.5 mmol/L) within the first 72 hours.

Monitoring and evaluation: Nil

Research priorities: Nil

Health Equity: The additional blood tests may not be available at all healthcare facilities, which could potentially worsen inequities for those with limited access. However, it is possible to collect the samples at any facility and have them analysed at a different location, helping to reduce some of the access barriers.

Evidence to decision table: refer to Appendix G

Question 20. What neurological monitoring/ imaging is needed?

PICO: Should neurological monitoring/ imaging vs. no neurological monitoring/ imaging be used for monitoring babies with neonatal hypoglycaemia?

Recommendation 20:

Neurological monitoring and brain imaging should NOT be used routinely for monitoring babies with neonatal hypoglycaemia. [Conditional recommendation]

Consider using early MRI (within 6 days of onset of hypoglycaemia) for babies with severe (<1.0 mmol/L) or persistent hypoglycaemia to assist with counselling and prognosis.

Justification: Early MRI findings, particularly diffusion-weighted imaging, are moderately predictive of later neurodevelopmental outcomes after neonatal hypoglycaemia. This may be helpful in some cases, e.g. for counselling whānau, guiding management decisions, supporting Accident Compensation Commission claims and access to early neurodevelopmental therapy to optimise outcomes.

One study found that changes in cotside aEEG were not clinically useful for monitoring brain function in relation to neonatal hypoglycaemia.

Implementation considerations: Timely access to MRI can be challenging due to the high cost and limited availability. It is important to discuss this decision with a neonatologist, as this may involve transfer to a secondary or tertiary centre.

Monitoring and evaluation: Nil.

Research priorities: Nil.

Health Equity: Health equity may be increased if all whānauare offered access to MRI and are appropriately informed about the risks and benefits.

Evidence to decision table: refer to Appendix G

Question 21. What is the target blood glucose range for babies diagnosed with neonatal hypoglycaemia?

PICO: Should higher or lower minimum target blood glucose concentration vs. the most common minimum target during treatment (2.6 mmol/L) be used for babies being treated for neonatal hypoglycaemia?

Recommendation 21:

A target blood glucose of ≥2.6 mmol/L should be used for treating neonatal hypoglycaemia within the first 72 hours after birth. [Conditional recommendation]

A target blood glucose of ≥3.4 mmol/L should be used for treating neonatal hypoglycaemia after the first 72 hours after birth.

Justification: There is some evidence for supporting the most common target for treatment of ≥2.6 mmol/L and a lack of evidence to justify changing it.

Very low certainty evidence shows that using a lower threshold than 2.6 mmol/L has little to no effect on neurodevelopmental outcomes at 18 months. Low certainty evidence shows use of lower thresholds may result in a large increase in moderate hypoglycaemia (2.0 – 2.6 mmol/L), and a moderate increase in severe hypoglycaemia (<2.0 mmol/L).

Most guidelines recommend a target of ≥2.6 mmol/L for hypoglycaemia in babies, but some advocate for a higher target threshold in older babies. This is because severe and prolonged hypoglycaemia can sometimes indicate congenital hyperinsulinism, which is associated with a high risk of neurodevelopmental impairment.

A blood glucose concentration of 3.3 mmol/L is the threshold for onset of autonomic symptoms in adults experiencing hypoglycaemia, and is the lower target recommended by

some for babies with persistent hypoglycaemia (45). It was estimated that this would apply to approximately 4 per 1000 babies so would not have a large impact on feasibility or costs.

Implementation considerations: Consider additional investigations (see recommendation 18) and consultation with an paediatric endocrinologist if hypoglycaemia persists after 72 hours of age.

There are no data on resources required, but with a higher threshold, longer treatment would most likely be necessary.

Monitoring and evaluation: Blood glucose concentrations should be monitored regularly while babies are being treated for hypoglycaemia and for at least 12 hours after treatment stops and the baby is feeding adequately.

Research priorities:

Studies are needed on:

Outcomes of using the target of ≥2.6 mmol/L compared to lower or higher targets.

Health Equity: The impact on health equity is not clear.

Evidence to decision table: refer to Appendix G

Question 22. What are the benefits and risks of buccal dextrose gel for babies diagnosed with neonatal hypoglycaemia?

PICO: Should buccal dextrose gel vs. placebo gel or no gel be used for babies with neonatal hypoglycaemia?

Recommendation 22:

Babies diagnosed with neonatal hypoglycaemia should be treated with 40% oral dextrose gel. [Conditional recommendation]

Justification: Moderate certainty evidence shows that buccal dextrose gel results in a large increase in correction of hypoglycaemia, moderate reduction in admission to NICU and large reduction in separation of mother and baby for treatment of hypoglycaemia. No adverse effects were reported.

Treatment is feasible as it is already being used, and acceptable to caregivers and whānau.

Gel is inexpensive, cost effective, and can be used in any care setting.

Conditional recommendation because there is no information on babies born before 34 weeks' gestation, or effect of different doses and different timings of administration.

Implementation considerations: If baby is clinically stable and able to feed, administer 0.5 ml/kg (200 mg/kg) 40% dextrose gel.

Draw up the prescribed dose in an enteral syringe. Dry the buccal mucosa using a gauze swab. Apply gel to the buccal mucosa in small aliquots using a gloved finger, and massage it in gently. Offer the baby a feed immediately after administering the gel.

If the blood glucose concentration is < 2.0mmol/L, dextrose gel alone is unlikely to be sufficient treatment. Administer dextrose gel while arranging transfer to a facility where IV infusion is available.

Dextrose gel can be given to a baby while having skin-to-skin care.

Monitoring and evaluation: Repeat blood glucose concentration testing 30-60 minutes after administering dextrose gel and beginning the feed.

If the repeat blood glucose is < 2.6 mmol/L, repeat the dextrose gel and offer a feed, then test again 30-60 minutes after administering the second dose.

Continue clinical observations. If any subsequent blood glucose concentration is < 2.6 mmol/L, the clinical condition of the baby should be reviewed and consider referral for further investigation and treatment.

Research priorities:

Studies are needed on:

1. The effect of buccal dextrose gel for treatment of neonatal hypoglycaemia on long-term neurodevelopmental impairment.
2. The effect of buccal dextrose gel for treatment of babies born <34 weeks' gestation.
3. The most effective dose, frequency and mode of administration of buccal dextrose gel.

Health Equity: Severe or symptomatic hypoglycaemia is a medical emergency. Not all babies at risk of neonatal hypoglycaemia can be identified before birth, and hypoglycaemia can occur in babies without risk factors. Dextrose gel and capacity accurately to measure blood glucose concentrations should therefore be available as standard emergency equipment wherever newborns are cared for, including in community settings. Carers need appropriate education and resourcing for this.

Provide whānau with information on health benefits and potential adverse effects of dextrose gel treatment. Whānau should also be provided with resources that align with their cultural values. Provide whānau with information on dextrose treatment in multiple mediums (e.g., written, oral, visual).

Evidence to decision table: refer to Appendix G

Question 23. Should formula vs. control be used for treating neonatal hypoglycaemia?

Recommendation 23:

Formula may be considered as a treatment option for babies diagnosed with neonatal hypoglycaemia. [Conditional recommendation]

Justification: Low to very low certainty of evidence shows large to moderate effect of formula on the correction of neonatal hypoglycaemia, and reduction in recurrent hypoglycaemia.

The cost of formula for treatment of hypoglycaemia is likely comparable to that of dextrose gel and significantly lower than intravenous dextrose. Formula is widely available, but acceptability varies among different populations.

Use of formula as a treatment option for neonatal hypoglycaemia could help reduce the need for intravenous dextrose, which is more invasive, costly, and commonly involves NICU admission, with associated economic, emotional and social costs.

Implementation considerations: Consider giving formula 7 ml/kg (60 ml/kg/day) as an alternative to intravenous dextrose for babies whose hypoglycaemia persists after two doses of dextrose gel plus breastfeeding.

Whānau should be fully informed about the risks and benefits of both treatment options and be involved in joint decision making.

Ensure that formula is readily available in clinical settings with appropriate protocols to manage the supply and administration of formula as a treatment option for neonatal hypoglycaemia.

Carers should ensure that formula use does not undermine breastfeeding efforts, offering guidance to mothers on how to maintain or transition back to breastfeeding after the hypoglycaemia is corrected. Encourage mothers to express breast milk when formula is given as treatment to maintain breast milk supply.

Monitoring and evaluation: Repeat blood glucose concentration testing 60 minutes after administering the formula. Do not repeat formula if blood glucose concentration is ≥2.6

mmol/L. If the repeat blood glucose concentration is <2.6 mmol/L, prompt referral is required for consideration of intravenous dextrose.

Research priorities:

Studies are needed on:

1. Effect of formula compared to intravenous dextrose or donor human milk on correcting neonatal hypoglycaemia, NICU admission rates, and breastfeeding at hospital discharge.
2. The cultural acceptability to whānau of using formula for the treatment of neonatal hypoglycaemia.
3. The optimal amount of formula to be given for the treatment of neonatal hypoglycaemia.
4. The long-term neurological effects on infants treated with formula for neonatal hypoglycaemia.

Health Equity: Communication strategies should be adapted to align with the cultural values and preferences of whānau, particularly in communities where breastfeeding is strongly preferred. Whānau should be fully informed about the advantages and disadvantages of using formula as a treatment for hypoglycaemia.

Evidence to decision table: refer to Appendix G

Question 24. Should intravenous dextrose vs. other treatment or no treatment be used for treatment of neonatal hypoglycaemia?

Recommendation 24:

Intravenous (IV) dextrose should be given if blood glucose concentration remains < 2.6 mmol/L despite treatment with increased feeding and buccal dextrose gel. [Conditional recommendation]

Do NOT routinely give an initial bolus of IV dextrose.

Justification: Using IV dextrose is typically reserved for cases where oral treatment options have been exhausted, but there is very little evidence of benefits and harms.

There is some evidence that treatment of hypoglycaemic babies with an IV bolus is associated with more rapid change in blood glucose concentrations, including increased

incidence of high glucose concentrations, and that these are associated with adverse neurodevelopmental outcomes.

One before-and-after study showed that tailoring the dose of IV dextrose and use of an initial bolus depending on the glucose concentration resulted in similar time to resolution of hypoglycaemia but shorter NICU stay and reduced costs.

While IV dextrose itself is inexpensive, the costs associated with NICU care, including administration and staffing, can be significant.

The panel considered that evidence from randomised trials of IV dextrose compared to oral sucrose were not relevant when formulating this recommendation.

Implementation considerations: Start treatment with 30-60ml/kg/d 10% dextrose.

Continue feeding if possible.

Consider an initial bolus of 1-2ml/kg of 10% dextrose over 10min only if the initial blood glucose concentration is very low (< 1 mmol/L) or the baby has clinical signs.

It is important to have an open and honest discussion with parents about the uncertainty regarding the benefits of IV dextrose.

Monitoring and evaluation: Check blood glucose concentration after 1 hour and adjust infusion rate as necessary.

Continue regular monitoring of blood glucose concentrations during IV treatment.

Research priorities:

Studies are needed on:

1. The effects of IV dextrose bolus administration on short and longterm outcomes.
2. The optimal dosage and methods for administering IV dextrose
3. The optimal strategies for weaning babies off IV dextrose and onto full oral feeds.

Health Equity: IV treatment may not be available at all healthcare facilities, so may worsen inequities for those with limited access. Ensure that all babies at risk of neonatal hypoglycaemia and their whānau have prompt access to facilities that can provide IV treatment if needed.

Evidence to decision table: refer to Appendix G

Question 25. Should diazoxide vs. placebo be used for treating neonatal hypoglycaemia?

Recommendation 25:

Consider use of diazoxide if hypoglycaemia persists despite treatment with intravenous dextrose and is severe (<1.5 mmol/L) or unstable. [Conditional recommendation]

Justification: One randomised trial found that a low dose of diazoxide (3 mg/kg/day) for early management of severe or recurrent neonatal transitional hypoglycaemia may result in a large increase in the correction of hypoglycaemia after completing the loading dose (5 mg/kg). However, diazoxide did not reduce the time to resolution of hypoglycaemia.

One randomised trial conducted in India did not report on critical or important outcomes related to diazoxide use.

Evidence from five observational studies indicated that 71% of babies responded to diazoxide.

Diazoxide may be associated with serious side effects, including pulmonary hypertension, congestive heart failure, oedema, hypertrichosis (excessive hair growth), and necrotising enterocolitis. Most side effects resolve upon discontinuation of the drug, although hypertrichosis may persist for several weeks.

The cost of liquid diazoxide is moderate to high, at $620 per bottle, but costs are much lower (<$1) if prepared by a hospital pharmacy from tablets.

Oral administration of diazoxide may be preferable to parents compared to intravenous administration.

Implementation considerations: Diazoxide is not recommended as a first-line treatment due to significant potential adverse effects.

Discussions with whānau should include detailed information on dosing and possible side effects.

Input from endocrinology specialists is recommended for decision-making, and if hyperinsulinaemic hypoglycaemia is suspected.

Monitoring and evaluation: Plasma insulin concentration should be measured before starting diazoxide.

Babies should be monitored carefully for possible side effects of diazoxide.

Research priorities:

Studies are need on:

1. The long-term effect diazoxide
2. The optimal dosage of diazoxide to minimise the risk of side effects.

Health Equity: Whānau need to be fully informed of the health benefits and potential adverse effects of diazoxide. Refer to health equity summary on Page 30.

Evidence to decision table: refer to Appendix G

Question 26. Should glucagon vs. control be used for neonatal hypoglycaemia?

Recommendation 26:

Consider use of intramuscular glucagon for short-term management of neonatal hypoglycaemia until IV access can be established. [Conditional recommendation]

Justification: Three non-randomised studies showed a large effect in correcting hypoglycaemia, with a large increase in blood glucose concentrations.

The safety of glucagon for treatment of hypoglycaemia has been established in adults, and there is no evidence of differing safety in babies.

Nausea is reported by some adults using glucagon, but it is uncertain whether babies may experience this.

The cost of glucagon was considered moderate to negligible.

Long-term outcomes and safety in babies remain uncertain, necessitating comprehensive information sharing with families for informed decision-making.

Implementation considerations: Severe or symptomatic hypoglycaemia is an emergency. If there is difficulty or delay in starting IV glucose, give glucagon 0.2 mg/kg as an intramuscular injection. Establish an IV infusion as soon as possible. Intramuscular glucagon may not be effective in situations outside of hyperinsulinism, and IV glucose may still be necessary.

The increase in glucose concentration usually occurs within 5-20 minutes. The dose can be repeated after 1 hour if IV access remains problematic, but there may be a smaller increase in glucose concentration in response to the second dose.

In refractory hypoglycaemia, glucagon infusion 5-20 microgram/kg/h may be considered

Monitoring and evaluation: Measuring blood glucose concentration 30 minutes after giving IM glucagon.

Research priorities:

Studies are needed on:

The benefits, adverse effects and long-term outcomes of glucagon use in babies, including optimal dose and route of administration.

Health Equity: Whānau need to be fully informed of the health benefits and potential adverse effects of glucagon. Refer to health equity summary on Page 30.

Evidence to decision table: refer to Appendix G

Question 27. What care settings are appropriate?

PICO: Should secondary or tertiary level care settings vs. primary care setting be used for monitoring babies with neonatal hypoglycaemia?

Recommendation 27:

Consider caring for babies who require monitoring for neonatal hypoglycaemia at a primary care setting if timely and accurate blood glucose monitoring is possible, treatment can be initiated if required, e.g. with buccal dextrose gel, and the baby can be transferred promptly to a secondary or tertiary facility if necessary. [Conditional recommendation for either option]

Justification: Based on a UK study, the panel considered that even if all babies were cared for in a tertiary care unit, not all cases of hypoglycaemia would be detected.

Primary care settings are associated with better breastfeeding outcomes, while quicker access to hypoglycaemia treatment in secondary or tertiary settings may lead to improved outcomes.

However, the costs associated with transferring to secondary or tertiary care are considered moderate to high.

There is considerable variability in parental preferences, with some preferring a secondary or tertiary care setting regardless of distance, while others may prioritise proximity to home

Implementation considerations: Other considerations, including maternal health and stability of diabetes management, may play a role in the decision about place of birth.

All babies at risk of hypoglycaemia should have access to accurate blood glucose monitoring. Prompt treatment of hypoglycaemia is essential, so initial treatment such as dextrose gel should be available immediately.

If the blood glucose concentration is <2.0mmol/L, dextrose gel alone is unlikely to be sufficient treatment. Administer dextrose gel while arranging transfer to a facility where IV infusion is available.

Monitoring and evaluation: Nil.

Research priorities: Nil.

Health Equity: Refer to health equity summary on Page 30.

Evidence to decision table: refer to Appendix G

Question 28. Which babies are at increased risk of adverse long-term outcomes as a result of neonatal hypoglycaemia?

PICO: Should risk factors for adverse long-term outcomes vs. no risk factors for adverse long-term outcomes be used for guiding management of babies at risk of neonatal hypoglycaemia?

Recommendation 28:

No recommendation made.

Justification: In the follow-up of the hPOD trial, associations between neonatal hypoglycaemia and neurodevelopmental problems at 2 years were identified in children whose mothers had diabetes, but it was not possible to analyse outcomes separately for other risk groups.

Implementation considerations: Nil.

Monitoring and evaluation: Nil.

Research priorities:

Studies are needed on:

The long-term outcomes of neonatal hypoglycaemia for individual risk groups, and the effects of treatments of neonatal hypoglycaemia on these.

Health Equity: There are no data about whether Māori or other groups are at increased risk of adverse long-term outcomes after neonatal hypoglycaemia, so the effect on health equity is unknown.

Evidence to decision table: refer to Appendix G

Question 29. What care should be provided after the hypoglycaemia is resolved? (when to discharge, what follow-up is required, need for ongoing monitoring).

Recommendation 29:

Whānau of all babies born at risk, whether or not they develop neonatal hypoglycaemia, should be well informed before discharge about clinical signs that may indicate hypoglycaemia and how to seek help if these occur. [**Conditional recommendation**]

General practitioners and Well Child/ Tamariki Ora providers should be made aware of a history of neonatal hypoglycaemia and its relevance for later developmental surveillance.

Justification: Severe hypoglycaemia can occur after a period of normal glucose concentrations, including after hospital discharge.

Babies born at risk of neonatal hypoglycaemia have a high risk of later neurodevelopmental problems, whether or not they experienced hypoglycaemia.

Implementation considerations: Provide comprehensive information and support for families, including educating them about signs to watch for after discharge and what actions to take if concerned.

Education and resources are required for LMC's, Well Child/ Tamariki Ora providers, and general practitioners to be able to address parents' concerns and provide explanations for medical procedures like heel pricks.

Consider offering debriefing to address any concerns, provide information about follow-up care, and offer support to families during this transition period.

Monitoring and evaluation: Nil.

Research priorities:

Studies are needed on:

1. Educational resources that parents should receive at discharge that are acceptable and practical for whānau.
2. The effectiveness of community-based interventions for high-risk groups, including the impact of long-term surveillance programs, the best methods and ages for follow-up, and which outcomes are most relevant.
3. The most acceptable and feasible community-based follow-up approaches that iare not overly interventionalist.

Health Equity: Health equity is enhanced by recognising that not all whānau may utilise Well Child/Tamariki Ora services. Therefore, it is important to provide a variety of support options tailored to meet the unique needs of each whānau, ensuring they have the resources and guidance necessary to access the services that best fit their circumstances.
It is important to recognise the variability in whānau ability to ask questions depending on their health literacy and culture, therefore information provided needs to be delivered in a way that meets the needs of the receiver.
There are significant health equity issues regarding access to services, so it is critical to ensure that support reaches those who need it most.

3. Summary of recommendations for research

Evidence gaps were identified indicating the need for further research on:

Question 1: Antenatal expression of breastmilk for preventing neonatal hypoglycaemia

- The effects of expressing milk on maternal well-being, including factors such as stress related to the inability to express colostrum.

Question 2: Tight glycaemic control during pregrancy for preventing neonatal hypoglycaemia

- The effect of tight maternal glycaemic control on neonatal hypoglycaemia and long-term childhood outcomes.
- Factors influencing adherence to tight glycaemic control targets in pregnancy, and how whānau can be supported to achieve these, particularly in specific populations.
- Patient values and preferences regarding tight glycaemic control in pregnancy.
- The cost-effectiveness of tight glycaemic control in pregnancy.

Question 3: Tight glycaemic control during labour for preventing neonatal hypoglycaemia

- The effects of tight glycaemic control during labour in women with Type I diabetes, Type II diabetes, and gestational diabetes mellitus (GDM), including short-term and long-term maternal and neonatal/childhood outcomes. Given potential iatrogenic harms, separate recommendations may be needed for each group.

Question 4: Delayed cord clamping for preventing neonatal hypoglycaemia

Nil.

Question 5: Skin-to-skin contact for preventing neonatal hypoglycaemia

- The effect of skin-to-skin contact with adults other than the mother on neonatal hypoglycaemia.

Question 6: Thermal care for preventing neonatal hypoglycaemia

- The most effective strategies to prevent hypothermia and consequent hypoglycaemia, particularly in term infants and those at risk of hypoglycaemia, when skin-to-skin contact is not feasible.

Question 7: Early feeding for preventing neonatal hypoglycaemia

Nil.

Question 8: Expressed breastmilk for preventing neonatal hypoglycaemia

- The effectiveness of donor human milk in preventing and treating neonatal hypoglycaemia.
- The effectiveness of expressed breastmilk in treating neonatal hypoglycaemia beyond 48 hours after birth.

Question 9: Oral dextrose gel for preventing neonatal hypoglycaemia

- The effect of prophylactic oral dextrose gel for neonatal hypoglycaemia on later neurological disability.
- The effectiveness of prophylactic oral dextrose gel compared to other preventive interventions such as harvested colostrum, donor milk, or infant formula.

Question 10: Formula for preventing neonatal hypoglycaemia

Nil.

Question 11: Benefits and risks of testing

- Outcomes in children whose whānau declined screening for neonatal hypoglycaemia and the reasons for declining.

Question 12: Who to test

- The outcomes of screening versus not screening large-for-gestational-age infants.

Question 13: When to test

- Whether extending screening beyond 12 hours improves outcomes.
- The frequency and clinical significance of glucose concentrations <2.6 mmol/L after 12 hours in babies who previously had glucose concentrations ≥2.6 mmol/L.

Question 14: Best care for babies while testing

Nil.

Question 15: Which type of device should be used for testing

Nil.

Question 16: Operation threshold for neonatal hypoglycaemia

- Benefits and harm of changing to a lower or higher glucose threshold, particularly on later neurodevelopmental outcomes at least through school age.

Question 17: What clinical observations are needed

- The optimal protocols for clinical observations in babies at risk of hypoglycaemia, including the best predictors of hypoglycaemia and duration of monitoring.

Question 18: Role of interstitial or transcutaneous glucose measurement

- The potential utility of continuous glucose monitoring (CGM) when a baby is transitioning from intravenous dextrose to breastfeeding.
- The utility of CGM in late preterm and term babies at risk of hypoglycaemia.
- The clinical significance of low glucose episodes that would not have been detected without CGM,including their association with neurodevelopmental outcomes and the effect of treatment on these outcomes.
- The cost-effectiveness of using CGM in babies whose glucose concentrations are unstable.
- Whānau perspectives on using CGM in babies.

Question 19: Should metabolites other than glucose be measured?
Nil.

Question 20: What neurological monitoring/ imaging is needed?
Nil.

Question 21: Target blood glucose threshold

- Outcomes of using a target of ≥2.6 mmol/L compared to lower or higher targets.

Question 22: Buccal dextrose gel for treating neonatal hypoglycaemia

- The effect of buccal dextrose gel for treating neonatal hypoglycaemia on long-term neurodevelopmental outcomes.
- The effect of buccal dextrose gel for treatment of babies born <34 weeks' gestation.
- The most effective dose, frequency, and mode of administration of buccal dextrose gel.

Question 23: Formula for treating neonatal hypoglycaemia

- The effect of formula compared to intravenous dextrose or donor human milk in correcting neonatal hypoglycaemia, NICU admission rates, and breastfeeding at hospital discharge.
- The cultural acceptability to whānau of using formula for the treatment of neonatal hypoglycaemia.

- The optimal amount of formula to be given for the treatment of neonatal hypoglycaemia.
- The long-term neurological effects on infants treated withformula for neonatal hypoglycaemia.

Question 24: IV dextrose for treating neonatal hypoglycaemia

- The effect of intravenous dextrose bolus administration on on short and longtermoutcomes.
- The optimal dosage and methods for administering intravenous dextrose.
- The optimal strategies for weaning babies off intravenous dextrose and onto full oral feeds.

Question 25: Diazoxide for treating neonatal hypoglycaemia

- The long-term effects of diazoxide.
- The optimal dosage of diazoxide to minimise the risk of side effects.

Question 26: Glucagon for treating neonatal hypoglycaemia

- The benefits, adverse effects, and long-term outcomes of glucagon use in babies, including the optimal dose and route of administration.

Question 27: What care settings are appropriate?

Nil.

Question 28: Which babies are at increased risk of adverse long-term outcomes as a result of neonatal hypoglycaemia?

- The long-term outcomes of neonatal hypoglycaemia for individual risk groups, and the effects of treatments of neonatal hypoglycaemia on these. .

Question 29: What care should be provided after the hypoglycaemia is resolved?

- The most acceptable and practical Educational resources that parents should receive at discharge that are acceptable and practical for whānau.
- The effectiveness of community-based interventions for high-risk groups, including the impact of long-term surveillance programs, the best methods and ages for follow-up, and which outcomes are most relevant.

- The most acceptable and feasible community-based follow-up approaches that are not overly interventionalist.

References

1. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group 2013. Available from: guidelinedevelopment.org/handbook.
2. O'Brien M, Gilchrist C, Sadler L, Hegarty JE, Alsweiler JM. Infants eligible for neonatal hypoglycemia screening: A systematic review. JAMA pediatrics. 2023;177(11):1187-96.
3. Alsweiler JM, Harris DL, Harding JE, McKinlay CJD. Strategies to improve neurodevelopmental outcomes in babies at risk of neonatal hypoglycaemia. The Lancet Child & Adolescent Health. 2021;5(7):513-23.
4. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. Journal of Pediatrics. 2012;161(5):787-91.
5. Vannucci RC, Vannucci SJ. Glucose metabolism in the developing brain. Seminars in Perinatology. 2000;24(2):107-15.
6. Gu MH, Amanda F, Yuan TM. Brain injury in neonatal hypoglycemia: a hospital-based cohort study. Clinical Medicine Insights: Pediatrics. 2019;13:1179556519867953.
7. Zhang Y, Chen D, Ji Y, Yu W, Mao J. Dynamic magnetic resonance imaging findings in the early stages of neonatal hypoglycemic brain injury. European Journal of Pediatrics. 2022;181(12):4167-74.
8. Shah R, Harding J, Brown J, McKinlay C. Neonatal glycaemia and neurodevelopmental outcomes: a systematic review and meta-analysis. Neonatology. 2019;115(2):116-26.
9. Alsweiler JM, Heather N, Harris DL, McKinlay CJD. Application of the screening test principles to screening for neonatal hypoglycemia. Frontiers in Pediatrics. 2022;10:1048897.
10. Rajay AB, Harding JE, h PODSG. Variations in New Zealand and Australian guidelines for the management of neonatal hypoglycaemia: A secondary analysis from the hypoglycaemia Prevention with Oral Dextrose gel Trial (hPOD). Journal of Paediatrics and Child Health. 2022;58(5):820-9.
11. Nelson A. Best practice recommendations for engagement with Māori whānau in the neonatal intensive care unit. Auckland University of Technology: Auckland University of Technology; 2022.
12. Came HA, Herbert S, McCreanor T. Representations of Maori in health policy in Aotearoa from 2006-2016: a barrier to the pursuit of health equity. Critical Public Health. 2021;31(3):338-48.
13. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report: Implications for Decolonizing Health Systems. Health and Human Rights. 2020;22(1):209-20.
14. Ministry of Health New Zealand. The Guide to He Korowai Oranga – Māori Health Strategy 2014 [cited 2024 March 14]. Available from: https://www.health.govt.nz/system/files/documents/publications/guide-to-he-korowai-oranga-maori-health-strategy-jun14-v2.pdf
15. New Zealand Waitangi Tribunal. Waitangi Tribunal report, The Napier Hospital and health services report : WAI 692 Wellington, New Zealand: Legislation Direct; 2001 [cited 2024 March 14]. Available from: https://forms.justice.govt.nz/search/Documents/WT/wt_DOC_68596252/Wai692.pdf
16. Clark S. Hauora. Report on Stage One of the Health Services and Outcomes Kaupapa Inquiry (Wai 2575) Lower Hutt, New Zealand 2019 [cited 2024 March 14]. Available from:

https://forms.justice.govt.nz/search/Documents/WT/wt_DOC_195476216/Hauora%202023%20W.pdf
17. Word Health Organization (WHO). Closing the gap in a generation. Commision on Social Determinants of Health Final Report 2008 [cited 2024 March 14]. Available from: https://www.who.int/publications/i/item/WHO-IER-CSDH-08.1
18. Ministry of Health New Zealand. Tatau Kahukura: Māori Health Chart Book 2015 (3rd edition) Wellington: Ministry of Health. 2015 [cited 2024 March 14]. Available from: https://www.health.govt.nz/publication/tatau-kahukura-maori-health-chart-book-2015-3rd-edition
19. United Nations. United Nations declaration on the rights of indigenous peoples 2007 [cited 2024 March 14]. Available from: https://www.un.org/development/desa/indigenouspeoples/wp-content/uploads/sites/19/2018/11/UNDRIP_E_web.pdf
20. Jowitt L. Gestational diabetes in New Zealand ethnic groups. Integrative Molecular Medicine. 2016;3.
21. Edmonds LK, Sibanda N, Geller S, Cram F, Robson B, Filoche S, et al. He Tamariki Kokoti Tau: Tackling preterm incidence and outcomes of preterm births by ethnicity in Aotearoa New Zealand 2010-2014. International Journal of Gynecology & Obstetrics. 2021;155(2):239-46.
22. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
23. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
24. Whānau Experiences Study Group. Whānau Experiences study: Experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished data. 2024.
25. Graham R, Masters-Awatere B. Experiences of Maori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
26. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ. 2016;353:i2089.
27. Alonso-Coello P, Schunemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ. 2016;353:i2016.
28. Barth JH, Misra S, Aakre KM, Langlois MR, Watine J, Twomey PJ, et al. Why are clinical practice guidelines not followed? Clinical Chemistry and Laboratory Medicine. 2016;54(7):1133-9.
29. Lotfi T, Hajizadeh A, Moja L, Akl EA, Piggott T, Kredo T, et al. A taxonomy and framework for identifying and developing actionable statements in guidelines suggests avoiding informal recommendations. Journal of Clinical Epidemiology. 2022;141:161-71.
30. Ministry of Health New Zealand. Maternal Mental Health Service Provision in New Zealand: Stocktake of district health board services 2021 [cited 2024 March 14]. Available from: https://www.health.govt.nz/system/files/documents/publications/maternal_mental_health_service_provision_in_new_zealand-19_nov.pdf

31. National Health and Medical Research Council (NHMRC). Guidelines for guidelines 2021. Available from: https://www.nhmrc.gov.au/guidelinesforguidelinesAustralia
32. Stats New Zeaalnd Tatauranga Aotearoa. 2018 Census ethnic group summaries 2020. Available from: https://www.stats.govt.nz/tools/2018-census-ethnic-group-summaries
33. AGREE Next Steps Consortium (2017). The AGREE II Instrument [Electronic version] 2017. Available from: http://www.agreetrust.org
34. GRADEpro GDT: GRADEpro Guideline Development Tool [Software],. McMaster University and Evidence Prime; 2024.
35. Auckland District Health Board. Collecting colostrum during pregnancy (harvesting) 2019. Available from: https://www.nationalwomenshealth.adhb.govt.nz/assets/Womens-health/Documents/Policies-and-guidelines/Collecting-Colostrum-During-Pregnancy.pdf
36. Te Whatu Ora Health New Zealand. Testing for, diagnosing and managing gestational diabetes (diabetes of pregnancy): Te whakamātau, te tautohu me te whakahaere i te mate huka hapūtanga. . Forthcoming 2024.
37. New Zealand College of Midwives. Consensus Statement: Facilitating the birth of the placenta 2024 [cited 2024 March 14]. Available from: https://www.midwife.org.nz/wp-content/uploads/2024/04/Facilitating-the-Birth-of-the-Placenta-1.pdf
38. Word Health Organization (WHO). Delayed umbilical cord clamping for improved maternal and infant health and nutrition outcomes 2023 [cited 2024 March 14]. Available from: https://www.who.int/tools/elena/interventions/cord-clamping
39. National Institute for Health and Care Excellence. Intrapartum care NICE guideline [NG235] 2023 [updated 29 September 2023]. Available from: https://www.nice.org.uk/guidance/ng235
40. Word Health Organization (WHO). Early initiation of breastfeeding to promote exclusive breastfeeding 2023 [cited 2024 March 14]. Available from: https://www.who.int/tools/elena/interventions/early-breastfeeding#:~:text=WHO%20Recommendations,the%20first%20hour%20after%20delivery
41. United Nations International Children's Emergency Fund (UNICEF) United Kingdom. Skin-to-skin contact [cited 2024 March 14]. Available from: https://www.unicef.org.uk/babyfriendly/baby-friendly-resources/implementing-standards-resources/skin-to-skin-contact/
42. Te Whatu Ora Health New Zealand. Observation of Mother and Baby in the Immediate Postnatal Period: Consensus statements guiding practice Hospitals and specialist care, Maternity, Women's health; 2012 [cited 2024 March 14]. Available from: https://www.tewhatuora.govt.nz/publications/observation-of-mother-and-baby-in-the-immediate-postnatal-period-consensus-statements-guiding-practice
43. World Health Organization (WHO). Guidelines for the management of neonatal hypoglycemia 2019 [cited 2024 March 14]. Available from: https://platform.who.int/docs/default-source/mca-documents/policy-documents/operational-guidance/ARE-MN-62-01-OPERATIONALGUIDANCE-2015-eng-Neonatal-Hypoglycemia-Guideline.pdf
44. Stanley CA, Weston PJ, Harris DL, De Leon DD, Harding JE. Role of beta-hydroxybutyrate measurement in the evaluation of plasma glucose concentrations in newborn infants. Archives of disease in childhood Fetal and neonatal edition. 2024.
45. Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, et al. Recommendations from the Pediatric Endocrine Society for evaluation and management of

persistent hypoglycemia in neonates, infants, and children. The Journal of Pediatrics. 2015;167(2):238-45.

Appendix A.

1.Clinical questions developed by the Guideline Panel

<table>
<tr><td colspan="3">For every question, consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau.</td></tr>
<tr><td>Main questions</td><td>Additional points</td><td>Key outcomes</td></tr>
<tr><td>1. What are parental and cultural priorities in screening and management of neonatal hypoglycaemia?</td><td>• Informed consent issues including before and after birth.</td><td rowspan="3">Critical for making a decision:
• Hypoglycaemia
• Neurodevelopmental impairment
• Admission to special care nursery or neonatal intensive care nursery
• Adverse effects
• Fully breastfeeding at hospital discharge

Important but not critical:
• Separation from the mother for treatment of hypoglycaemia before discharge home
• Hypoglycaemic injury on brain imaging
• Breastmilk feeding exclusively (baby only receives breast milk without any other drink or food) from birth to hospital discharge
• Duration of initial hospital stay</td></tr>
<tr><td>2. What is the best working definition (operational threshold) of neonatal hypoglycaemia?</td><td>• Definition may vary for different babies and at different ages.</td></tr>
<tr><td>3. How should neonatal hypoglycaemia be diagnosed?
A. What are the benefits and risks of testing?
B. Who to test?
a) Which babies are at increased risk of adverse longterm outcomes as a result of neonatal hypoglycaemia?
b) Which babies are at increased risk of neonatal hypoglycaemia?
c) Which babies should be tested for neonatal hypoglycaemia?
d) Which signs and symptoms are indications for testing?</td><td>• Hypoglycaemia is a sign of impaired metabolic transition
• Limited long-term evidence is available, we need to consider both short-term and long-term outcomes.
• Testing approach may need to vary in different care settings.
• Should this differ for babies who have and have not had a previous test indicating a low glucose, and for</td></tr>
</table>

C. How to test? a) How should blood glucose concentrations be measured? i. Which sample? ii. Which type of device? iii. How/where should the results be recorded? b) Should metabolites other than glucose be measured? c) What is the role of interstitial or transcutaneous glucose measurement? D. When to test? a) What age should testing start? b) How often should testing be performed? c) When should testing stop? E. What is the best care for babies while being tested?	those who are recovering and weaning off the treatment. • E. e.g. Involving the parents, testing when the mother is holding the baby or during skin-to-skin contact, pain relief	• Cost (Cost of intervention, cost of neonatal care and life-long cost) **Of limited importance:** • Time to blood glucose normalisation after intervention • Receipt of treatment for hypoglycaemia during initial hospital stay • Number of episodes of hypoglycaemia • Severity of hypoglycaemia • Duration of treatment
4. How should at-risk babies be managed to prevent hypoglycaemia? A. Does skin-to-skin contact reduce the risk of neonatal hypoglycaemia? B. Does early feeding reduce the risk of neonatal hypoglycaemia? C. Are babies given expressed breast milk (mother's own or donor human milk) less likely to	• Consider all interventions with and without breastfeeding B. including all kinds of feeding e.g. breastfeeding, formula, expressed breastmilk (both	

develop neonatal hypoglycaemia? D. Are babies given prophylactic oral dextrose gel less likely to develop neonatal hypoglycaemia? E. Are babies who had delayed cord clamping less likely to develop neonatal hypoglycaemia? F. Are babies given thermal care (measures to reduce heat loss) less likely to develop neonatal hypoglycaemia? G. Are there any other interventions that should be used to prevent neonatal hypoglycaemia?	mother's own and donor, antenatal or postnatal)	
5. How should neonatal hypoglycaemia be treated? A. What is the target blood glucose range for babies diagnosed with neonatal hypoglycaemia? B. What are the benefits and risks of different treatments for babies diagnosed with neonatal hypoglycaemia? a) Initial vs ongoing b) For babies with different risk factors for hypoglycaemia c) For babies with different blood glucose concentrations d) In different care settings e) For babies with other conditions, e.g., sepsis, HIE	• Consider short and long-term outcomes. B. Need to consider if there are any other differences if the treatment is given by different routes (e.g., cup vs tube feed)	

i. Feeding (any type) ii. Breastfeeding iv. Expressed breast milk v. Infant formula vi. Buccal dextrose gel vii. Intravenous dextrose viii. Diazoxide ix. Glucagon x. Other medications	iv. Mother's own or donor human milk, pasteurised or not vii. Including dose ix. Including intranasal, intravenous, intramuscular, and glucagon analogues	
6. How should babies who develop hypoglycaemia be monitored? A. What additional investigations are needed? B. What clinical observations are needed? C. What neurological monitoring/ imaging is needed? D. What care settings are appropriate?	C. e.g. EEG, CT, MRI D. When to transfer a baby community to higher level care? When to admit to NICU? When to refer to a specialist?	
7. What care should be provided after the hypoglycaemia is resolved? A. When to discharge? B. What follow-up is required? C. Ongoing monitoring	When has hypoglycaemia has resolved? i.e., when is metabolic transition complete? (can't necessarily tell this from blood glucose)	

	Guidance on steps if the hypoglycaemia is not resolved.	
8. To be considered in developing an implementation plan A. Patient information B. Ensuring equitable health outcomes C. Testing equipment		

2.Relationship between clinical questions developed by the Guideline Panel and questions posed in the Evidence-to-Decision frameworks in PICO* format

Question for Guideline Development	Evidence to Decision Document
1. What are parental and cultural priorities in screening and management of neonatal hypoglycaemia?	No EtD
2. What is the best working definition (operational threshold) of neonatal hypoglycaemia?	Should higher or lower blood glucose concentrations vs. blood glucose concentration of 2.6 mmol/L be used for defining of neonatal hypoglycaemia?
3. **How should neonatal hypoglycaemia be diagnosed?**	
A. What are the benefits and risks of testing?	Should testing for neonatal hypoglycaemia vs. not testing be used for babies at risk of neonatal hypoglycaemia?
B. Who to test? a) Which babies are at increased risk of adverse longterm outcomes as a result of neonatal hypoglycaemia? b) Which babies are at increased risk of neonatal hypoglycaemia? c) Which babies should be tested for neonatal hypoglycaemia?	Should risk factors for adverse long-term outcomes vs. no risk factors for adverse long-term outcomes be used for babies at risk of neonatal hypoglycaemia?

d) Which signs and symptoms are indications for testing?	Should expanded or restricted criteria vs. current criteria be used for screening for neonatal hypoglycaemia?
C. How to test? a) How should blood glucose concentrations be measured? i. Which sample? ii. Which type of device? iii. How/where should the results be recorded? b) Should metabolites other than glucose be measured? c) What is the role of interstitial or transcutaneous glucose measurement?	Should a point-of-care testing method be used to screen for hypoglycaemia in neonates? Should measurement of other metabolites in addition to glucose vs. measurement of glucose alone be used for diagnosing and monitoring of neonatal hypoglycaemia? Should continuous glucose monitoring vs. intermittent blood glucose testing be used for babies at risk of or diagnosed with neonatal hypoglycaemia?
D. When to test? a) What age should testing start? b) How often should testing be performed? c) When should testing stop?	Should other timings vs. start at 1-2 hours, intervals of 3-4 hours, finish after 12 hours of glucose concentrations above the threshold be used for testing neonatal hypoglycaemia?

E. What is the best care for babies while being tested?	Should specific pain management strategies vs. control/ placebo/ no intervention be used for pain management during blood sampling for neonatal hypoglycaemia?
4. **How should at-risk babies be managed to prevent hypoglycaemia?**	
A. Does skin-to-skin contact reduce the risk of neonatal hypoglycaemia?	Should skin-to-skin contact vs. no skin-to-skin contact be used for the prevention of neonatal hypoglycaemia?
B. Does early feeding reduce the risk of neonatal hypoglycaemia?	Should early feeding vs. delayed feeding be used for the prevention of neonatal hypoglycaemia?
C. Are babies given expressed breast milk (mother's own or donor human milk) less likely to develop.	Should expressed breastmilk vs. other or no intervention be used for preventing or treating neonatal hypoglycaemia?
D. Are babies given prophylactic oral dextrose gel less likely to develop neonatal hypoglycaemia?	Should oral dextrose gel vs. placebo be used for preventing neonatal hypoglycaemia?
E. Are babies who had delayed cord clamping less likely to develop neonatal hypoglycaemia?	Should delayed cord clamping vs. early cord clamping be used for the prevention of neonatal hypoglycaemia?

F. Are babies given thermal care (measures to reduce heat loss) less likely to develop neonatal hypoglycaemia?	Should thermal care vs. routine care be used for prevention of neonatal hypoglycaemia?
G. Are there any other interventions that should be used to prevent neonatal hypoglycaemia?	Should expression of breast milk vs. no expression of breast milk be used for preventing neonatal hypoglycaemia? Should formula vs control be used for preventing neonatal hypoglycaemia? Should tighter maternal glycaemic control during pregnancy in women with diabetes vs. less-tight maternal glycaemic control during pregnancy be used for preventing neonatal hypoglycaemia? Should tight intrapartum glycaemic control vs. less tight or no intrapartum glycaemic control be used for neonatal hypoglycaemia?
5. **How should neonatal hypoglycaemia be treated?**	

A. What is the target blood glucose range for babies diagnosed with neonatal hypoglycaemia?	Should higher minimum target blood glucose concentration vs. most common minimum target during treatment (2.6mmol/L) be used for babies being treated for neonatal hypoglycaemia?
B. What are the benefits and risks of different treatments for babies diagnosed with neonatal hypoglycaemia? a) Initial vs ongoing b) For babies with different risk factors for hypoglycaemia c) For babies with different blood glucose concentrations d) In different care settings e) For babies with other conditions, e.g., sepsis, HIE	Data, if available, are included and discussed in the relevant EtDs.
i. Feeding (any type) ii. Breastfeeding iv. Expressed breast milk v. Infant formula – with expressed breast milk as compared	Should expressed breastmilk vs. other or no intervention be used for preventing or treating neonatal hypoglycaemia? Should formula vs control be used for treating neonatal hypoglycaemia?

vi. Buccal dextrose gel	Should buccal dextrose gel vs. placebo gel or no gel be used for babies with neonatal hypoglycaemia?
vii. Intravenous dextrose	Should intravenous dextrose vs. other treatment or no treatment be used for treatment of neonatal hypoglycaemia?
viii. Diazoxide	Should diazoxide vs. placebo be used for treating neonatal hypoglycaemia?
ix. Glucagon	Should glucagon vs. control be used for neonatal hypoglycaemia?
x. Other medications	No EtD
6. **How should babies who develop hypoglycaemia be monitored?**	
A. What additional investigations are needed?	No EtD

B. What clinical observations are needed?	Should clinical observations vs. other/no clinical observations be used for monitoring babies with neonatal hypoglycaemia?
C. What neurological monitoring/ imaging is needed?	Should neurological monitoring/ imaging vs. no neurological monitoring/ imaging be used for monitoring babies with neonatal hypoglycaemia?
D. What care settings are appropriate?	Should secondary or tertiary level care settings vs. primary care setting be used for monitoring babies with neonatal hypoglycaemia?
7. **What care should be provided after the hypoglycaemia is resolved?** A. When to discharge? B. What follow-up is required? C. Ongoing monitoring	No EtD
8. **To be considered in developing an implementation plan** A. Patient information	No EtD

B. Ensuring equitable health outcomes C. Testing equipment	

*PICO: P-Population, I-Intervention, C-Comparison, O- Outcome

Appendix B. Members of the Te Tohu Waihonga Guideline Group

Name	Organisations	Discipline/Content Expertise
Governance Group		
Jane Harding (Co-chair)	Liggins Institute, University of Auckland	Neonatologist
Lisa Kremer (Co-chair)	School of Pharmacy, University of Otago	Neonatal Pharmacist
Jane Alsweiler	Department of Paediatrics: Child and Youth Health, University of Auckland	Neonatologist
Caroline Crowther	Liggins Institute, University of Auckland	Maternal Fetal Medicine Subspecialist
Violet Clapham	New Zealand College of Midwives	National Midwifery Advisor
Lesley Dixon*	New Zealand College of Midwives	Midwifery Advisor
Luling Lin	Liggins Institute, University of Auckland	Research Synthesis and Clinical Guideline Development
Chris McKinlay*	Department of Paediatrics: Child and Youth Health, University of Auckland	Neonatologist
Haunui Royal	Liggins Institute, University of Auckland	Cultural Advisor
Guideline Panel (In addition to those above)		
Jane Alsweiler	Perinatal Society of Australia and New Zealand	Neonatologist
David Barker	New Zealand Neonatal Network	Paediatrician
Kasey Brown	Pacific Pharmacists Association	Pharmacist Prescriber

Astrid Budden	Royal Australian and New Zealand College of Obstetricians and Gynaecologists	Obstetrician
Norma Campbell*	Midwifery Leaders group	Midwifery
Liza Edmonds	Paediatric Society of New Zealand	Neonatologist
Gwen Glazzard	New Zealand College of Midwives	Midwife
Roslyn Gasparini	New Zealand Nurses Organisation	Neonatal nurse/ Discharge and home care
Deborah Harris	Nurse Practitioners New Zealand	Neonatal nurse practitioner
Pip Kelleher*	Neonatal trust	Consumer
Katarina Komene	Nga Maia Māori Midwives Aotearoa	Midwife
Jessie McQuinn	Consumer representative	Consumer
Lisa Nathan	Pasifika Midwives Aotearoa	Midwife
Heranush Reyes	ONTRACK Consumer network	Consumer
Jenny Rogers	Liggins Institute, University of Auckland	Clinical trial coordinator
Raffaela Slight	Midwifery Leaders group	Midwifery
Sarah Wills	New Zealand Breastfeeding Association	Lactation consultant
Esko Wiltshire	New Zealand Paediatric Endocrinology Society	Paediatric endocrinologist
Evidence synthesis team		
Name	**Position**	
Luling Lin	Research fellow	

Jane Harding	Professor of Neonatology
Caroline Crowther	Professor of Maternal and Perinatal Health
Estelle Watson	Research associate
Lily Roberts	Research associate
Maria Cokin	Research associate
Libby Lord	Clinical intern
Caitlyn Ulyatt	Clinical intern
Orla Walsh	Clinical intern
Sophie St Clair	Clinical intern
Ariba Iqbal	Clinical intern
GRADE methodologists	
Name	**Organisation**
Sue Brennan	Melbourne GRADE Centre, School of Public Health and Preventive Medicine, Monash University
Max Murano	Melbourne GRADE Centre, School of Public Health and Preventive Medicine, Monash University

***** Member of the original group but withdrew during the development process and was not involved in the Panel meetings or formulation of recommendations.

Appendix C. Terms of Reference

Structure of the Aotearoa New Zealand Clinical Practice Guideline for Neonatal Hypoglycaemia

Development of the Aotearoa New Zealand Clinical Practice Guideline for Neonatal Hypoglycaemia will be overseen by two groups; the Governance Group and the Guideline Panel. The purpose of this document is to describe the responsibilities of these two groups.

Terms of reference for the Governance Group

Responsibilities

1. Provide advice, expertise, and direction on the development of the guidelines for neonatal hypoglycaemia in Aotearoa New Zealand.
2. Ensure the guideline is developed in accordance with best practice in guideline methodology, including the AGREEII standard.
3. Identify and invite members to join the Guideline Panel.
4. Provide administrative support for the Guideline Panel, including preparation of papers and organisation of meetings.
5. Oversee all aspects of development of the Guideline, including review of the evidence, drafting the guideline including recommendations, consultation with stakeholders, publication and dissemination.
6. Consult widely to develop an evidence-based guideline that will function as a useful resource for health professionals and will be of interest and relevance to pregnant women and their whānau in all Aotearoa New Zealand health care contexts.
7. Ensure that the Governance Group and the Guideline Panel uphold the five principles in Te Tiriti o Waitangi and both groups work towards achieving health equity for Māori.
8. Ensure that the Guideline recommendations will help meet the health needs for Māori.
9. Produce a plan for the dissemination, implementation and ongoing monitoring of clinical uptake of the guideline recommendations.

Meetings

All members of the Governance Group will participate in discussions. Every effort will be made to reach consensus decisions. All members of the Governing Group will disclose any competing interests. The Governance Group will meet quarterly to review progress. A subgroup of the Governance Group will function as a management group and meet at least monthly to address logistics and oversee preparation of materials. Meetings will usually be teleconferences. All meetings will be chaired by Professor Jane Harding. Minutes will be taken by Dr Luling Lin and circulated to members.

Reference

https://www.health.govt.nz/our-work/populations/maori-health/he-korowai-oranga/strengthening-he-korowai-oranga/treaty-waitangi-principles

Terms of reference for the Panel Members

Responsibilities

The Panel Members will participate in the development, review and revision of the Aotearoa New Zealand Clinical Practice Guideline for Neonatal Hypoglycaemia. The role of the Panel Members will include:

- Uphold the principles of Te Tiriti o Waitangi and addressing health equity
- Providing advice, expertise and direction in relation to the Guideline
- Confirming key clinical questions and outcomes
- Reviewing evidence and formulating recommendations
- Signing off recommendations and disseminating for consultation among the related organisations
- Disseminating the finalised Guideline to ensure clinical uptake of the Guideline

Framework for meeting Te Tiriti o Waitangi obligations

In accordance with The Waitangi Tribunal Health Services and Outcomes findings, to meet the obligations of Te Tiriti o Waitangi, the principles that the Governance and Panel group members will apply are:

1. **Tino rangatiratanga**: Māori representation occurs in the Governance and the Panel membership, where Māori are able to exert tino rangatiratanga and mana motuhake and have their voices heard within this structure to influence design, delivery, and monitoring for this guideline. Both the Governance and Panel members will ensure that an equity statement is included in all sections of the guideline.
2. **Equity**: All members of this group must commit to achieving equitable health outcomes for Māori infants who this guideline will apply to, and will do this by ensuring that all aspects of this guideline will be viewed with an equity lens for Māori by and with Māori.
3. **Active protection**: All members will be active in their commitment to achieving equitable health outcomes for Māori infants and will be accountable to ensuring an equity lens has been applied to the entirety of this guideline.
4. **Options**: All members will ensure that Māori models of health care (including and not limited to Kaupapa Māori services) are considered in this guideline.
5. **Partnership & Participation**: Membership of the Governance and Panel Groups include Māori representation across multiple health care professional groups. Both the Governance and Panel Groups are to purposely work in partnership to create this guideline.

The panel members will commit to

- Attending scheduled Panel Group meetings
- Making timely comments/feedback and taking action to ensure timeline targets are achieved
- Notifying members of the Governance Group, as soon as practical, if any matter arises which may be deemed to affect the development of the Guideline

The panel Members will expect

- To be provided with complete, accurate and meaningful information in a timely manner
- To be given reasonable time to make key decisions
- To be alerted to potential risks and issues that could impact the project, as they arise
- To participate in open and honest discussions to ensure all members are clear about discussion points and outcomes

Meetings

All members of the panel group will participate in discussions in a minimum of two half-day and two one-day meetings. Every effort shall be made to reach a consensus decision. Meetings will be via teleconference or in person. All meetings will be co-chaired by Professor Jane Harding and Dr Lisa Kremer. Minutes will be taken by Dr Luling Lin and circulated to all Panel Members after the meeting. Any expenses incurred by panel members in relation to preparation of the Guideline will be reimbursed.

Glossary

Disclaimer: many of the descriptions used in this glossary are specific interpretations for this guideline, and do not denote the fullness of meaning normally associated with the word or term. All efforts have been made to uphold the taonga of each kupu within the writing of this guideline.

Tino rangatiratanga	Cultural and social responsibility
Mana motuhake	Justice and equity, reflected through power and authority

Reference

https://www.health.govt.nz/our-work/populations/maori-health/he-korowai-oranga/strengthening-he-korowai-oranga/treaty-waitangi-principles

https://waitangitribunal.govt.nz/assets/Documents/Publications/WT-Principles-of-the-Treaty-of-Waitangi-as-expressed-by-the-Courts-and-the-Waitangi-Tribunal.pdf

https://waitangitribunal.govt.nz/assets/Documents/Publications/WT-Principles-of-the-Treaty-of-Waitangi-as-expressed-by-the-Courts-and-the-Waitangi-Tribunal.pdf

Appendix D. Thresholds for Decision-Making For Key Outcomes

Outcome	Judgement of effect size	Threshold (absolute risk difference per 1,000 babies)
Critical outcomes		
Neonatal hypoglycaemia	Trivial	<20
	Small	20-49
	Moderate	50 - 100
	Large	>100
Neurodevelopmental impairment	Trivial	<10
	Small	10-19
	Moderate	20-50
	Large	>50
Admission to special care nursery or neonatal intensive care nursery	Trivial	<20
	Small	20-49
	Moderate	50-100
	Large	>100
Adverse effects (Depending on outcome, this one for mortality, more minor effects thresholds would be higher)	Trivial	<1
	Small	1-10
	Moderate	10-20
	Large	>20
Fully breastfeeding at hospital discharge	Trivial	<20
	Small	20-49
	Moderate	50 - 100
	Large	>100
Important but not critical		
Separation from the mother for treatment of hypoglycaemia before discharge home	Trivial	<20
	Small	20-49
	Moderate	50 - 100
	Large	>100
Hypoglycaemic injury on brain imaging	Trivial	<10
	Small	10-19
	Moderate	20-50
	Large	>50
Breastmilk feeding exclusively (baby only receives breast milk without any other drink or food) from birth to hospital discharge	Trivial	<20
	Small	20-49
	Moderate	50 - 100
	Large	>100
Duration of initial hospital stay (days)	Trivial	<0.5
	Small	0.5-0.9
	Moderate	1-2
	Large	>2
	Trivial	<10
	Small	10-99

Cost (Cost of intervention, cost of neonatal care and life-long cost, NZD per baby for whānau)	Moderate	100-200
	Large	>200
Cost (Cost of intervention, cost of neonatal care and life-long cost, NZD per baby for health system)	Trivial	<100
	Small	100-499
	Moderate	500-1000
	Large	>1000

Appendix E. The Values Summary Document

Is there important uncertainty about or variability in how much people value the main outcomes?

Parents' values influence how they perceive and experience their children's experiences with neonatal hypoglycaemia and associated prevention, screening, treatment and follow up.

1. Hypoglycaemia [critical]

In the Whānau Experiences Study (1), whānau/families with diverse cultural backgrounds, including Māori, Pacific and Asian ethnicities, were studied because these groups have a higher likelihood of having a baby born at risk of neonatal hypoglycaemia. When their babies were at risk of hypoglycaemia, different families experienced varied reactions, with parents encountering a range of emotions and attitudes, including guilt and nervousness, and feeling overwhelmed by other issues and problems that were occurring at the same time.

Consideration for Māori

Whānau Māori expressed a desire for optimal health outcomes for their pēpi and emphasised the importance of being informed about the reasons for hypoglycaemia testing. They also conveyed feelings of responsibility and guilt regarding their baby's need for such testing.

Considerations for Pacific

Several mothers expressed anxiety about neonatal hypoglycaemia, even if in some cases their at-risk babies did not actually develop hypoglycaemia. Heightened anxiety during this time may also be attributable to other health issues experienced by these babies. Some Pacific parents from Whānau Experiences study (1) who had previously had children at risk of hypoglycaemia found it less alarming to be informed about the risk of neonatal hypoglycaemia, compared to parents who were experiencing this for the first time.

Consideration for Asian

Among the Asian mothers participating in the Whānau Experiences study who recalled being informed about their baby's risk of hypoglycaemia, approximately half reported feeling nervous or guilty, while the other half did not recall being significantly affected. One parent recounted not fully grasping the information due to a language barrier but agreed to the gel treatment out of fear that hypoglycaemia could harm their baby.

Summary: Uncertain value, possible variability

2. Neurodevelopmental impairment [critical]

In the Whānau Experiences study (1), parents indicated experiencing varying emotions and attitudes towards the possibility of long-term neurodevelopment outcomes of their babies. However, there was a consistent expectation among them for more extensive long-term follow-up for babies at risk of neonatal hypoglycaemia. A qualitative study conducted in Aotearoa New Zealand (Māori were included but not reported separately) explored the experiences of parents of children born at risk of neonatal hypoglycaemia who participated

in a follow-up study (2). The study found that parents were strongly focused on the impact of their children's outcomes on lifelong goals, including psychosocial development. Another study examined the perspectives of young adults regarding their participation in medical research during childhood (3). Out of 17 participants, five emphasised the importance of measuring children's cognitive development, while five others expressed interest in neurodevelopmental outcomes. Several studies have delved into parents' perspectives on neurodevelopmental outcomes following preterm birth, revealing that while developmental concerns are paramount to many parents, they also harbour apprehensions about various other health outcomes (4-6).

Considerations for Māori

Whānau Māori seek comprehensive support and clarity from healthcare providers regarding the well-being of their children, desiring ongoing monitoring and information throughout their lives.

Considerations for Pacific

A few Pacific mothers from the Whānau Experience Study reported that the future implications of their child being at risk of neonatal hypoglycaemia were inadequately explained. None of the Pacific families interviewed recalled receiving information at hospital discharge. Half of the participants expressed a desire for more follow-up and monitoring opportunities. Among Pacific participants, 40% suggested additional follow-up, due to heightened anxiety regarding their child's long-term health stemming from the risk of hypoglycaemia at birth. One Pacific parent recounted feeling worried upon learning about the potential impact of hypoglycaemia on their baby's brain, expressing a desire for more information. However, they also acknowledged that not all parents might desire such detailed information.

Consideration for Asian

In the Whānau Experiences Study, one Asian parent would have liked to be informed more about long-term effects of untreated hypoglycaemia. Around half of the participants wished for more monitoring of their baby's health after birth. A few would have appreciated a follow-up to summarise the baby's risk of hypoglycaemia at birth and the implications for the future.

Summary: High value, no important variability

3. Adverse effects [critical]

Parents may approach medical interventions with caution, particularly if they perceive them as risky or uncertain. In the Whānau Experience Study (1), some parents expressed concern about the potential adverse effects of treatment or intervention. In addition, a study conducted in United Kingdom involving breastfeeding mothers (n = 688) found that the majority (80.9%) would consider antenatal expression of breastmilk if it was proven to be helpful, but most (58.6%) were unsure if it was advisable, reporting concerns about pain, and inducing preterm labour (4).

Consideration for Māori

Whānau Māori want the very best health outcomes for their pēpi and were highly receptive of health care professionals and their actions.

Consideration for Pacific

Some Pacific mothers participating in the Whānau experience study (1) expressed concern about giving treatments preventatively (e.g., insulin) during pregnancy. They felt it would be causing unnecessary harm and wouldn't benefit the unborn child.

Consideration for Asian

Some Asian mothers from Whānau Experience Study (1) expressed concerns about the potential effects of antenatal treatments or actions aimed at controlling their blood glucose concentrations on their unborn babies.

Summary: High value, no important variability

4. Breastfeeding outcomes

- Fully breastfeeding at discharge [critical]
- Breastfeeding exclusively from birth to discharge [important]

In the Whānau Experiences study (1) mothers reported a strong preference for breastfeeding over formula feeding as a therapeutic measure for neonatal hypoglycaemia. Some mothers express a desire to hold their babies at the breast for early and continuous feeding to help prevent hypoglycaemia.

Consideration for Māori

Whānau Māori value being offered the opportunity to and then being supported to breastfeed their pēpi/baby during blood glucose testing.

Consideration for Pacific

All Pacific mothers wanted to breastfeed their baby. Most (80%) had a strong preference to exclusively breastfeed and not use formula as a form of treatment.

Consideration for Asian

A few Asian mothers noted that they had difficulty with switching to the recommended formula feeding because they had always planned to exclusively breastfeed.

Summary: High value, no important variability

5. Admission and treatment outcomes:

- Admission to special care nursery or neonatal intensive care nursery [critical]
- Separation from the mother for treatment of hypoglycaemia before discharge home [important]
- Duration of initial hospital stay [important]

Avoiding long complicated hospital stays and admission of the baby to neonatal intensive care nursery (NICU) are important to parents (1). A study conducted in Aotearoa New Zealand (including Māori but not separately reported) explored mothers' experiences of being a parent in a neonatal unit. Their babies were admitted for 15 days on average, and for reasons ranging from prematurity, hypoglycaemia, small for gestational age, and

intrauterine growth restriction. They found that parents' experiences of parenthood in a neonatal unit were often characterised by feelings of detachment from their babies, negative emotions, and a sense of lacking control. However, in contrast, some mothers expressed gratitude for their neonatal stay, citing it as an opportunity to learn about their baby's needs and care requirements (7).

Consideration for Māori

Whānau Māori shared experiences of being separated from pēpi following birth, emphasising the emotional toll of brief separations in the early moments. They noted that the resulting distress had a lasting negative effect on the whānau.

Consideration for Pacific

Some Pacific women reported anxiety around admissions to NICU and separation from their newborn during the vulnerable period post-birth. A few Pacific women were concerned about the risk of hypoglycaemia lengthening the hospital stay for both themselves and their babies.

Consideration for Asian

A few Asian participants expressed finding the hospital environment challenging, and struggled with long, complicated hospital stays.

Summary: High value, probably no important variability

6. Other critical or import outcomes.

- Hypoglycaemic injury on brain imaging [important]
- Cost [important]

No evidence available on these two outcomes.

Summary: Uncertain value and variability

References:

1. Whānau Experiences Study Group. Whānau Experiences study: Experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished data. 2024.
2. Franke N, Rogers J, Wouldes T, Ward K, Brown G, Jonas M, et al. Experiences of parents whose children participated in a longitudinal follow-up study. Health expectations : an international journal of public participation in health care and health policy. 2022;25(4):1352-62.
3. Franke N, Wouldes TA, Brown GTL, Ward K, Rogers J, Harding JE. Perspectives of adult offspring of participants recruited to a randomised trial in pregnancy: a qualitative study. Archives of Disease in Childhood. 2023:archdischild-2023-326017.
4. Fair FJ, Watson H, Gardner R, Soltani H. Women's perspectives on antenatal breast expression: a cross-sectional survey. Reproductive health. 2018;15(1):58.
5. Jaworski M, Janvier A, Bourque CJ, Mai-Vo TA, Pearce R, Synnes AR, et al. Parental perspective on important health outcomes of extremely preterm infants. Archives of Disease in Childhood. 2022;107(5):495-500.

6. Luu TM, Pearce R. Parental voice - what outcomes of preterm birth matter most to families? Seminars in Perinatology. 2022;46(2):151550.
7. Gibson C. Babies and babble: parents' experiences of the neonatal unit and the role of the babble app Massey University, Auckland, New Zealand 2020.

Appendix F. Excerpts from the Values Summary Document for Inclusion in each Evidence to Decision Document (EtD)

Uncertain value, possible variability

- Hypoglycaemia [critical]
- Adverse effect [critical]

High value, no important variability

- Neurodevelopmental impairment [critical]
- Fully breastfeeding at hospital discharge [critical]
- Breastfeeding exclusively from birth to hospital discharge [important]

High value, probably no important variability

- Admission to special care nursery or neonatal intensive care nursery [critical]
- Separation from the mother for treatment of hypoglycaemia before discharge home [important]
- Duration of initial hospital stay [important]
- Uncertain value and variability
- Hypoglycaemic injury on brain imaging [important]
- Cost [important]

Appendix G. Evidence to Decision Documents (EtDs)

Features of the Evidence to Decision Document Format

- We have *italicised* the repeated sections across all EtDs: the first paragraph of the background section, as well as the Value and Equity sections.
- Where additional material is included within one of the *italicised* sections with repeated content, it is underlined to indicate this portion is new.
- Each EtD includes a Values section and an Equity section, which contain summaries of information from the respective core documents (see Appendices E, F and section 1.2).
- For 'Desirable' and 'undesirable' effects, we first interpret where the point estimate lies in relation to the threshold. We then decide how certain we are in that effect, considering where the confidence interval lies in relation to the threshold. This is captured in our overall rating in the 'Certainty of Evidence' section. We are careful not to 'double count' the confidence interval by somehow integrating it in our description of the point estimate.
- For the 'Balance of Effect' section, we take into account both certainty and the point estimate.

Question 1.

Should expression of breastmilk vs. no expression of breastmilk be used for preventing neonatal hypoglycaemia ?	
POPULATION:	Babies at risk of neonatal hypoglycaemia
INTERVENTION:	expression of breastmilk
COMPARISON:	no expression of breastmilk
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.*

	The expression of breastmilk may be associated with improved lactogenesis (breastmilk production) and has been incorporated into many neonatal hypoglycaemia management guidelines worldwide.
CONFLICT OF INTERESTS:	CC, DH, JA, JH, JR and LL are authors of cited paper.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Maternal expression of breastmilk compared to no expression results in** (1): • Neonatal hypoglycaemia (RCT: small reduction (36 fewer per 1,000); Cohort study: little to no effect) [critical] • Fully breastfeeding at hospital discharge (RCT: moderate increase (73 more per 1,000); non-randomised study of intervention: little to no effect; Cohort study: large increase (279 more per 1000)) [critical] • Moderate reduction in duration of initial hospital stay (1.2 days fewer) [important] No studies reported on the following outcomes: neurodevelopmental impairment, admission to special care nursery or neonatal intensive care nursery, hypoglycaemic injury on brain imaging, breastmilk feeding exclusively from birth to hospital discharge, cost.	**Maternal expression of breastmilk compared to no expression results in** (1): Little to no effect on any breastfeeding after hospital discharge (2 RCTs: 604 babies, RR [95% CI]: 1.01 [0.94 to 1.08]) or exclusive breastfeeding three to four months after birth (2 RCTs: 604 babies, RR [95% CI]: 1.09 [0.95 to 1.25]).

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no expression of breast milk	Risk difference with expression of breast milk
Neonatal hypoglycaemia [critical]- RCT	630 (1 RCT)	⨁⨁⨁◯ Moderate[a]	**RR 0.92** (0.77 to 1.10)	Study population	
				454 per 1,000	**36 fewer per 1,000** (104 fewer to 45 more)
				Study population	

Neonatal hypoglycaemia [critical]- Cohort study	303 (1 non-randomised study)	⊕◯◯◯ Very low[a,b]	**OR 1.01** (0.74 to 1.39)	395 per 1,000	**2 more per 1,000** (69 fewer to 81 more)
Neurodevelopmental impairment [critical] - not measured	-	-	-	-	-
Admission to special care nursery or neonatal intensive care nursery [critical] - not measured	-	-	-	-	-
Fully breastfeeding at hospital discharge [critical]- RCT	632 (1 RCT)	⊕⊕◯◯ Low[a,c]	**RR 1.15** (0.99 to 1.33)	Study population	
				489 per 1,000	**73 more per 1,000** (5 fewer to 161 more)
Fully breastfeeding at hospital discharge [critical]- non-randomised study of intervention	656 (1 non-randomised study)	⊕◯◯◯ Very low[a,b]	**RR 1.01** (0.97 to 1.05)	Study population	
				930 per 1,000	**9 more per 1,000** (28 fewer to 47 more)
Fully breastfeeding at hospital discharge [critical]- cohort study	313 (1 non-randomised study)	⊕⊕◯◯ Low[b,d]	**RR 1.50** (1.29 to 1.74)	Study population	
				558 per 1,000	**279 more per 1,000** (162 more to 413 more)
Hypoglycaemic injury on brain imaging [important] - not measured	-	-	-	-	-
Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	-	-	-	-	-
Duration of initial hospital stay [important]	632 (1 RCT)	⊕⊕◯◯ Low[a,c]	-	The mean duration of initial	MD **1.2 days lower**

					hospital stay [important] was **70.9** days	(9.88 lower to 7.48 higher)
Cost - not measured	-	-	-	-	-

a.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
b.Downgraded two levels for very serious risk of bias due to high risk of the included study (studies).
c.Downgraded one level for serious risk of bias due to some concerns risk of the included study.
d.Upgraded one level for large effect.
*Absolute effects were calculated based on the control group risk

Considerations for Māori
No additional data available

Considerations or Pacific
No additional data available

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Maternal expression of breastmilk compared to no expression** (1): Moderate increase in separation from mother for treatment of neonatal hypoglycaemia (58 more per 1,000) [important] No studies reported on adverse effect for the baby	The DAME randomised trial (2) conducted in Australia (n=635) in women with pre-existing or gestational diabetes compared expressing breastmilk twice per day from 36 weeks' gestation to standard care (usual midwifery and obstetric care, supplemented by support from a diabetes educator). This study reported that 17/317 (5%) of women with diabetes who expressed breastmilk developed hypoglycaemia within 30 minutes of expressing, however, maternal hypoglycaemia was

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no expression of breast milk	Risk difference with expression of breast milk
Adverse effects [critical] - not measured	-	-	-	-	-
				Study population	

Separation from mother for treatment of hypoglycaemia before discharge home [important]	89 (1 RCT)	⊕◯◯◯ Very low[a,b]	**RR 1.16** (0.69 to 1.95)	364 per 1,000	**58 more per 1,000** (113 fewer to 345 more)	

a.Downgraded one level for serious risk of bias due to some concerns risk of the included study.

b.Downgraded two levels for very serious imprecision due to the wide confidence interval and small sample size.

Considerations for Māori

No additional data available

Considerations or Pacific

No additional data available

not evident from data provided by the women of their first three blood glucose concentrations after expressing: mean 5.6 mmol/L (SD 1.04, range 3.8 to 13.6; n=199). 10/317 (3%) of women had abdominal pain, and none (0%) had vaginal bleeding within 4 hours after expressing breastmilk. Breastmilk expression did not affect neonatal deaths, preterm births, admission for respiratory support, or neonatal encephalopathy with or without seizures.

Another RCT conducted in the US randomised pregnant women (n=45) to either antenatal expression or a control group that received lactation education handouts. The study reported no significant issues with breastmilk expression. Gestational age at birth, the onset of delayed lactogenesis, neonatal intensive care unit admissions, and the use of infant formula were similar between the breastmilk expression group and the control group (3).

However, some women experienced challenges with antenatal breastmilk expression, including difficulty learning the technique, pain, discomfort, lack of privacy, hand fatigue, perceived decreased fetal movement unrelated to fetal compromise, transient uterine muscle tightening, and feelings of awkwardness during expression (3)(4).

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Outcomes	Importance	Certainty of the evidence (GRADE)
Neonatal hypoglycaemia [critical]- RCT	CRITICAL	⊕⊕⊕◯ Moderate[a]
Neonatal hypoglycaemia [critical]- Cohort study	CRITICAL	⊕◯◯◯ Very low[a,b]
Neurodevelopmental impairment [critical] - not measured	CRITICAL	-
Admission to special care nursery or neonatal intensive care nursery [critical] - not measured	CRITICAL	-
Adverse effects [critical] - not measured	CRITICAL	-
Fully breastfeeding at hospital discharge [critical]- RCT	CRITICAL	⊕⊕◯◯ Low[a,c]
Fully breastfeeding at hospital discharge [critical]- non-randomised study of intervention	CRITICAL	⊕◯◯◯ Very low[a,b]
Fully breastfeeding at hospital discharge [critical]- cohort study	CRITICAL	⊕⊕◯◯ Low[b,d]
Separation from mother for treatment of hypoglycaemia before discharge home [important]	CRITICAL	⊕◯◯◯ Very low[c,e]
Hypoglycaemic injury on brain imaging [important] - not measured	IMPORTANT	-
Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	IMPORTANT	-
Duration of initial hospital stay [important]	IMPORTANT	⊕⊕◯◯ Low[a,c]
Cost - not measured	IMPORTANT	-

a.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.

	b.Downgraded two levels for very serious risk of bias due to high risk of the included study (studies). c.Downgraded one level for serious risk of bias due to some concerns risk of the included study. d.Upgraded one level for large effect. e.Downgraded two levels for very serious imprecision due to the wide confidence interval and small sample size. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	***Excerpts from Values summary document*** ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Expression of breastmilk compared to no expression of breastmilk** Very low certainty evidence showed • Small reduction in neonatal hypoglycaemia [critical] • Large increase in fully breastfeeding at hospital discharge [critical] • Small reduction in duration of initial hospital stay [important] • Uncertain effect on the separation of the baby from the mother for any treatment [important] • No adverse effects for the baby, but some adverse effects for some mothers **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	All the studies included are of antenatal expression, not expression of breastmilk after the birth.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No evidence of the resources required.	Resources required to collect and store expressed breastmilk postnatally are expected to be variable. Some of the necessary resources for obtaining expressed breastmilk include: Breastmilk pump: This may be manual or electric with variable quality and price. Storage: If it is given to the baby within 4 hours, expressed breastmilk can be stored at room temperature. Expressed breastmilk can also be refrigerated if it will be given after 48

		hours, and frozen if given within two weeks of collection. Cleaning expressing equipment: washing with detergent and water, sterilising (boiling or sterilising solution).
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not find any studies about the required resources.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	We did not find any studies about the required resources.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (7)*. However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (8)*.* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (7)*.* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (8)*.* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)*(7). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (5)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (9)(10)(11)*.*	

	Additionally, a systematic literature review by Graham et al. (12) *provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (12). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (5). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (6)*. Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (6)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Women felt positive and prepared for their baby's birth after engaging in the antenatal expression of breastmilk (13). Some also reported confidence and mastery of breastmilk expression (14). A study conducted in United States among non-diabetic mothers (n=45) reported that, of the 18 participants who received the antenatal milk expression intervention, most mothers practised expression at least once each day (80% (12/15) at 37 weeks; 61% (11/18) at 38 weeks; 71% (10/14) at 39 weeks, and 100% (7/7) at 40 weeks) (3). All 18 participants in the intervention group reported practising expression of breastmilk on at least 60% of days between enrolment into the RCT and the birth of their babies and 16/18 (89%) of women on at least 80% of days. Maternal breastmilk expression was, however, reported to be associated with difficulty learning the technique, pain, social pressure, discomfort, lack of privacy, time and energy	

	consumption, hand fatigue and feelings of awkwardness while expressing, which may limit acceptability (3)(14)(15). Antenatal breastmilk expression was associated with high satisfaction among the study participants (4). Another survey conducted in the UK involving 688 breastfeeding mothers reported that more than half participants (58.6%) were unsure if antenatal breast expression was a good idea; however, 80.9% would consider doing antenatal breast expression if it was found to be helpful to prepare for breastfeeding. Participants expressed concerns about the potential harm of antenatal breast expression, including procedure-related pain and the risk of inducing preterm labour (16). **Considerations for Māori** A qualitative study on factors influencing feeding practices among Māori mothers aged 15-24 years revealed that these mothers consistently emphasised the significance of healthcare professionals dedicating time to provide support and guidance in breastfeeding, including the expression of breastmilk. They valued being taught how to express breastmilk because it provided milk to feed their sick babies, even when they had cracked or sore nipples (15). Many stressed the need for both manual hand expression and the use of a breast pump to supply breastmilk for their babies and to relieve painful nipples. Some also shared their personal experiences with hand expression, highlighting its discomfort and lack of enjoyment (15). **Considerations or Pacific** No additional data available	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Expression of breastmilk is feasible in Aotearoa New Zealand. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Oladimeji OI, Harding JE, Crowther CA, Lin L. Expressed breast milk and maternal expression of breast milk for the prevention and treatment of neonatal hypoglycemia: a systematic review and meta-analysis. Maternal Health, Neonatology and Perinatology 2023;9(1):12.
2. Forster DA, Moorhead AM, Jacobs SE, Davis PG, Walker SP, McEgan KM, et al. Advising women with diabetes in pregnancy to express breastmilk in late pregnancy (Diabetes and Antenatal Milk Expressing [DAME]): a multicentre, unblinded, randomised controlled trial. Lancet. 2017;389(10085):2204-13.
3. Demirci JR, Glasser M, Himes KP, Sereika SM. Structured antenatal milk expression education for nulliparous pregnant people: results of a pilot, randomized controlled trial in the United States. International Breastfeeding Journal; 2022;17(1):50.
4. Johnsen M, Klingenberg C, Brand M, Revhaug A, Andreassen G. Antenatal breastmilk expression for women with diabetes in pregnancy - a feasibility study. International Breastfeeding Journal; 2021;16(1):56.
5. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.

6. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]. Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
7. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-54
8. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. Journal of pediatrics. 2012;161(5):787-91.
9. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
10. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
11. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
12. Graham R, Masters-Awatere B. Experiences of Maori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
13. Sweet L. Expressed breast milk as 'connection' and its influence on the construction of 'motherhood' for mothers of preterm infants: a qualitative study. International Breastfeeding Journal. 2008;3(1):30
14. Foudil-Bey I, Murphy MSQ, Dunn S, Keely EJ, El-Chaar D. Evaluating antenatal breastmilk expression outcomes: a scoping review. International Breastfeeding Journal. 2021;16(1):25.
15. Gosman, Helen. What influences infant feeding decisions for Māori mothers aged 15-24 years?. New Zealand: Eastern Institute of Technology, Hawke's Bay, Master's thesis; 2015.
16. Fair FJ, Watson H, Gardner R, Soltani H. Women's perspectives on antenatal breast expression: a cross-sectional survey. Reproductive health. 2018;15(1):58.

Question 2.

Should tighter maternal glycaemic control during pregnancy in women with diabetes vs. less-tight maternal glycaemic control during pregnancy be used for preventing neonatal hypoglycaemia?	
POPULATION:	Newborn babies whose mothers have diabetes
INTERVENTION:	tighter maternal glycaemic control during pregnancy in women with diabetes
COMPARISON:	less-tight maternal glycaemic control during pregnancy
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies)

	3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factor (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Neonatal hypoglycaemia is a common problem in babies of diabetic mothers. These babies are at increased risk of low blood glucose concentrations, owing to the sudden halt in abundant glucose supply via the placenta at the time of cord clamping. Rates of diabetes, including gestational diabetes mellitus (GDM) are rising globally. This places more babies at risk of hypoglycaemia, with the subsequent risk of neurodevelopmental impairment due to this condition. A potential strategy for minimising the risk of hypoglycaemia in the baby is achieving tight glycaemic control in the mother. Therefore, we aimed to explore whether tight glycaemic control in mothers with diabetes is more effective than less tight control as a prevention strategy for neonatal hypoglycaemia and its sequelae.
CONFLICT OF INTERESTS:	CC, CM, DH, JA, JH, JR and LL are authors of the cited studies.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Tighter maternal glycaemic control during pregnancy compared to less-tight maternal glycaemic control results in** (1): • Little to no effect on neonatal hypoglycaemia [critical], and duration of initial hospital stay [important] • Small reduction in admission to special care nursery or neonatal intensive care nursery (22 fewer per 1,000) [critical] • Small reduction on adverse effects (composite of mortality or serious morbidity) [critical] (7 fewer per 1,000) • Little to no effect on duration of initial hospital stay [important] No studies reported the following outcomes: neurodevelopmental impairment, fully breastfeeding at hospital discharge, separation from the mother for treatment of hypoglycaemia before discharge home, hypoglycaemic injury on brain imaging, breastmilk feeding exclusively from birth to hospital discharge, cost. The systematic review only included women with gestational diabetes (1).	The targets for glycaemic control in women with gestational diabetes vary widely across international recommendations, and the evidence base that forms these recommendations is unclear.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with less-tight maternal glycaemic control during pregnancy	Risk difference with tighter maternal glycaemic control during pregnancy in women with diabetes
Neonatal hypoglycaemia [critical]	1556 (3 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 0.92** (0.72 to 1.18)	Study population	
				209 per 1,000	**17 fewer per 1,000** (59 fewer to 38 more)
Neurodevelopmental impairment [critical] - not measured	-	-	-	-	-
Admission to special care nursery or neonatal intensive care nursery [critical]	1161 (2 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 0.59** (0.33 to 1.04)	Study population	
				53 per 1,000	**22 fewer per 1,000** (35 fewer to 2 more)
				Study population	

Adverse effects - Composite of mortality or serious morbidity (as defined by trial) [critical]	1550 (3 RCTs)	⊕⊕◯◯ Low[a,b]	**RR 0.84** (0.55 to 1.29)	46 per 1,000	**7 fewer per 1,000** (21 fewer to 13 more)
Fully breastfeeding at hospital discharge [critical] - not measured	-	-	-	-	-
Separation from the mother for treatment of hypoglycaemia before discharge home [important] - not measured	-	-	-	-	-
Hypoglycaemic injury on brain imaging [important] - not measured	-	-	-	-	-
Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	-	-	-	-	-
Duration of initial hospital stay [important]	1101 (1 RCT)	⊕⊕⊕◯ Moderate[b]	-	The mean duration of initial hospital stay [important] was **4.18** days	mean **0.07 days fewer** (0.75 fewer to 0.61 more)
Cost [important] - not reported	-	-	-	-	-

a.Downgraded one level for serious risk of bias due to insufficient detail to permit a judgement about random sequence generation, allocation concealment, attrition bias, and reporting bias.

	b.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm. *Absolute effects were calculated based on the control group risk Another systematic review assessing glycaemic control targets was undertaken by Prutsky in 2024 (2) in observational studies involving 9433 diabetic women. These studies included women with type 1 and type 2 diabetes, in addition to gestational diabetes. The results of this review indicated that tighter glycaemic targets (fasting glucose target of <5.0 mmol/L) were associated with a significant reduction in neonatal hypoglycaemia (odds ratio 0.65 (0.49 to 0.85), p = 0.01) compared to a fasting glucose target of <6.1 mmol/L, as was the less tight glycaemic target (fasting glucose target of <5.6 mmol/L) (OR 0.68 (0.48 to 0.96), p = 0.03). **Considerations for Māori** In the TARGET randomised trial in Aotearoa New Zealand, the effects of tighter glycaemic control during pregnancy on the outcomes listed above were also very similar for the 148/1100 (13.5%) Māori babies randomised compared to the findings for the whole cohort (unpublished data from (3). *In the Sugar Babies study of 514 babies in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)*(4). **Considerations for Pacific** In the TARGET randomised trial in Aotearoa New Zealand, the effects of tighter glycaemic control during pregnancy on the outcomes listed above were also very similar for the 123/1100 (11.2%) Pacific babies randomised compared to the findings for the whole cohort (unpublished data from (3). *In the Sugar Babies study of 514 babies in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)*(4)	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	No studies reported adverse events for babies associated with tighter glycaemic control during pregnancy (1). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Tighter maternal glycaemic control during pregnancy compared to less-tight maternal glycaemic control results in some undesirable effects for mothers (1): • May increase the risk of developing hypertensive disorder of pregnancy (12 more per 1,000) • Increased use of pharmacological therapy (174 more per 1,000) • Large reduction in treatment adherence (417 fewer per 1,000)

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		

Outcomes	Importance	Certainty of the evidence (GRADE)
Neonatal hypoglycaemia [critical]	CRITICAL	⊕⊕⊕◯ Moderate[a]
Neurodevelopmental impairment [critical] - not measured	CRITICAL	-
Admission to special care nursery or neonatal intensive care nursery [critical]	CRITICAL	⊕⊕◯◯ Low[a,b]
Adverse effects - Composite of mortality or serious morbidity (as defined by trial) [critical]	CRITICAL	⊕⊕◯◯ Low[a,b]
Fully breastfeeding at hospital discharge [critical] - not measured	CRITICAL	-
Separation from the mother for treatment of hypoglycaemia before discharge home [important] - not measured	IMPORTANT	-
Hypoglycaemic injury on brain imaging [important] - not measured	IMPORTANT	-

Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	IMPORTANT	-
Duration of initial hospital stay [important]	IMPORTANT	⊕⊕⊕◯ Moderate[b]
Cost [important] - not reported	IMPORTANT	-

a.Downgraded one level for serious risk of bias due to insufficient detail to permit a judgement about random sequence generation, allocation concealment, attrition bias, and reporting bias.
b.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.

The observational nature of these studies inevitably resulted in the authors concluding they had a moderate to high risk of bias, in addition to insufficient covariate adjustment.

Considerations for Māori

Because of small numbers included in the available trials, the findings are less certain for Māori babies.

Considerations or Pacific

Because of small numbers included in the available trials, the findings are less certain for Pacific babies.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	***Excerpts from Values summary document*** ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]*	

	• *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Tighter maternal glycaemic control during pregnancy compared to less-tight maternal glycaemic control Low certainty evidence showed: • Little to no effect on neonatal hypoglycaemia [critical] • Small reduction in adverse effects [critical] • Small reduction on the admission to special care nursery or neonatal intensive care nursery [critical] **Considerations for Māori** Limited evidence suggests that the effects are similar for Māori babies. **Considerations or Pacific** Limited evidence suggests that the effects are similar for Pacific babies.	• May increase the risk of developing hypertensive disorder of pregnancy • Increased use of pharmacological therapy • Large reduction in treatment adherence
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Cost of glycaemic control medicines: Insulin glargine (5 cartridges of 100 IU) = NZ $94.50 (Pharmac, NZ). Metformin (1000 tablets of 500mg) = NZ $14.74 (Pharmac, NZ). Glibenclamide (100 tablets of 5mg) = NZ $7.50 (Pharmac, NZ). Recommending tighter glycaemic control will drive higher use of pharmacological agents to achieve such targets. Although the cost of individual medications is relatively minor, the increasing prevalence of gestational diabetes will result in a greater proportion of women requiring drug treatment, and therefore increased costs.	

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There is no evidence that directly compares the required resources for tighter versus less-tight maternal glycaemic control during pregnancy. We are reasonably sure about the costs and resource requirements in the Aotearoa New Zealand setting.	

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	There are no studies that assess the specific cost-effectiveness of tighter maternal glycaemic control in women with diabetes, particularly in the context of preventing neonatal hypoglycaemia. However, the finding of increased use of pharmacological therapy in women in the tighter glycaemic control group (61% in tighter vs 47% in less-tight) indicates an inevitable higher cost for this intervention group (insulin, metformin, glibenclamide were used in the included trials) (1). An Australian study found that treatment of mild gestational diabetes incurred additional health system costs of AU $53,985, but also prevented serious perinatal complications and perinatal death. The authors therefore concluded this was a justifiable cost, particularly in high-income settings (5).	While these studies indicate some benefit from a cost-effectiveness perspective in treatment of women with gestational diabetes, this evidence does not address the specific comparison of tight vs less-tight glycaemic control or women with other types of diabetes.

	A systematic review on the cost-effectiveness of screening and managing gestational diabetes concluded that treatment may be cost-effective, but this is often not outweighed by the cost of screening the whole pregnant population (6).	

Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	A systematic review demonstrated that indigenous women (Australia, Canada, Aotearoa New Zealand, USA) had both a higher prevalence of pre-existing diabetes and gestational diabetes (10). Only one study was included from Aotearoa New Zealand, but this indicated higher rates of gestational diabetes diagnosis in Māori (7.9%) and Pacific (8.1%) māmā compared to NZ Europeans (3.3%) (11). In Aotearoa New Zealand, the prevalence of diabetes in 2022 is approximately two times higher in adults aged 25 – 39 years of Māori (11.2%), Pacific (11.4%) and Indian (16.8%) ethnicity compared to those of European ethnicity (6.1%) (12). The disproportionate burden of diabetes on different ethnic populations demands an equitable approach to intervention. However, there is no clear evidence of benefit with tighter maternal glycaemic control, suggesting minimal impact on health equity through this intervention. ***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social*	

	determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions. ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (13*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (4*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (13*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (4*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (13*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (8*), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (14, 15, 16*).* *Additionally, a systematic literature review by Graham et al.* (7*) provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst Whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (7*).* ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (8*).*	

	Other considerations *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (9*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (9*), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Tighter glycaemic control in women with diabetes inherently requires a greater level of drug therapy to achieve these narrower targets. The acceptability of achieving tighter glycaemic control has not been adequately explored. The systematic review reported reduced medication adherence in the tight control group, suggesting that the intervention may be less acceptable or too difficult to achieve (1). **Consideration for Māori** In the Whānau Experiences study (8), Whānau Māori want the very best health outcomes for their pēpi and are highly perceptive of health care professionals and their actions. **Consideration for Pacific** In the Whānau Experience study (8), some Pacific mothers expressed anxiety about taking any medications or undergoing treatments while pregnant. A few of the Pacific women interviewed expressed concern about receiving treatments, e.g., insulin, preventatively. They did not see the benefit and were concerned about the harm.	It has been reported that metformin is more acceptable for pregnant women than insulin in the treatment of gestational diabetes (17). Treatment with metformin resulted in better post-prandial glycaemic control and lower risk of hypoglycaemic events when compared to insulin (18).
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no	The RCTs included in the systematic review suggest that implementing tighter glycaemic control is feasible for women with gestational diabetes, including in Aotearoa New Zealand	

○ Probably yes ○ Yes ● Varies ○ Don't know	(1). However, they found that tighter glycaemic targets were associated with a large decrease in adhering to treatment (28.9% tight control vs 70.6% less-tight control, RR 0.41 [0.32, 0.52], 1 study, 395 women) (1). Reduction in treatment adherence suggests that tighter glycaemic control may not be feasible for some women. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know

ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Hofer OJ, Martis R, Alsweiler J, Crowther CA. Different intensities of glycaemic control for women with gestational diabetes mellitus. Cochrane Database of Systematic Reviews. 2023;10(10):CD011624.
2. Prutsky GJ, Domecq JP, Wang Z, Carranza Leon BG, Elraiyah T, Nabhan M, et al. Glucose targets in pregnant women with diabetes: a systematic review and meta-analysis The Journal of Clinical Endocrinology & Metabolism. 2013;98(11):4319-24.
3. Crowther CA, Samuel D, Hughes R, Tran T, Brown J, Alsweiler JM, TARGET Study Group. Tighter or less tight glycaemic targets for women with gestational diabetes mellitus for reducing maternal and perinatal morbidity: A stepped-wedge, cluster-randomised trial. PLOS Medicine. 2022;19(9):e1004087.
4. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
5. Moss JR., Crowther CA., Hiller JE, Willson KJ, Robinson JS, The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Costs and consequences of treatment for mild gestational diabetes mellitus – evaluation from the ACHOIS randomised trial. BMC Pregnancy Childbirth. 2007;28(7), 27.
6. Fitria N, van Asselt ADI, Postma MJ. Cost-effectiveness of controlling gestational diabetes mellitus: a systematic review. The European Journal of Health Economics. 2019; 20(3):407-417
7. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
8. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
9. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]. Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
10. Voaklander B, Rowe S, Sanni O, Campbell S, Eurich D, Ospina MB. Prevalence of diabetes in pregnancy among Indigenous women in Australia, Canada, New Zealand, and the USA: a systematic review and meta-analysis.. The Lancet Global Health. 2020;8(5):e681-e698.
11. Yapa M, Simmons D. Screening for gestational diabetes mellitus in a multiethnic population in New Zealand. Diabetes Research and Clinical Practice. 2000;48(3):217-23.
12. Ministry of Health New Zealand. Virtual Diabetes Register and web tool. 2023 [cited 2 February 2024]. Available from: https://www.tewhatuora.govt.nz/for-health-professionals/data-and-statistics/virtual-diabetes-tool/#virtual-diabetes-register-web-tool
13. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
14. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
15. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
16. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
17. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP; MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. The New England Journal of Medicine. 2008;8;358(19):2003-15.
18. Picón-César MJ, Molina-Vega M, Suárez-Arana M, González-Mesa E, Sola-Moyano AP, Roldan-López R, et al. Metformin for gestational diabetes study: metformin vs insulin in gestational diabetes: glycemic control and obstetrical and perinatal outcomes: randomized prospective trial. American Journal of Obstetrics and Gynecology. 2021;225(5):517.e1-517.e17.

Question 3.

Should tight intrapartum glycaemic control vs. less tight or no intrapartum glycaemic control be used for neonatal hypoglycaemia?	
POPULATION:	Pregnant women with diabetes and their babies
INTERVENTION:	tight intrapartum glycaemic control
COMPARISON:	less tight or no intrapartum glycaemic control
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation

BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Currently, the National Institute for Health and Care Excellence (NICE) guidelines in the UK (1) recommend maintenance of maternal blood glucose concentrations between 4 and 7 mmol/L over the intrapartum period for women with diabetes to reduce the incidence of neonatal hypoglycaemia. This guideline was based on evidence from eight observational studies which found that there was an increased chance of neonatal hypoglycaemia if the mothers had higher intrapartum blood glucose concentrations. However, others have found no association between the control of intrapartum maternal glucose concentrations and neonatal hypoglycaemia. In addition, there have been reports of an association between receipt of intravenous glucose during labour and hypoglycaemia in the baby after birth, but these are inconsistent.
CONFLICT OF INTERESTS:	CC, DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Tight intrapartum glycaemic control compared to less tight or no intrapartum glycaemic control** associated with (2): • Neonatal hypoglycaemia (RCT: little to no effect; Cohort studies: large reduction (112 fewer per 1,000)) [critical] • Admission to special care nursery or neonatal intensive care nursery (RCT: large increase (112 fewer per 1,000); Cohort studies: large reduction (146 fewer per 1,000)) [critical] • Little to no effect on duration of initial hospital stay [important] • No studies reported on the following outcomes: fully breastfeeding at hospital discharge, separation from the mother for treatment of hypoglycaemia before discharge home, neonatal hypoglycaemic injury on brain imaging, cost.	**Tight intrapartum glycaemic control compared to less tight or no intrapartum glycaemic control** associated with (2): • Receipt of treatment for neonatal hypoglycaemia during the initial hospital stay (RCT: little to no effect; Cohort studies: moderate reduction (80 fewer per 1,000) • Moderate reduction in APGAR score <7 at 5 minutes (cohort studies: 53 fewer per 1,000)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with less tight or no intrapartum glycaemic control	Risk difference with tight intrapartum glycaemic control
Neonatal Hypoglycaemia [critical]-RCT	76 (1 RCT)	⨁◯◯◯ Very low[a]	**RR 1.00** (0.45 to 2.24)	Study population	
				237 per 1,000	**0 fewer per 1,000** (130 fewer to 294 more)
Neonatal Hypoglycaemia [critical] -Cohort	6152 (11 non-randomised studies)	⨁⨁◯◯ Low[b,c,d]	**OR 0.44** (0.31 to 0.63)	Study population	
				225 per 1,000	**112 fewer per 1,000** (143 fewer to 70 fewer)
Admission to special care nursery or neonatal intensive care nursery [critical]- RCT	76 (1 RCT)	⨁◯◯◯ Very low[a]	**RR 5.00** (0.61 to 40.81)	Study population	
				26 per 1,000	**105 more per 1,000** (10 fewer to 1,048 more)
Admission to special care nursery or neonatal intensive care nursery [critical]- Cohort	1077 (4 non-randomised studies)	⨁⨁⨁⨁ High[d]	**OR 0.45** (0.28 to 0.74)	Study population	
				321 per 1,000	**146 fewer per 1,000** (204 fewer to 62 fewer)
Fully breastfeeding at hospital discharge [critical] - not measured	-	-	-	-	-
Separation from the mother for treatment of hypoglycaemia before discharge	-	-	-	-	-

home [important] - not measured					
Hypoglycaemic injury on brain imaging [important] - not measured	-	-	-	-	-
Duration of initial hospital stay [important]	53 (1 non-randomised study)	⨁◯◯◯ Very low[c,e]	-	The mean duration of initial hospital stay [important] was **4.67** days	MD **0 days** (3.6 lower to 3.6 higher)
Cost [important] - not measured	-	-	-	-	-

a.Downgraded three levels for extremely serious imprecision due to a very wide confidence interval that appreciably crosses the threshold(s) of interest.
b.Downgraded one level for serious inconsistency due to significant heterogeneity.
c.Downgraded one level for serious risk of bias due to moderate to low quality assessment results.
d.Upgraded two levels for very large effect.
e.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
*Absolute effects were calculated based on the control group risk

Considerations for Māori
No additional data available
Considerations or Pacific
No additional data available

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Tight intrapartum glycaemic control compared to less tight or no intrapartum glycaemic control** associated with (2): • Uncertain effect on neurodevelopmental impairment [critical] • Two cohort studies reported no difference in adverse effects • Caesarean section (RCT: moderate decrease (52 fewer per 1,000); Cohort studies: large increase (112 more per 1,000) [adverse effect, critical] • Large reduction in breastfeeding exclusively from birth to hospital discharge (RCT: 105 fewer per 1,000) [important]	**Tight intrapartum glycaemic control compared to less tight or no intrapartum glycaemic control** associated with (2) • Little to no effect on maternal hypoglycaemia

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with less tight or no intrapartum glycaemic control	Risk difference with tight intrapartum glycaemic control
Neurodevelopmental impairment [critical]- Cohort	131 (1 non-randomised study)	⊕◯◯◯ Very low[a]	**OR 1.26** (0.58 to 2.73)	Study population	
				359 per 1,000	**55 more per 1,000** (114 fewer to 246 more)
Adverse effects (investigator defined) [critical]- Cohort	263 (1 non-randomised study)	⊕◯◯◯ Very low[b,c]	-	Two cohort studies reported no difference in respiratory distress syndrome, perinatal death, neonatal death or shoulder dystocia.	
Caesarean section [critical]- RCT	76 (1 RCT)	⊕◯◯◯ Very low[d]	**RR 0.78** (0.32 to 1.87)	Study population	
				237 per 1,000	**52 fewer per 1,000** (161 fewer to 206 more)
Caesarean section [critical]- Cohort	1759 (4 non-randomised studies)	⊕⊕◯◯ Low	**OR 1.62** (1.10 to 2.39)	Study population	
				314 per 1,000	**112 more per 1,000** (21 more to 208 more)

Breastmilk feeding exclusively from birth to hospital discharge [important]	76 (1 RCT)	⊕◯◯◯ Very low[d]	**RR 0.81** (0.51 to 1.28)	Study population	
				553 per 1,000	**105 fewer per 1,000** (271 fewer to 155 more)

a.Downgraded two levels for very serious imprecision due to the wide confidence interval and small sample size.
b.Downgraded one level for serious risk of bias due to moderate to low quality assessment results.
c.Downgraded one level for imprecision due to no numbers being reported
d.Downgraded three levels for extremely serious imprecision due to a very wide confidence interval that appreciably crosses the threshold(s) of interest.
*Absolute effects were calculated based on the control group risk

Considerations for Māori
No additional data available

Considerations or Pacific
No additional data available

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Outcomes	Importance	Certainty of the evidence (GRADE)
Neonatal Hypoglycaemia [critical]-RCT	CRITICAL	⊕◯◯◯ Very low[a]
Neonatal Hypoglycaemia [critical] -Cohort	CRITICAL	⊕⊕◯◯ Low[b,c,d]
Neurodevelopmental impairment [critical]- Cohort	CRITICAL	⊕◯◯◯ Very low[e]

Admission to special care nursery or neonatal intensive care nursery [critical]- RCT	CRITICAL	⊕◯◯◯ Very low[a]
Admission to special care nursery or neonatal intensive care nursery [critical]- Cohort	CRITICAL	⊕⊕⊕⊕ High[d]
Adverse effects (investigator defined) [critical]- Cohort	CRITICAL	⊕◯◯◯ Very low[c,f]
Caesarean section [critical]- RCT	CRITICAL	⊕◯◯◯ Very low[a]
Caesarean section [critical]- Cohort	CRITICAL	⊕⊕◯◯ Low
APGAR score <7 at 5 miniutes [critical]	CRITICAL	⊕⊕⊕◯ Moderate[c,d]
Fully breastfeeding at hospital discharge [critical] - not measured	CRITICAL	-
Separation from the mother for treatment of hypoglycaemia before discharge home [important] - not measured	IMPORTANT	-
Hypoglycaemic injury on brain imaging [important] - not measured	IMPORTANT	-
Breastmilk feeding exclusively from birth to hospital discharge [important]	IMPORTANT	⊕◯◯◯ Very low[a]
Duration of initial hospital stay [important]	IMPORTANT	⊕◯◯◯ Very low[c,g]
Cost [important] - not measured	IMPORTANT	-

a.Downgraded three levels for extremely serious imprecision due to a very wide confidence interval that appreciably crosses the threshold(s) of interest.

	b.Downgraded one level for serious inconsistency due to significant heterogeneity. c.Downgraded one level for serious risk of bias due to moderate to low quality assessment results. d.Upgraded two levels for very large effect. e.Downgraded two levels for very serious imprecision due to the wide confidence interval and small sample size. f.Downgraded one level for imprecision due to no numbers being reported g.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	***Excerpts from Values summary document*** ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability***	

	• *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Tight intrapartum glycaemic control compared to less tight or no intrapartum glycaemic control** associated with • Very low certainty evidence showed: • Large reduction in neonatal hypoglycaemia [critical] • Uncertain effect on neurodevelopmental impairment [critical] • Large reduction in admission to special care nursery or neonatal intensive care nursery [critical] • Large increase in caesarean section [adverse effect, critical] • Uncertain effect on breastfeeding exclusively from birth to hospital discharge [important] • Uncertain effect on duration of initial hospital stay [important] **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	• Moderate reduction on receipt of treatment for neonatal hypoglycaemia during the initial hospital stay • Little to no effect on maternal hypoglycaemia • Moderate reduction on APGAR score <7 at 5 minutes
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Cost for IV Insulin (Injection 100 u per ml, 3 ml) = NZ $ 94.50 (Pharmac, NZ) Intrapartum glycaemic control requires close monitoring of maternal blood glucose concentrations and the initiation of an insulin infusion if these values are elevated. Continued monitoring of glucose concentrations requires staff time and has a cost, as does the administration of IV dextrose and insulin if required.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We are reasonably sure about the costs of medication in the Aotearoa New Zealand setting. We are less certain about the costs of staff time.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There is no direct evidence regarding tighter intrapartum glycaemic control and cost-effectiveness.	Newer methods of glycaemic control management may alter costs. For example, continuous subcutaneous insulin infusion which has shown to be as safe and effective as standard intravenous insulin infusion, and allows women to self-manage their insulin. Women who are already using this approach through their pregnancy don't have to swap methods in labour (3). Newer monitoring methods may also reduce costs such as electronic glucose management systems (e.g. glucostabiliser) or continuous glucose monitoring, a cost from NZ $ 1,000 to several thousand dollars.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?***	

	Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%) (6). *However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (7). *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)*(6). *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (7). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (6). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (4)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (8)(9)(10). *Additionally, a systematic literature review by Graham et al.* ((11) *provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (11). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (4). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (5). *Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (5)*, 71% of women reported that they had paid for at least one*	

	pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Tighter intrapartum control would require more frequent monitoring which may be less acceptable, but we found no studies regarding healthcare providers' or consumers' views on intrapartum glycaemic control protocols. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No studies have directly reported on the feasibility of tight intrapartum glycaemic control. In Aotearoa New Zealand, the gestational diabetes clinical practice guideline has no recommendations for glycaemic control in labour (12). **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know

UNDESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

REFERENCES SUMMARY

1. National Institute for Health and Care Excellence (NICE). Diabetes in pregnancy: management from preconception to the postnatal period. London: National Institute for Health and Care Excellence (NICE); 2020 Dec 16.
2. Ulyatt CM, Roberts LF, Crowther CA, Harding JE, Lin L. Intrapartum maternal glycaemic control for the prevention of neonatal hypoglycaemia: a systematic review and meta-analysis. BMC Pregnancy and Childbirth. 2024;13;24(1):423.
3. Yap Y, Modi A, Lucas N. The peripartum management of diabetes. BJA Education; 2020;20(1):5-9.
4. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
5. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]. Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
6. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-54
7. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. Journal of pediatrics. 2012;161(5):787-91.
8. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
9. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
10. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
11. Graham R, Masters-Awatere B. Experiences of Maori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
12. Ministry of Health. Screening, diagnosis and management of gestational diabetes in New Zealand: A clinical practice guideline. Wellington: Ministry of Health. December 2014 [cited 2 February 2024]. Available from: https://www.tewhatuora.govt.nz/assets/Publications/Diabetes/screening-diagnosis-management-of-gestational-diabetes-in-nz-clinical-practive-guideline-dec14-v2.pdf

Question 4.

Should delayed cord clamping vs. early cord clamping be used for preventing neonatal hypoglycaemia?	
POPULATION:	Babies at risk of neonatal hypoglycaemia
INTERVENTION:	delayed cord clamping
COMPARISON:	early cord clamping
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:**

	1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Waiting to clamp and cut the umbilical cord after birth allows time for the transfer of blood from the placenta to the baby. Delayed cord clamping has been shown to provide a variety of short- and long-term benefits for the baby. These include increased neonatal haemoglobin concentrations, and in preterm babies, decreased incidence of intraventricular haemorrhage, prevention of hypotension, increased Apgar scores and decreased mortality. Once the cord is clamped and placental blood supply ceases, the newborn must adjust from dependence on their mother for fuel to initiating endogenous glucose production. Failure to adapt to this sudden interruption of glucose supply when the cord is clamped is the most common reason for neonatal hypoglycaemia. Placental transfusion through delayed cord clamping provides extra blood and may potentially help protect against hypoglycaemia, but there is a paucity of information on this.
CONFLICT OF INTERESTS:	CC, DH, JA JH, JR and LL are authors of cited paper.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?

<table>
<tr><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr>
<td>○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know</td>
<td>
Delayed cord clamping compared to early cord clamping results in (1):

Small reduction in neonatal hypoglycaemia (27 fewer per 1,000) [critical]
Moderate reduction in neurodevelopmental impairment at 12 to 24 months (35 fewer per 1,000) [critical]
Little to no effect on neurodevelopmental impairment at 24 to 48 months [critical]
Little to no effect on admission to special care nursery or neonatal intensive care nursery [critical]
Moderate reduction in neonatal mortality (19 fewer per 1,000) [adverse effects, critical]
Small increase in fully breastfeeding at hospital discharge [critical]
Little to no effect on duration of initial hospital stay [important]

There is no data for the following outcomes: separation from the mother for treatment of hypoglycaemia before discharge home, hypoglycaemic injury on brain imaging, breastmilk feeding exclusively from birth to hospital discharge, cost.
<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow-up</th><th rowspan="2">Certainty of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
<tr><th>Risk with early cord clamping</th><th>Risk difference with delayed cord clamping</th></tr>
<tr><td>Hypoglycaemia [critical]</td><td>446 (6 RCTs)</td><td>⨁◯◯◯ Very low[a,b,c]</td><td>RR 0.87 (0.53 to 1.30)</td><td>Study population</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td>207 per 1,000</td><td>27 fewer per 1,000 (97 fewer to 62 more)</td></tr>
<tr><td>Neurodevelopmental impairment at 12 to 24 months [critical]</td><td>1448 (2 RCTs)</td><td>⨁⨁◯◯ Low[a,c]</td><td>RR 0.86 (0.71 to 1.04)</td><td>Study population</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td>252 per 1,000</td><td>35 fewer per 1,000 (73 fewer to 10 more)</td></tr>
</table>
</td>
<td>
Delayed cord clamping compared to early cord clamping results in (1)
Little to no effect on blood glucose concentration during hospital stay, receipt of treatment for hypoglycaemia during initial hospital stay and severity of hypoglycaemia (1).
Half of the studies were conducted in high-income countries, and the other half were conducted in low-income countries.
Neonatal mortality reduction, with data predominantly from high-income countries, is observed only for preterm babies, as no events have been reported in term babies.
In subgroup analyses, there was no interaction between gestational age (term vs preterm babies) and neonatal hypoglycaemia, neurodevelopmental impairment at 24 to 48 months, fully breastfeeding at hospital discharge, admission to special care nursery or neonatal intensive care nursery and duration of initial hospital stay.
Another systematic review and individual participant meta-analysis found that delayed cord clamping reduced the number of babies <32 weeks' gestation who needed later blood transfusion (13 trials; 2,128 babies; RR, 0.59; 95% CI, 0.47–0.73) (2).
</td>
</tr>
</table>

Neurodevelopmental impairment at 24 to 48 months [critical]	673 (2 RCTs)	⊕⊕◯◯ Low[a,c]	**RR 0.97** (0.76 to 1.24)	Study population		
				249 per 1,000	**7 fewer per 1,000** (60 fewer to 60 more)	
Admission to special care nursery or neonatal intensive care nursery [critical]	3122 (14 RCTs)	⊕⊕⊕◯ Moderate[a]	**RR 1.08** (0.81 to 1.45)	Study population		
				69 per 1,000	**5 more per 1,000** (13 fewer to 31 more)	
Adverse effects-neonatal mortality [critical]	3041 (15 RCTs)	⊕⊕⊕◯ Moderate[a]	**RR 0.73** (0.55 to 0.98)	Study population		
				72 per 1,000	**19 fewer per 1,000** (32 fewer to 1 fewer)	
Fully breastfeeding at hospital discharge [critical]	1564 (5 RCTs)	⊕⊕◯◯ Low[a,c]	**RR 1.04** (0.99 to 1.09)	Study population		
				711 per 1,000	**28 more per 1,000** (7 fewer to 64 more)	
Separation from the mother for treatment of hypoglycaemia before discharge home [important] - not measured	-	-	-	-	-	
Hypoglycaemic injury on brain imaging [important] - not measured	-	-	-	-	-	

Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	-	-	-	-	-
Duration of initial hospital stay [important]	2082 (15 RCTs)	⊕⊕⊕◯ Moderate[c]	-	The mean duration of initial hospital stay [important] was **24.5** days	MD **0.19 days lower** (0.59 lower to 0.2 higher)
Cost [important] - not measured	-	-	-	-	-

a.Downgraded one level of serious risk of bias due to overall moderate quality of this outcome.
b.Downgraded one level of serious indirectness due to variation in the definition of neonatal hypoglycaemia.
c.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
*Absolute effects were calculated based on the control group risk
Considerations for Māori
No additional data available
Considerations or Pacific
No additional data available

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate	**Considerations for Māori** No additional evidence available **Considerations for Pacific**	Delayed cord clamping may increase the following risks for preterm babies:

○ Large ○ Varies ○ Don't know	No additional evidence available	• hypothermia on admission (8 trials, 1,995 babies, RR 1.28 (1.06–1.56) (2) • polycythaemia (haematocrit >65%) (13 trials, 2,529 babies, RR 2.65 (1.61-4.37)) (3) • jaundice (mean difference in peak bilirubin +4.43 (1.15 to 7.71) µmol/L, 15 trials, 2,358 babies) (4) Most studies did not include babies who needed immediate resuscitation after birth. In cases where babies assigned to delayed cord clamping were deemed to require immediate resuscitation at birth, they frequently did not undergo the intervention, and occasionally, their outcomes were not included in the analysis.

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	<table><tr><th>Outcomes</th><th>Importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Hypoglycaemia [critical]</td><td>CRITICAL</td><td>⊕◯◯◯ Very low[a,b,c]</td></tr><tr><td>Neurodevelopmental impairment at 12 to 24 months [critical]</td><td>CRITICAL</td><td>⊕⊕◯◯ Low[a,c]</td></tr><tr><td>Neurodevelopmental impairment at 24 to 48 months [critical]</td><td>CRITICAL</td><td>⊕⊕◯◯ Low[a,c]</td></tr><tr><td>Admission to special care nursery or neonatal intensive care nursery [critical]</td><td>CRITICAL</td><td>⊕⊕⊕◯ Moderate[a]</td></tr></table>	

Adverse effects- neonatal mortality [critical]	CRITICAL	⊕⊕⊕◯ Moderate[a]	
Fully breastfeeding at hospital discharge [critical]	CRITICAL	⊕⊕◯◯ Low[a,c]	
Separation from the mother for treatment of hypoglycaemia before discharge home [important] - not measured	IMPORTANT	-	
Hypoglycaemic injury on brain imaging [important] - not measured	IMPORTANT	-	
Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	IMPORTANT	-	
Duration of initial hospital stay [important]	IMPORTANT	⊕⊕⊕◯ Moderate[c]	
Cost [important] - not measured	IMPORTANT	-	

a.Downgraded one level of serious risk of bias due to overall moderate quality of this outcome.
b.Downgraded one level of serious indirectness due to variation in the definition of neonatal hypoglycaemia.
c.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.

Considerations for Māori

No additional evidence available

Considerations for Pacific

No additional evidence available

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability	***Excerpts from Values summary document*** ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]*	

● Probably no important uncertainty or variability ○ No important uncertainty or variability	***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Delayed cord clamping compared to early cord clamping:** Low certainty evidence showed • Small reduction in neonatal hypoglycaemia [critical] • Moderate reduction in neurodevelopmental impairment at 12 to 24 months [critical] • Little to no effect on neurodevelopmental impairment at 24 to 48 months [critical] • Little to no effect on admission to special care nursery or neonatal intensive care nursery [critical] • Moderate reduction on neonatal mortality [adverse effects, critical] • Small increase in fully breastfeeding at hospital discharge [critical] • Little to no effect on duration of initial hospital stay [important] **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	**Delayed cord clamping compared to early cord clamping may increase the following for preterm babies:** • hypothermia on admission • polycythaemia (haematocrit >65%) • jaundice

Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost of delayed cord clamping itself is generally minimal as it does not involve any expensive equipment or procedures. It simply involves waiting a short period of time before clamping and cutting the umbilical cord, which can be easily incorporated into standard birth practices. However, additional training is necessary for handling preterm babies, involving tasks such as maintaining appropriate warmth, recognising when delayed cord clamping should be reconsidered if the baby requires resuscitation, and securing intravenous access, especially in severely polycythemic preterm babies.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not do a systematic search for evidence about resource requirements.	
Cost effectiveness		

Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The need for any additional staffing time or training may be offset by long-term cost savings due to improved health outcomes. Delayed cord clamping may lead to potential cost savings due to its potential to reduce the risk of neonatal mortality in preterm babies.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.*	

	Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings? *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (7). *However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (8). *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (7). *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (8). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (7). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (5)*, participants expressed appreciation for the inclusion of prayer, karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (9)(10)(11). *Additionally, a systematic literature review by Graham et al.* (12) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst Whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (5). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (5). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (6). *Most pregnancy,*	

	hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey (6) *71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A recent study conducted in both private and public practice settings in Australia revealed that midwives strongly advocate for delayed cord clamping to be recognised as the standard procedure (13). Midwives were more likely to discuss cord clamping timing with parents and to clamp the cord later than obstetricians (14). In another recent study conducted in five tertiary hospitals in Saudi Arabia, a majority of midwives and obstetricians believed that delayed cord clamping is advantageous for both term and preterm babies, with potential benefits including enhanced long-term neurological development (15). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In a 2009 survey in Aotearoa New Zealand, 86% of midwives (n = 257; 3.5% Māori; 0.8% Pacific) reported leaving the umbilical cord unclamped for at least 3 minutes after vaginal birth (16) for healthy full-term babies. In an observational study conducted in Aotearoa New Zealand, which included term vaginal births (n=55, ethnicity not reported), the overall median cord clamping time was 3.5 minutes (IQR 2.18 to 5.68 minutes). There was a longer median cord clamping time associated with	

	midwife-facilitated births (4.06 minutes; IQR 2.68–6.65 minutes) compared to obstetrician-facilitated births (2.13 minutes; IQR 1.48–3.28 minutes) (17). Delayed cord clamping is recommended in current international and national guidelines (18)(19)(20)(21). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies

EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Watson ED, Roberts LF, Harding JE, Crowther CA, Lin L. Umbilical cord milking and delayed cord clamping for the prevention of neonatal hypoglycaemia: a systematic review and meta-analysis. BMC Pregnancy and Childbirth. 2024;8;24(1):248.
2. Seidler AL, Libesman S, Hunter KE, Barba A, Aberoumand M, Williams JG, et al. Deferred cord clamping, cord milking, and immediate cord clamping at preterm birth: a systematic review and individual participant data meta-analysis. The Lancet; 2023;9;402(10418):2223-2234.
3. Fogarty M, Osborn DA, Askie L, Seidler AL, Hunter K, Lui K, Simes J, Tarnow-Mordi W. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis.. American Journal of Obstetrics and Gynecology. 2018;218(1):1-18.
4. Rabe H, Gyte GM, Díaz-Rossello JL, Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database of Systematic Reviews. 2019;17;9(9):CD003248.
5. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
6. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]. Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
7. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
8. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
9. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
10. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
11. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
12. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
13. Peberdy L, Young J, Massey D, Kearney L. Maternity health professionals' perspectives of cord clamp timing, cord blood banking and cord blood donation: a qualitative study. BMC Pregnancy and Childbirth. 2020 16;20(1):410.
14. Peberdy L, Young J, Massey D, Kearney L. Australian maternity healthcare professionals' knowledge, attitudes and practices relevant to cord blood banking, donation and clamp timing: A cross-sectional survey. Women Birth. 2021;34(6):e584-e591.
15. Ibrahim NO, Sukkarieh HH, Bustami RT, Alshammari EA, Alasmari LY, Al-Kadri HM. Current umbilical cord clamping practices and attitudes of obstetricians and midwives toward delayed cord clamping in Saudi Arabia. Annals of Saudi Medicine. 2017;37(3):216-224.
16. Richards J. Wanting the best for newborns: umbilical cord clamping practices of midwives in Aotearoa/New Zealand. Master's thesis, Otago Polytechnic, Dunedin New Zealand; 2010 [cited 2 February 2024]. Available from: https://online.op.ac.nz/assets/OPRES/0a2bd4327f/Richards-Wanting-the-best-for-newborns-2010.pdf
17. Hewitt T, Baddock S, Patterson J. Timing of cord clamping: an observational study of cord clamping practice in a maternity hospital in Aotearoa New Zealand. New Zealand College of Midwives Journal; 2022;37:19-26.

18. Royal College of Midwives. Midwifery care in labour guidance for all women in all settings: third stage of labour. RCM Midwifery Blue Top Guidance. 20 November 2018. No. 1 [cited 2 February 2024]. Available from: https://www.rcm.org.uk/media-releases/2018/november/new-guidance-for-midwifery-care-in-labour/
19. The Royal College of Obstetricians and Gynaecologists. Clamping of the umbilical cord and placental transfusion. Scientific impact paper No 14. 2015 [cited 2 February 2024]. Available from: https://www.rcog.org.uk/guidance/browse-all-guidance/scientific-impact-papers/clamping-of-the-umbilical-cord-and-placental-transfusion-scientific-impact-paper-no-14/
20. Canterbury District Health Board. Umbilical cord clamping - this guideline refers to umbilical cord clamping in term infants and preterm infants. Women's Health Service, Christchurch Women's Hospital. 2019 [cited 2 February 2024].Available from: https://edu.cdhb.health.nz/Hospitals-Services/Health-Professionals/maternity-care-guidelines/Documents/GLM0049-Umbilical-Cord-Clamping.pdf
21. National Institute for Health and Care Excellence (NICE). Intrapartum care for healthy women and babies. London: National Institute for Health and Care Excellence (NICE); 2020 Dec 14.

Question 5.

Should skin-to-skin contact vs. no skin-to-skin contact be used for the prevention of neonatal hypoglycaemia?	
POPULATION:	Babies at risk of neonatal hypoglycaemia
INTERVENTION:	skin-to-skin contact
COMPARISON:	no skin-to-skin contact
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:**

	1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment are recommended to reduce the risk of later developmental problems.* Skin-to-skin contact between the mother and baby after birth has been demonstrated to promote breastfeeding and parent-infant bonding. Kangaroo Mother Care (KMC) specifically refers to extended skin-to-skin contact (at least 8 hours per day) for preterm and low birthweight babies, in combination with exclusive breastfeeding support. Skin-to-skin contact has been suggested to play a role in preventing neonatal hypoglycaemia, perhaps through encouraging early breastfeeding and/or helping the baby maintain a normal body temperature.
CONFLICT OF INTERESTS:	CC, DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Skin-to-skin contact compared to no skin-to-skin contact results in or is associated with** (1): • Large reduction in neonatal hypoglycaemia (111 fewer per 1,000) [critical] • Small reduction in admission to special care nursery or neonatal intensive care nursery (24 fewer per 1,000) [critical] • Large increase in fully breastfeeding at hospital discharge (157 more per 1,000) [critical] • Small reduction in the separation from the mother for treatment of hypoglycaemia before discharge home (40 fewer per 1,000) [important]	**Skin-to-skin contact compared to no skin-to-skin contact results in** (1): • Large reduction in hypothermia (140 fewer per 1,000) • Moderate reduction in hyperthermia (81 fewer per 1,000)

- Large increase in exclusive breastmilk feeding from birth to hospital discharge (324 more per 1,000) [important]
- Large reduction in duration of initial hospital stay (2.37 days fewer) [important]
- No studies reported the following outcomes: neurodevelopmental impairment, hypoglycaemic injury on brain imaging, cost

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no skin-to-skin contact	Risk difference with skin-to-skin contact
Hypoglycaemia [critical]	922 (7 RCTs)	⨁⨁◯◯ Low[a,b,c]	**RR 0.32** (0.13 to 0.76)	Study population	
				163 per 1,000	**111 fewer per 1,000** (141 fewer to 39 fewer)
Neurodevelopmental impairment [critical] - not measured	-	-	-		
Admission to special care nursery or neonatal intensive care nursery [critical]	673 (4 RCTs)	⨁◯◯◯ Very low[d,e,f]	**RR 0.85** (0.45 to 1.60)	Study population	
				160 per 1,000	**24 fewer per 1,000** (88 fewer to 96 more)
Fully breastfeeding at hospital discharge [critical]	1341 (10 RCTs)	⨁◯◯◯ Very low[d,g,h]	**RR 1.24** (1.01 to 1.54)	Study population	
				656 per 1,000	**157 more per 1,000** (7 more to 354 more)
Separation from the mother for treatment of hypoglycaemia before discharge home [important]	816 (1 non-randomised study)	⨁⨁◯◯ Low	**OR 0.50** (0.25 to 1.00)	Study population	
				83 per 1,000	**40 fewer per 1,000**

- Large increase exclusive breastmilk feeding from discharge to 3 months (205 more per 1,000) and 3 to 6 months (271 more per 1,000)

Follow-up of an RCT conducted in Colombia (2) found no overall differences in mean intelligence scores at 20 years between the adults who received skin-to-skin contact during the neonatal period and those who received standard care (139 participants, mean score 87.5 ± 13.8 vs 125 participants, 88.4 ± 13.9). However, a subgroup of 63 children who were identified as neurologically vulnerable (determined by neurologic examination, no details provided) at 6 months of age showed higher scores in intelligence and attention in adulthood if they had received skin-to-skin contact during the neonatal period. Moreover, young adults who had received skin-to-skin contact during the neonatal period had larger volumes of brain structures associated with intelligence, attention, memory, and coordination compared to those who received standard care (195 participants).

Harrison 2019 (3) found that neonatal skin-to-skin contact could improve learning and autonomic development in 3-month-old babies with complex

					(61 fewer to 0 fewer)
Hypoglycaemic injury on brain imaging [important] - not measured	-	-	-	-	-
Exclusive breastmilk feeding from birth to hospital discharge [important]	1250 (1 non-randomised study)	⨁⨁⨁◯ Moderate[d,i]	**OR 4.30** (3.19 to 5.81)	Study population	
				465 per 1,000	**324 more per 1,000** (270 more to 370 more)
Duration of initial hospital stay [important]	3437 (31 RCTs)	⨁◯◯◯ Very low[a,c,g,h]	-		MD **2.37 days fewer** (3.66 fewer to 1.08 fewer)
Cost [important] - not measured	-	-	-	-	-

a.Downgraded two levels of very serious risk of bias due to overall low study quality.
b.Downgraded one level for serious indirectness due to the definition of neonatal hypoglycaemia varied.
c.Upgraded one level for large effect.
d.Downgraded one level for serious risk of bias due to overall moderate to low study quality.
e.Downgraded one level for inconsistency due to significant heterogeneity.
f.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
g.Downgraded two levels for very serious inconsistency due to unexplained substantial heterogeneity.
h.Downgraded one level for publication bias due to asymmetry in the funnel plot.
i.Upgraded two levels for very large effect.
*Absolute effects were calculated based on the control group risk

Considerations for Māori
No additional data available
Considerations for Pacific

congenital heart disease (20 participants). They reported increased engagement with a learning task (reduced parasympathetic activation), improved heart rate variability regulation during the task and greater recovery afterwards (reduced heart rate).

Study setting
Most of these studies (1) were conducted in low-, lower-middle- or upper-middle-income countries, limiting the relevance of findings to Aotearoa New Zealand. In high-income countries, two studies assessed neonatal hypoglycaemia and three assessed duration of initial hospital stay. In these studies, no difference in outcome was seen between the skin-to-skin and control groups. The one study assessing exclusive breastmilk feeding from birth to discharge was conducted in a high-income country.

	No additional data available	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Two studies found no difference in frequency (4)(5) or severity (5) of adverse events (apnoea (stopping breathing), desaturation (low blood oxygen) and regurgitation) in the skin-to-skin group compared to the control. Skin-to-skin contact has been identified as a potential risk factor for sudden unexpected postnatal collapse, which can lead to developmental problems in childhood or death (6)(7) However, only two cases were identified from 62,968 apparently healthy term babies (0.003%) (6). The authors concluded this rare potential complication does not outweigh the many benefits of skin-to-skin contact but highlights the need for monitoring babies during skin-to-skin contact.	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no skin-to-skin contact	Risk difference with skin-to-skin contact
Adverse effects [critical]	0 (2 RCTs)	⨁⨁◯◯ Low[a,b]	-	Two RCTs (n=151 babies) reported that the frequency of adverse events, including apnoea, desaturations and regurgitations were no different between the two groups.	

a.Downgraded one level for serious risk of bias due to overall moderate to low study quality.
b.Downgraded one level for imprecision due to no numbers being reported.

Considerations for Māori
No additional data available

Considerations for Pacific
No additional data available

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		

Outcomes	Importance	Certainty of the evidence (GRADE)
Hypoglycaemia [critical]	CRITICAL	⨁⨁◯◯ Low[a,b,c]
Neurodevelopmental impairment [critical] - not measured	CRITICAL	-
Admission to special care nursery or neonatal intensive care nursery [critical]	CRITICAL	⨁◯◯◯ Very low[d,e,f]
Adverse effects [critical]	CRITICAL	⨁⨁◯◯ Low[d,g]
Fully breastfeeding at hospital discharge [critical]	CRITICAL	⨁◯◯◯ Very low[d,h,i]
Separation from the mother for treatment of hypoglycaemia before discharge home [important]	CRITICAL	⨁⨁◯◯ Low
Hypoglycaemic injury on brain imaging [important] - not measured	IMPORTANT	-
Exclusive breastmilk feeding from birth to hospital discharge [important]	IMPORTANT	⨁⨁⨁◯ Moderate[d,j]
Duration of initial hospital stay [important]	IMPORTANT	⨁◯◯◯ Very low[a,c,h,i]
Cost [important] - not measured	IMPORTANT	-

a.Downgraded two levels of very serious risk of bias due to overall low study quality.
b.Downgraded one level for serious indirectness due to the definition of neonatal hypoglycaemia varied.
c.Upgraded one level for large effect.
d.Downgraded one level for serious risk of bias due to overall moderate to low study quality.
e.Downgraded one level for inconsistency due to significant heterogeneity.
f.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
g.Downgraded one level for imprecision due to no numbers being reported.

	h.Downgraded two levels for very serious inconsistency due to unexplained substantial heterogeneity. i.Downgraded one level for publication bias due to asymmetry in the funnel plot. j.Upgraded two levels for very large effect. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	***Excerpts from Values summary document*** ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects		

Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	**Skin-to-skin contact compared to no skin-to-skin contact results in or is associated with** • Low certainty evidence showed • Large reduction in neonatal hypoglycaemia • Uncertain effect on admission to special care nursery or neonatal intensive care nursery • Large increase in fully breastfeeding at hospital discharge • Small reduction in the separation from the mother for treatment of hypoglycaemia before discharge home • Large increase in exclusive breastmilk feeding from birth to hospital discharge • Large reduction in the duration of initial hospital stay **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	**Skin-to-skin contact compared to other treatment may result in** • Large reduction in hypothermia • Moderate reduction in hyperthermia • Large increase in exclusive breastmilk feeding from discharge to 3 months and 3 to 6 months
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not do a systematic search for evidence about resource requirements. Skin-to-skin contact does not require any specific equipment, so the resources required are the training of health professionals and the time taken to educate parents and implement skin-to-skin. In the UK, the costs of establishing a program implementing skin-to-skin contact came from training staff and paying support staff to run the program, rather than any costs directly related to skin-to-skin contact (8).	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	We are uncertain about the cost of staff time.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Lowson conducted an economic evaluation of a skin-to-skin program implemented in 18 UK neonatal units and found that skin-to-skin contact saved at least GBP £7.40 for every £1 invested due to reduced duration of hospital stay and reduced morbidity (8).	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?***	

	There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions. ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (11)*. However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (12)*.* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (11)*.* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (12). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (11). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (9)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (13)(14)(15)*.* *Additionally, a systematic literature review by Graham et al.* (16) *provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (16) ***Consideration for Pacific***	

	Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work (9). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (10)*. Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (10)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the Whāunua Experience study (9), all mothers believed "skin-to-skin" and holding baby to the breast was the best way to comfort the child during the testing for neonatal hypoglycaemia. Some parents who were not offered the opportunity to support their child would have valued having the choice. **Considerations for Māori** Whānau Māori valued being offered skin-to-skin contact and then supported to breastfeed their pēpi during testing. All of these women believed that skin-to-skin by holding baby to their breast was the most effective way to soothe the baby. **Considerations for Pacific** Some Pacific mothers express a desire to hold their babies at the breast for early and continuous feeding to address concerns about potential hypoglycaemia	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no	Skin-to-skin contact is a routine practice in Aotearoa New Zealand. Kangaroo care is encouraged and practised in many hospitals and birthing centres as part of postnatal care.	

○ Probably yes ● Yes ○ Varies ○ Don't know	**Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know

ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Lord LG, Harding JE, Crowther CA, Lin L. Skin-to-skin contact for the prevention of neonatal hypoglycaemia: a systematic review and meta-analysis. BMC Pregnancy and Childbirth. 2023;21;23(1):744.
2. Charpak N, Tessier R, Ruiz JG, Hernandez JT, Uriza F, Villegas J, et al. Twenty-year follow-up of kangaroo mother care versus traditional care. Pediatrics. 2017;139(1):e20162063.
3. Harrison TM, Chen CY, Stein P, Brown R, Heathcock JC. Neonatal Skin-to-skin contact: implications for learning and autonomic nervous system function in infants with congenital heart disease. Biological Research For Nursing. 2019;21(3):296-306.
4. Linnér A, Lode Kolz K, Klemming S, Bergman N, Lilliesköld S, Markhus Pike H, Westrup B, Rettedal S, Jonas W. Immediate skin-to-skin contact may have beneficial effects on the cardiorespiratory stabilisation in very preterm infants. Acta Paediatrica. 2022;111(8):1507-1514.
5. Rojas MA, Kaplan M, Quevedo M, Sherwonit E, Foster L, Ehrenkranz RA, et al. Somatic growth of preterm infants during skin-to-skin care versus traditional holding: a randomized, controlled trial. Journal of Developmental and Behavioral Pediatrics. 2003;24(3):163-8.
6. Dageville C, Pignol J, De Smet S. Very early neonatal apparent life-threatening events and sudden unexpected deaths: incidence and risk factors. Acta Paediatr. 2008;97(7):866-9.
7. Fleming PJ. Unexpected collapse of apparently healthy newborn infants: the benefits and potential risks of skin-to-skin contact. Archives of Disease in Childhood.Fetal and Neonatal Edition. 2012;97(1):F2-3.
8. Lowson K, Offer C, Watson J, McGuire B, Renfrew MJ. The economic benefits of increasing kangaroo skin-to-skin care and breastfeeding in neonatal units: analysis of a pragmatic intervention in clinical practice. International Breastfeeding Journal. 2015; 20;10:11.
9. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
10. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]. Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
11. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
12. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
13. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
14. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
15. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
16. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.

Question 6.

Should thermal care vs. routine care be used for prevention of neonatal hypoglycaemia?	
POPULATION:	Babies at risk of neonatal hypoglycaemia
INTERVENTION:	thermal care
COMPARISON:	routine care
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation

BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (baby of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Thermal care is an essential component of newborn care. It is a high-impact intervention that helps ensure the functional integrity of various neonatal biological systems. Since thermoregulation requires energy, low or decreasing body temperature may result in lower blood glucose concentrations. This means that thermal care may play a role in preventing neonatal hypoglycaemia. The intervention aimed at maintaining warmth typically involves a) applying barriers to heat loss on various body parts after birth, such as plastic bags, caps, or wraps; b) use external heat sources like skin-to-skin contact or heated/gel/chemical mattresses (1). For skin-to-skin contact, please refer to the skin-to-skin EtD.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Preterm/ low birthweight babies** Plastic bag/ wrap vs routine care (1) • Moderate reduction in hypoglycaemia (72 fewer per 1,000) [critical] • Large reduction in the duration of initial hospital stay (6.35 days lower) [important] Thermal mattress, thermal nest or thermal blanket: vs routine care (1)(2)(3)(4) • Little to no effect on hypoglycaemia [critical] • Moderate reduction in mortality (14 fewer per 1,000) [adverse effects, critical] • Large reduction in the duration of initial hospital stay (5 days lower) [important] **Term babies** Delaying bathing by at least 6 hours compared to early bathing (5) • Small reduction in hypoglycaemia (30 fewer per 1,000) [critical] • Small increase in fully breastfeeding at hospital discharge (44 more per 1,000) [critical] No studies reported any other critical or important outcomes.	**Preterm/ low birthweight babies** Plastic bag/ wrap vs routine care (1) • Little to no effect on initial blood glucose concentration • Large reduction in hypothermia on admission to NICU (244 fewer per 1,000) Thermal mattress vs routine care (1) • May increase core body temperature on admission to NICU (0.65 °C higher) • Large reduction in moderate hypothermia (<36°C) on

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with routine care	Risk difference with thermal care
Plastic wrap or bag: hypoglycaemia (Preterm/LBW) [critical]	389 (3 RCTs)	⊕⊕⊕◯ Moderate[a]	**RR 0.70** (0.47 to 1.03)	Study population	
				240 per 1,000	**72 fewer per 1,000** (127 fewer to 7 more)
Plastic wrap or bag: duration of initial hospital stay (Preterm/LBW) [important]	126 (2 RCTs)	⊕⊕◯◯ Low[b]	-	The mean plastic wrap or bag: duration of initial hospital stay (Preterm/LBW) [important] ranged from **46.6** days	MD **6.35 days lower** (17.37 lower to 4.56 higher)
Thermal mattress: hypoglycaemia (Preterm/LBW) [critical]	102 (1 RCT)	⊕◯◯◯ Very low[b,c]	**RR 1.02** (0.47 to 2.18)	Study population	
				204 per 1,000	**4 more per 1,000** (108 fewer to 241 more)
Thermal mattress: mortality (Preterm/LBW) [critical]	102 (1 RCT)	⊕◯◯◯ Very low[b,c]	**RR 0.31** (0.01 to 7.40)	Study population	
				20 per 1,000	**14 fewer per 1,000** (20 fewer to 131 more)
Thermal mattress: duration of initial hospital stay (Preterm/LBW) [important]	102 (1 RCT)	⊕◯◯◯ Very low[b]	-	The mean thermal mattress: duration of initial hospital stay (Preterm/LBW) [important] was **54** days	MD **5 days lower** (17.27 lower to 7.27 higher)
Thermal mattress, thermal nest or thermal blanket:	301 (2 RCTs)	⊕⊕◯◯ Low[c,d]	**RR 1.01** (0.60 to 1.71)	Study population	
				329 per 1,000	**3 more per 1,000**

admission to NICU (413 fewer per 1,000)

A network meta-analysis (6) showed plastic bag and wrap were equally effective at maintaining body temperature. The plastic bag or wrap with thermal mattress was the most beneficial intervention for body temperature compared to routine care.

Term babies

<u>Delaying bathing by at least 24 hours compared to early bathing</u> (5)

- Moderate reduction in hypothermia (61 fewer per 1,000)

A study found no difference between cotton swaddling, aluminium coated fabric and a combination of the two in preventing hypothermia and hypoglycaemia when transferring the baby from the delivery room to the nursery (7).

A systematic review found that maternal warming during caesarean section with warmed air or fluid compared to no warmed air or fluid is likely to result in little to no effect on neonatal body temperature (8).

hypoglycaemia (Preterm/LBW) [critical]						(132 fewer to 233 more)
Early vs delayed bathing (6 hours): hypoglycaemia (Term) [critical]	2775 (3 non-randomised studies)	⨁◯◯◯ Very low[e]	**OR 0.39** (0.23 to 0.66)	Study population		
				49 per 1,000	**30 fewer per 1,000** (38 fewer to 16 fewer)	
Early vs delayed bathing (6 hours): fully breastfeeding at hospital discharge (Term) [critical]	6768 (6 non-randomised studies)	⨁◯◯◯ Very low[e]	**OR 1.20** (1.08 to 1.34)	Study population		
				584 per 1,000	**44 more per 1,000** (19 more to 69 more)	

a.Downgraded one level for serious indirectness due to large variations in the types of intervention.
b.Downgraded two levels for very serious imprecision due to wide confidence interval and small sample size.
c.Downgraded one level for serious risk of bias due to overall moderate to low quality of the included study (studies).
d.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
e.Downgraded two levels for very serious risk of bias due to overall low quality of the included study (studies).
*Absolute effects were calculated based on the control group risk

Considerations for Māori

No additional data available

Considerations for Pacific

No additional data available

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Preterm/ low birthweight babies** Plastic bag/ wrap compared to routine care (1) • Small increase in hyperthermia on admission to NICU (34 more per 1,000) [adverse effects, critical] Thermal mattress, thermal nest or thermal blanket vs routine care vs routine care (1)(2)(3)(4) • Uncertain effect on hyperthermia (no events occurred in most groups) [adverse effects, critical] • No skin reactions with thermal mattress or thermal blanket [adverse effects, critical] **Term babies** No studies reported any other critical or important outcomes.	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with routine care	Risk difference with thermal care
Plastic wrap or bag: hyperthermia on admission to NICU (Preterm/LBW) [critical]	1523 (12 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 3.91** (2.05 to 7.44)	Study population	
				12 per 1,000	**34 more per 1,000** (12 more to 75 more)
Thermal mattress: hyperthermia (Preterm/LBW) [critical]	126 (2 RCTs)	⨁◯◯◯ Very low[b,c]	**RR 4.63** (0.23 to 94.10)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a.Downgraded one level for imprecision due to small event rate.
b.Downgraded one level for serious risk of bias due to overall moderate to low quality of the included study (studies).
c.Downgraded two levels for very serious imprecision due to wide confidence interval and small sample size.
*Absolute effects were calculated based on the control group risk

Considerations for Māori

	No additional data available **Considerations for Pacific** No additional data available	

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Outcomes	Importance	Certainty of the evidence (GRADE)
Plastic wrap or bag: hypoglycaemia (Preterm/LBW) [critical]	CRITICAL	⨁⨁⨁◯ Moderate[a]
Plastic wrap or bag: duration of initial hospital stay (Preterm/LBW) [important]	IMPORTANT	⨁⨁◯◯ Low[b]
Plastic wrap or bag: hyperthermia on admission to NICU (Preterm/LBW) [critical]	CRITICAL	⨁⨁⨁◯ Moderate[c]
Thermal mattress: hypoglycaemia (Preterm/LBW) [critical]	CRITICAL	⨁◯◯◯ Very low[b,d]
Thermal mattress: hyperthermia (Preterm/LBW) [critical]	NOT IMPORTANT	⨁◯◯◯ Very low[b,d]
Thermal mattress: mortality (Preterm/LBW) [critical]	CRITICAL	⨁◯◯◯ Very low[b,d]
Thermal mattress: duration of initial hospital stay (Preterm/LBW) [important]	IMPORTANT	⨁◯◯◯ Very low[b]
Thermal mattress, thermal nest or thermal blanket: hypoglycaemia (Preterm/LBW) [critical]	CRITICAL	⨁⨁◯◯ Low[d,e]
Early vs delayed bathing (6 hours): hypoglycaemia (Term) [critical]	CRITICAL	⨁◯◯◯ Very low[f]
Early vs delayed bathing (6 hours): fully breastfeeding at hospital discharge (Term) [critical]	CRITICAL	⨁◯◯◯ Very low[f]

	a.Downgraded one level for serious indirectness due to large variations in the types of intervention. b.Downgraded two levels for very serious imprecision due to wide confidence interval and small sample size. c.Downgraded one level for imprecision due to small event rate. d.Downgraded one level for serious risk of bias due to overall moderate to low quality of the included study (studies). e.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm. f.Downgraded two levels for very serious risk of bias due to overall low quality of the included study (studies). **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	***Excerpts from Values summary document*** ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]*	

	• *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Very low certainty evidence showed **Preterm/ low birthweight babies** <u>Plastic bag/ wrap compared to routine care</u> • Moderate reduction in hypoglycaemia [critical] • Large reduction in the duration of initial hospital stay [important] • Small increase in hyperthermia on admission to NICU [adverse effects, critical] • Little to no effect on initial blood glucose concentration • Large reduction in hypothermia on admission to NICU <u>Thermal mattress thermal nest or thermal blanket compared to routine care</u> • Little to no effect on hypoglycaemia [critical] • Uncertain effect on duration of initial hospital stay [important] • Uncertain effect on hyperthermia [adverse effects, critical] • Uncertain effect on mortality [adverse effects, critical] • No skin reactions with thermal mattress or thermal blanket [adverse effects, critical] • May increase core body temperature on admission to NICU • Large reduction in moderate hypothermia on admission to NICU **Term babies** <u>Delaying bathing by at least 6 hours compared to early bathing is associated with</u> • Uncertain effect on hypoglycaemia [critical] • Uncertain effect on fully breastfeeding at hospital discharge [critical] <u>Delaying bathing by at least 24 hours compared to early bathing is associated with</u>	

	• Moderate reduction in hypothermia **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	

Resources required
How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The plastic Neo-wraps used in Aotearoa New Zealand cost NZ$36 for a box of ten. The TransWarmer gel thermal mattress used in Aotearoa New Zealand costs NZ$100 each.	

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	We are reasonably certain about the cost of the Neo-wraps and TransWarmer mattress as they are being used in Aotearoa New Zealand.	

Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No information was found on the cost-effectiveness of the interventions.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (11)*. However, in the Sugar Babies study of 514 babies*	

	at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%) (12). *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (11). *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (12). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (11). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (9)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (13)(14)(15). *Additionally, a systematic literature review by Graham et al.* (16) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (16). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (9). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (10). *Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (10)*, 71% of women reported that they had paid for at*	

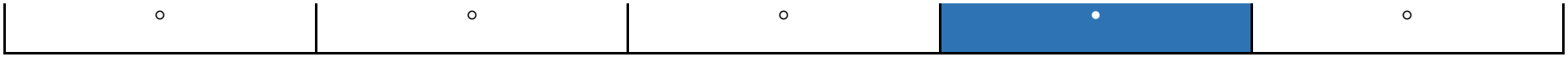
	least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Two studies, conducted in Mexico and Canada, found that the use of plastic wrap was acceptable to neonatal staff (17)(18). Three studies reported that plastic wrap did not interfere with resuscitation (19)(20)(17), whilst two found that resuscitation affected the placement of the wrap (21)(22). Measuring oxygen saturation and body temperature was more challenging for babies in the plastic wrap. Little evidence was available on other interventions, but delayed bathing was suggested to be unacceptable to women in rural Uganda, due to the baby's perceived 'dirtiness' or 'vulnerability' (23). **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The Neo-Wrap and TransWarmer mattress are currently used in Aotearoa New Zealand. The use of plastic wraps is feasible in Aotearoa New Zealand as they are already recommended in the Starship Guidelines for use in babies <32 weeks gestation for preventing hypothermia (24). **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention



REFERENCES SUMMARY

1. McCall EM, Alderdice F, Halliday HL, Vohra S, Johnston L. Interventions to prevent hypothermia at birth in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews. 2018;12;2(2):CD004210.
2. Chawla S, Amaram A, Gopal SP, Natarajan G. Safety and efficacy of trans-warmer mattress for preterm neonates: results of a randomized controlled trial. Journal of Perinatology. 2011;31(12):780-4.
3. Shabeer MP, Abiramalatha T, Devakirubai D, Rebekah G, Thomas N. Standard care with plastic bag or portable thermal nest to prevent hypothermia at birth: a three-armed randomized controlled trial. Journal of Perinatology. 2018;38(10):1324-1330.
4. Hsu KH, Chiang MC, Lin SW, Lin JJ, Wang YC, Lien R. Thermal blanket to improve thermoregulation in preterm infants. Pediatric Critical Care Medicine. 2015;16(7):637-43.
5. Priyadarshi M, Balachander B, Gupta S, Sankar MJ. Timing of first bath in term healthy newborns: a systematic review. Journal of Global Health. 2022;17;12:12004.
6. Abiramalatha T, Ramaswamy VV, Bandyopadhyay T, Pullattayil AK, Thanigainathan S, Trevisanuto D, et al. Delivery room interventions for hypothermia in preterm neonates: a systematic review and network meta-analysis. JAMA pediatrics. 2021;175(9):e210775.
7. Chanvorachote P, Jirachotdecho K, Suksumek N. A randomized controlled trial of evaluating the efficacy of alternative swaddles for body temperature control of newborns. In Vivo. 2022;36(4):1966-1970.
8. Sultan P, Habib AS, Cho Y, Carvalho B. The effect of patient warming during caesarean delivery on maternal and neonatal outcomes: a meta-analysis. British Journal of Anaesthesia. 2015;115(4):500-10
9. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
10. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]. Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
11. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
12. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
13. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
14. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
15. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
16. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
17. Vohra S, Roberts RS, Zhang B, Janes M, Schmidt B. Heat Loss Prevention (HeLP) in the delivery room: a randomized controlled trial of polyethylene occlusive skin wrapping in very preterm infants. The Journal of Pediatrics. 2004;145(6):750-3.
18. Cardona Torres LM, Amador Licona N, Garcia Campos ML, Guizar-Mendoza JM. Polyethylene wrap for thermoregulation in the preterm infant: a randomized trial. Indian Pediatrics. 2012;49(2):129-32.
19. Knobel RB, Wimmer JE Jr, Holbert D. Heat loss prevention for preterm infants in the delivery room. Journal of Perinatology. 2005;25(5):304-8
20. Vohra S, Frent G, Campbell V, Abbott M, Whyte R. Effect of polyethylene occlusive skin wrapping on heat loss in very low birth weight infants at delivery: a randomized trial. Journal of Pediatrics. 1999;134(5):547-51
21. Simon P, Dannaway D, Bright B, Krous L, Wlodaver A, Burks B, et al. Thermal defense of extremely low gestational age newborns during resuscitation: exothermic mattresses vs polyethylene wrap. Journal of Perinatology. 2011;31(1):33-7.
22 Smith J, Usher K, Alcock G, Buettner P. Application of plastic wrap to improve temperatures in infants born less than 30 weeks gestation: a randomized controlled trial. Neonatal Network. 2013;32(4):235-45
23. Byaruhanga RN, Nsungwa-Sabiiti J, Kiguli J, Balyeku A, Nsabagasani X, Peterson S. Hurdles and opportunities for newborn care in rural Uganda. Midwifery. 2011;27(6):775-80.
24. Newborn Services Clinical Practice Committee, Starship Child Health. Hypothermia prevention in infants less than 32 weeks gestation. 30 April 2015 [cited 2 February 2024]. Available from: https://starship.org.nz/guidelines/hypothermia-prevention-in-infants-less-than-32-weeks-gestation/

Question 7.

Should early feeding vs. delayed feeding be used for the prevention of neonatal hypoglycaemia?

POPULATION:	Newborn babies at risk of neonatal hypoglycaemia
INTERVENTION:	early feeding
COMPARISON:	delayed feeding
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn infants over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.*

	Poor feeding may be a risk factor for neonatal hypoglycaemia, and early feeding has been widely recommended to prevent hypoglycaemia. For example, clinical practice guidelines from Queensland Health (1), the British Association of Perinatal Medicine (2) and WHO (3)recommend that breastfeeding be 2023) recommend that breastfeeding be initiated within an hour of birth for the prevention of hypoglycaemia. However, the evidence supporting an association between early feeding and blood glucose concentrations or hypoglycaemia is limited, and the results are mixed (4).
CONFLICT OF INTERESTS:	CC, DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Early feeding compared to delayed feeding may be associated with** (4): • Large reduction in the incidence of neonatal hypoglycaemia (cohort studies: 278 fewer per 1,000; cross-sectional 137 fewer per 1,000) [critical] • Neonatal mortality (RCT: little to no effect; cohort study: small reduction (5 fewer per 1,000); cross-sectional study: moderate reduction (11 fewer per 1,000)) [adverse effect, critical] • Little to no effect on postpartum haemorrhage [adverse effect, critical] • Large increase in fully breastfeeding at hospital discharge (Cohort study, 442 more per 1,000) [critical] • Little to no effect on duration of initial hospital stay [important] No studies reported the following outcomes: neurodevelopmental impairment [critical], admission to special care nursery or neonatal intensive care nursery [critical], separation from the mother for treatment of hypoglycaemia before discharge home [important], hypoglycemic injury on brain imaging [important], cost [important].	Early feeding compared to delayed feeding may be associated with little to no difference in mean blood glucose concentration 1-3 hours after birth (4). In the systematic review (4) of studies reporting neonatal hypoglycaemia, 5/6 were conducted in India. Neonatal hypoglycaemia was defined as <2.5mmol/L or <2.2mmol/L. Early feeding was defined as within 1 hour of birth in two studies, within 2 hours in two studies, and undefined in two studies. Babies were breastfed in two studies and mode of feeding was undefined in four studies. Babies were preterm in one study, late preterm or term in two studies,

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with delayed feeding	Risk difference with early feeding
Hypoglycaemia (cohort studies) [critical]	744 (4 non-randomised studies)	⨁⨁◯◯ Low[a,b,c]	**OR 0.19** (0.10 to 0.35)	Study population	
				385 per 1,000	**278 fewer per 1,000** (326 fewer to 205 fewer)
Hypoglycaemia (cross-sectional study) [critical]	196 (1 non-randomised study)	⨁◯◯◯ Very low[d]	**OR 0.48** (0.24 to 0.96)	Study population	
				323 per 1,000	**137 fewer per 1,000** (220 fewer to 9 fewer)
Neurodevelopmental impairment [critical] - not measured	-	-	-	-	-
Admission to special care nursery or neonatal intensive care nursery [critical] - not measured	-	-	-	-	-
Adverse effects - neonatal mortality (RCT) [critical]	4271 (1 RCT)	⨁◯◯◯ Very low[b]	**RR 1.01** (0.14 to 7.14)	Study population	
				1 per 1,000	**0 fewer per 1,000** (1 fewer to 6 more)
Adverse effects - neonatal mortality (cohort studies) [critical]	132265 (3 non-randomised studies)	⨁⨁◯◯ Low	**OR 0.51** (0.37 to 0.72)	Study population	
				11 per 1,000	**5 fewer per 1,000** (7 fewer to 3 fewer)
				Study population	

term in one study and gestational age was not specified in two studies. All studies reporting adverse events were conducted in low- or lower-middle-income countries. Babies were breastfed in six of these studies, and the mode of feeding was undefined in one study. Babies were preterm in one study, and gestational age was unspecified in six studies.

Of the studies reporting on mean blood glucose concentration 1-3 hours after birth, 3/4 were conducted in a high-income country. Babies were late preterm or term in three studies, and gestational age was not defined in one study.

Adverse effects - neonatal mortality (cross-sectional study) [critical]	3182 (1 non-randomised study)	⊕⊕◯◯ Low	**OR 0.54** (0.32 to 0.92)	25 per 1,000	**11 fewer per 1,000** (17 fewer to 2 fewer)	
Adverse effects - postpartum haemorrhage (RCT) [critical]	4271 (1 RCT)	⊕⊕◯◯ Low[b]	**RR 0.94** (0.77 to 1.16)	Study population		
				83 per 1,000	**5 fewer per 1,000** (19 fewer to 13 more)	
Fully breastfeeding at hospital discharge (cohort) [critical]	99632 (1 non-randomised study)	⊕⊕⊕⊕ High[a]	**OR 7.76** (7.54 to 7.99)	Study population		
				390 per 1,000	**442 more per 1,000** (438 more to 446 more)	
Separation from the mother for treatment of hypoglycaemia before discharge home [important] - not measured	-	-	-	-	-	
Hypoglycaemic injury on brain imaging [important] - not measured	-	-	-	-	-	
Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	-	-	-	-	-	
Duration of initial hospital stay (cohort) [important]	1673 (1 non-randomised study)	⊕◯◯◯ Very low	-	The mean duration of initial hospital stay (cohort) [important] was **2.3** days	MD **0.2 days fewer** (0.31 fewer to 0.09 fewer)	

Cost [important] - not measured	-	-	-	-	-	

a.Upgraded two levels due to very large effect.
b.Downgraded one level for serious risk of bias due to overall moderate to low quality of included studies (study).
c.Downgraded one level for serious indirectness due to variations in feeding timings across studies.
d.Downgraded two levels for very serious riks of bias due to the overall low quality of included studies (study).
*Absolute effects were calculated based on the control group risk

Considerations for Māori
No additional evidence available
Considerations for Pacific
No additional evidence available

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No studies reported adverse events associated with early feeding (4). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Outcomes**	**Importance**	**Certainty of the evidence (GRADE)**
	Hypoglycaemia (cohort studies) [critical]	CRITICAL	⨁⨁◯◯ Low[a,b,c]
	Hypoglycaemia (cross-sectional study) [critical]	CRITICAL	⨁◯◯◯ Very low[d]
	Neurodevelopmental impairment [critical] - not measured	CRITICAL	-
	Admission to special care nursery or neonatal intensive care nursery [critical] - not measured	CRITICAL	-
	Adverse effects - neonatal mortality (RCT) [critical]	CRITICAL	⨁◯◯◯ Very low[b]
	Adverse effects - neonatal mortality (cohort studies) [critical]	CRITICAL	⨁⨁◯◯ Low
	Adverse effects - neonatal mortality (cross-sectional study) [critical]	CRITICAL	⨁⨁◯◯ Low
	Adverse effects - postpartum haemorrhage (RCT) [critical]	CRITICAL	⨁⨁◯◯ Low[b]
	Fully breastfeeding at hospital discharge (cohort) [critical]	CRITICAL	⨁⨁⨁⨁ High[a]
	Separation from the mother for treatment of hypoglycaemia before discharge home [important] - not measured		-
	Hypoglycaemic injury on brain imaging [important] - not measured		-
	Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured		-
	Duration of initial hospital stay (cohort) [important]	IMPORTANT	⨁◯◯◯ Very low
	Cost [important] - not measured		-
	a.Upgraded two levels due to very large effect.		

	b.Downgraded one level for serious risk of bias due to overall moderate to low quality of included studies (study). c.Downgraded one level for serious indirectness due to variations in feeding timings across studies. d. Downgraded two levels for very serious riks of bias due to the overall low quality of included studies (study). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	***Excerpts from Values summary document*** ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects		

Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Early feeding compared to delayed feeding: Low certainty evidence showed associations of • Large reduction in the hypoglycaemia [critical] • Small reduction in neonatal mortality [adverse effect, critical] • Little to no effect on postpartum haemorrhage [adverse effect, critical] • Large increase in fully breastfeeding at hospital discharge [critical] • Uncertain effect on duration of initial hospital stay [important] **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Little to no effect on mean blood glucose concentration 1-3 hours after birth.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Early feeding is unlikely to require additional resources. However, the location and timing of the resources required may change. The typical price range for 900g of formula in the community setting is approximately NZ$17 to $50. Pasteurised donor human milk costs NZ$33 cents per mL.	
Certainty of evidence of required resources		

What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not do a systematic search for evidence about resource requirements.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	We found no studies reporting the cost-effectiveness of early feeding (within an hour of birth) compared to delayed feeding (more than an hour after birth).	Early breastmilk feeding is associated with higher rates of exclusive breastmilk feeding later in infancy (5). In the United States, failure to comply with recommendations to exclusively breastfeed through to six months is estimated to cost US $13 billion annually (from medical care and indirect costs) and result in 911 preventable deaths per year (6).
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?***	

○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	*There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (9*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (10*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (9*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (10*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (9*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** In 6,685 singletons enrolled in the Growing Up in New Zealand cohort (11), breastfeeding initiation occurred for 97%. Compared to children of European mothers, children whose mothers were of Māori ethnicity were less likely to initiate breastfeeding. *In the Whānau Experience study* (7*), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (12, 13, 14*).* *Additionally, a systematic literature review by Graham et al.* (15*) provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving*	

	healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming" (15*).* ***Consideration for Pacific*** In 6,685 singletons enrolled in the *Growing Up in New Zealand* cohort, breastfeeding initiation occurred for 97%. Compared to children of European mothers, children whose mothers were of Pacific ethnicity were less likely to initiate breastfeeding (11). *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (7*).* ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (8*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (8)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cultural practices may delay feeding when understanding of early feeding benefits is lacking (16). One study highlights the need for a 'culturally aware and sensitive approach' to encouraging early milk feeding initiation due to cultural practices, such as those among Muslim women, that take precedence immediately after birth (17). In the Whānau Experiences study (7) of whānau/families with diverse cultural backgrounds including Māori, Pacific, and Asian ethnicities (studied because these groups have a higher likelihood of having a baby born at risk of neonatal hypoglycaemia), mothers reported a strong preference for breastfeeding. **Considerations for Māori** Whānau Māori value being offered and then supported to breastfeed their pēpi during testing. **Considerations for Pacific** One Pacific woman suggested that holding her baby at her breast for early and continuous feeding reduced hypoglycaemia risk.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The Starship Child Health guideline for management of hypoglycaemia in the neonate advises breastfeeding is initiated within 1 hour of birth, prior to the first blood glucose concentration measurement (18). A 2014 study of compliance with clinical guidelines suggested only 9/22 neonatal units in Australia and Aotearoa New Zealand complied with the clinical guideline recommendation to feed babies within an hour of birth (19). Another study found feeding within an hour of birth was less likely among mothers giving birth for the first time, and those delivering by emergency or elective caesarean (20). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know

RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Queensland Clinical Guidelines. Hypoglycaemia- newborn. Guideline No. MN23.8-V13-R28. Queensland Health. 2023 [cited 2 February 2024]. Available from: https://www.health.qld.gov.au/qcg
2. Levene I, Wilkinson D. Identification and management of neonatal hypoglycaemia in the full-term infant (British Association of Perinatal Medicine-Framework for Practice). Archives of disease in childhood - Education and Practice. 2019;104(1):29-32.
3. World Health Organization (WHO). Breastfeeding. 2023 [cited 2 February 2024]. Available from: https://www.who.int/health-topics/breastfeeding#tab=tab_2
4. Roberts LF, Harding JE, Crowther CA, Watson E, Wang Z, Lin L. Early feeding for the prevention of neonatal hypoglycaemia: a systematic review and meta-analysis. Neonatology. 2024;121(2):141-156.
5. Difrisco E, Goodman KE, Budin WC, Lilienthal MW, Kleinman A, Holmes B. Factors associated with exclusive breastfeeding 2 to 4 weeks following discharge from a large, urban, academic medical center striving for baby-friendly designation. The Journal of Perinatal Education. 2011;20(1):28-35.
6. Bartick M, Reinhold A. The burden of suboptimal breastfeeding in the United States: a pediatric cost analysis. Pediatrics. 2010;125(5):e1048-56.
7. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
8. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
9. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
10. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
11. Castro T, Grant C, Wall C, Welch M, Marks E, Fleming C, et al. Breastfeeding indicators among a nationally representative multi-ethnic sample of New Zealand children. The New Zealand Medical Journal. 2017;1;130(1466):34-44.
12. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
13. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.

14. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
15. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
16. Sharma IK, Byrne A. Early initiation of breastfeeding: a systematic literature review of factors and barriers in South Asia. International Breastfeeding Journal. 2016;18;11:17.
17. Chertok IR, Raz I, Shoham I, Haddad H, Wiznitzer A. Effects of early breastfeeding on neonatal glucose levels of term infants born to women with gestational diabetes. Journal of Human Nutrition and Dietetics; 2009;22(2):166-9.
18. Newborn Services Clinical Practice Committee, Starship Child Health. Hypoglycaemia in the neonate. 16 April 2024 [cited 2 September 2024]; Available from: https://starship.org.nz/guidelines/hypoglycaemia-in-the-neonate/
19. Sundercombe SL, Raynes-Greenow CH, Turner RM, Jeffery HE. Do neonatal hypoglycaemia guidelines in Australia and New Zealand facilitate breast feeding?. Midwifery.2014;30(12):1179-86
20. Carberry AE, Raynes-Greenow CH, Turner RM, Jeffery HE. Breastfeeding within the first hour compared to more than 1 hour reduces risk of early-onset feeding problems in term neonates: a cross-sectional study. Breastfeeding Medicine. 2013;8(6):513-4.

Question 8.

Should expressed breastmilk vs. other or no intervention be used for preventing or treating neonatal hypoglycaemia?	
POPULATION:	Babies at risk or with neonatal hypoglycaemia
INTERVENTION:	expressed breastmilk
COMPARISON:	other or no intervention
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies)

	5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (baby of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* While expressed breast milk provides optimal feeds for the baby, the effectiveness in preventing and treating neonatal hypoglycaemia is uncertain.
CONFLICT OF INTERESTS:	CC, DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	**Expressed breastmilk (mother's or donor's) compared to other or no intervention** (1) • Uncertain effect on preventing or treating neonatal hypoglycaemia [critical] • Large reduction in duration of initial hospital stay (RCT: 9.33 days lower; non-randomised study of intervention: 2 days lower) [important] • No studies reported any other critical or important outcomes	Rees et al (2) reported that among hypoglycaemic breastfed babies, there was a significant increase in blood glucose concentrations of 0.5 mmol/L when breastfeeding was supplemented with donor human milk and 0.4 mmol/L when supplemented with formula. In contrast, Harris et al (3) reported a

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with other or no intervention	Risk difference with expressed breast milk
Neonatal hypoglycaemia	20 (1 RCT)	⨁◯◯◯ Very low[a,b]	-	One study reported no hypoglycaemic episodes in both groups (n=20).	
Neurodevelopmental impairment - not measured	-	-	-	-	-
Admission to special care nursery or neonatal intensive care nursery - not measured	-	-	-	-	-
Fully breastfeeding at hospital discharge - not measured	-	-	-	-	-
Separation from the mother for treatment of hypoglycaemia before discharge home - not measured	-	-	-	-	-
Hypoglycaemic injury on brain imaging - not measured	-	-	-	-	-
Breastmilk feeding exclusively from birth to hospital discharge - not measured	-	-	-	-	-
Duration of initial hospital stay - RCT	53 (1 RCT)	⨁◯◯◯ Very low[a,c]	-	The mean duration of initial hospital	MD **9.33 days lower** (32.07 lower

significant additional increase in blood glucose concentration with formula feeds (+0.21 mmol/L, 95% CI 0.04 to 0.37) but no additional change in the blood glucose concentration of hypoglycaemic babies fed mother's expressed breastmilk (-0.1 mmol/L, 95% CI -0.21 to 0.05) in the first 48 hours after birth.

Offering expressed breastmilk to newborns in the NICU provides mothers with an emotional and psychological connection to their babies (4).

Early attainment of full enteral feeds with expressed breastmilk (mother's or donor's) is associated with a lower risk of septicaemia among preterm, extremely low birth weight babies (5).

				stay - RCT was **89.33** days	to 13.4 higher)
Duration of initial hospital stay- non-randomised study of intervention	143 (1 non-randomised study)	⨁◯◯◯ Very low[a,c]	-	The mean duration of initial hospital stay- non-randomised study of intervention was **45.3** days	MD **2 days lower** (12.39 lower to 8.39 higher)
Cost - not measured	-	-	-	-	-

a.Downgraded one level of risk of bias due to overall unclear risk of bias.
b.Downgraded three levels of extreme serious imprecision due to the small sample size and no event occurring in each group.
c.Downgraded one level of serious imprecision due to wide confidence interval.
*Absolute effects were calculated based on the control group risk

Considerations for Māori

No additional data available

Considerations for Pacific

No additional data available

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No data on the outcome of interest. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	Mother's milk can become contaminated if not handled properly during expression, collection, transport, and storage, potentially leading to neonatal infections (6). Several outbreaks and case reports of neonatal infections have been previously linked to contaminated human milk containing Staphylococcus aureus, Escherichia coli, Serratia spp., Pseudomonas spp., Salmonella spp., Cytomegalovirus, and Acinetobacter baumannii pathogens, making safety and infection control an important issue in the NICU (7)(8). Screening breastmilk donors can mitigate the risk of infection. Infant formula can also become contaminated during handling (9)(10)(11) and has been associated with cases of foodborne illness in babies, including bacterial infections such as Salmonella, Cronobacter sakazakii (formerly Enterobacter sakazakii), and E. coli (12)(13)(14).
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Outcomes	Importance	Certainty of the evidence (GRADE)
Neonatal hypoglycaemia	CRITICAL	⊕◯◯◯ Very low[a,b]
Neurodevelopmental impairment - not measured	CRITICAL	-
Admission to special care nursery or neonatal intensive care nursery - not measured	CRITICAL	-
Adverse effects - not measured	CRITICAL	-
Fully breastfeeding at hospital discharge - not measured	CRITICAL	-
Separation from the mother for treatment of hypoglycaemia before discharge home - not measured	IMPORTANT	-
Hypoglycaemic injury on brain imaging - not measured	IMPORTANT	-
Breastmilk feeding exclusively from birth to hospital discharge - not measured	IMPORTANT	-
Duration of initial hospital stay - RCT	IMPORTANT	⊕◯◯◯ Very low[a,c]
Duration of initial hospital stay- non-randomised study of intervention	IMPORTANT	⊕◯◯◯ Very low[a,c]
Cost - not measured	IMPORTANT	-

a.Downgraded one level of risk of bias due to overall unclear risk of bias.
b.Downgraded three levels of extreme serious imprecision due to the small sample size and no event occurring in each group.
c.Downgraded one level of serious imprecision due to wide confidence interval.

Considerations for Māori

No additional data available

	Considerations for Pacific No additional data available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	***Excerpts from Values summary document*** ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Expressed breastmilk (mother's or donor's) compared to other or no intervention** • Very low certainty evidence showed • Uncertainty effect on neonatal hypoglycaemia • Uncertainty effect on the duration of hospital stay **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	Conflicting evidence on the effect on blood glucose concentrations. Expressed breastmilk may improve the emotional and psychological connection mothers have with their babies.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The resources required to collect and store expressed breastmilk are variable. The typical price range for 900g of formula in the community setting is approximately NZ $20 to $50. Pasteurised donor human milk costs NZ$33 per mL. However, the cost associated with collecting, storing, and feeding the baby with the mother's expressed breastmilk remains uncertain. The required resources can differ significantly based on various factors, including the method of expression (such as hand, manual, or electric pumps purchased by mothers or provided by the hospital), the presence or absence of proper expressed breastmilk storage facilities, equipment cleaning and re-use practices, as well as pasteurisation.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Very low ○ Low ○ Moderate ○ High ○ No included studies	A formal assessment of the certainty of evidence of the cost of expressed breastmilk was not undertaken.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	A systematic review comprising seven studies conducted in upper-middle-income countries, all of which focused on NICU settings and very low birth weight babies, suggests that all of these studies indicate that donor human milk interventions are cost-effective or cost-saving (15). However, none of the included studies assessed neonatal hypoglycaemia outcomes.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	We found no evidence to ascertain the impact of expressed breastmilk or donor human milk on health equity. ***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and*	

	housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions. ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (17)*. However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (18)*.* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (17)*.* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (18)*.* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (17)*.* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (19)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (20)(21)(22)*.* *Additionally, a systematic literature review by Graham et al.* (Graham et al., 2020*) provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (23)*.* ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (19)*.*	

	Other considerations *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (16)*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (16)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	A survey conducted in Aotearoa New Zealand explored mothers' and health professionals' views and experiences about donor human milk (24). Most mothers (n=496, ethnicity not reported) donated (51.5%) or sought donor human milk (25.6%) for their babies and arranged donor human milk exchanges between individuals (51.9%). The health profession survey (n=283) reported that almost all respondents supported donor human milk use in hospitals (98.6%). The views of Māori participants were not reported separately. There is considerable variability in the maternal acceptability of giving expressed breastmilk to their babies. A study conducted in Eastern Africa (25) with 1,085 participants found that only 11% of respondents were willing to donate breastmilk, and 15% supported feeding their babies with expressed breastmilk. The primary reason for the low acceptance rate of breastmilk donation is the lack of information and misconceptions about the safety of breastmilk. In contrast, the majority (86%) of participants in a study conducted in the United States of America reported their willingness to donate breastmilk, and 77.4% of them agreed human milk banks are a viable alternative to feed babies when there is a shortage of formula feeds (26). **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	A qualitative study conducted in Australia, which involved participants selected from the admission register of the Neonatal Intensive Care Unit, found that mothers highly valued being taught how to express breastmilk. This skill enabled them to provide milk for their sick babies, influencing their feeding practices (4). In the Whāunua Experience Study (19), breastfeeding was highly valued by mothers, and the majority had a strong preference for breastfeeding as a treatment for neonatal hypoglycaemia compared to formula. **Considerations for Māori** Whānau Māori valued having supports in place to facilitate breastfeeding (19).

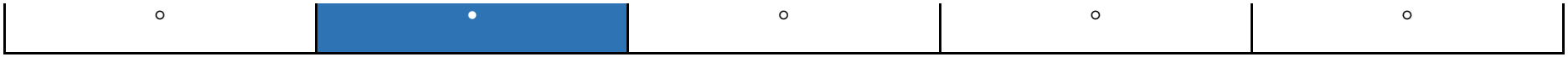
		Considerations for Pacific All Pacific mothers interviewed wanted to breastfeed their babies. Most (80%) had a strong preference to exclusively breastfeed and not use formula as a form of treatment. Only 2 participants (20%) accepted formula as a form of treatment (19).
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Establishing a human milk bank makes an adequate human milk supply more feasible. A study evaluating the milk bank established at Christchurch described the project as successful owing to the multidisciplinary team led by a neonatal nurse and the robust approach in its establishment, including detailed planning, audits, consultation processes, detailed mappings, literature reviews, and assessing its economic implications (27). However, it only prioritised pasteurised donated milk for preterm and unwell/sick babies admitted to the NICU (Waitaha Canterbury, Te Whatu Ora, Health New Zealand). Consequently, it is not currently an option for late preterm and term babies, who are most commonly considered for feeding as a treatment or preventative measure for hypoglycaemia. In the survey conducted in Aotearoa New Zealand, health professionals (n=232) felt human milk donation could be improved with better advocacy, access, affordability, and guideline development (24). Many guidelines on newborn care worldwide recommend giving newborn babies (both term and preterm babies) expressed breastmilk (mother's or donor's) to prevent or treat neonatal hypoglycaemia and for routine feeding of preterm babies admitted into neonatal intensive care or special care baby units (28)(29). **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	There are currently six human milk banks in Aotearoa New Zealand. However, cost presents a significant barrier, and the supply is limited. As a result, these milk banks can only serve prioritised groups. Most babies at risk of hypoglycaemia do not fall within the currently prioritised groups. Many maternity hospitals in Aotearoa New Zealand have expressing equipment available for mothers to express their breastmilk.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention



REFERENCES SUMMARY

1. Oladimeji OI, Harding JE, Crowther CA, Lin L. Expressed breast milk and maternal expression of breast milk for the prevention and treatment of neonatal hypoglycemia: a systematic review and meta-analysis. Maternal Health, Neonatology and Perinatology. 2023 9;9(1):12.
2. Rees D, Carr NR, Ponnapakkam A. Effect of donor breastmilk vs formula supplementation on blood glucose levels in neonates at risk for hypoglycemia. Pediatrics. 2021; 147 (3_MeetingAbstract): 330–332.
3. Harris DL, Gamble GD, Weston PJ, Harding JE. What happens to blood glucose concentrations after oral treatment for neonatal hypoglycemia?. The Journal of Pediatrics. 2017;190:136-141.
4. Sweet L. Expressed breast milk as connection and its influence on the construction of motherhood for mothers of preterm infants: a qualitative study. International Breastfeeding Journal. 2008;17;3:30.
5. Rønnestad A, Abrahamsen TG, Medbø S, Reigstad H, Lossius K, Kaaresen PI, et al. Late-onset septicemia in a Norwegian national cohort of extremely premature infants receiving very early full human milk feeding. Pediatrics. 2005;115(3):e269-76.
6. Madore LS, Fisher DJ. The role of breast milk in infectious disease. Clinics in Perinatology. 2021;48(2):359-378.
7. Shetty A, Barnes R, Adappa R, Doherty C. Quality control of expressed breast milk. The Journal of Hospital Infection. 2006;62(2):253-4.
8. Gad S, Sheta MM, Al-Khalafawi AI, Abu El-Fadl HA, Anany M, Sahmoud S, et al. Expressed breast milk contamination in neonatal intensive care unit. Pediatric Health, Medicine and Therapeutics. 2021;25;12:307-313.
9. Cahill SM, Wachsmuth IK, Costarrica Mde L, Ben Embarek PK. Powdered infant formula as a source of Salmonella infection in infants. Clinical Infectious Diseases. 2008;15;46(2):268-73.
10. Mathus-Vliegen LM, Binnekade JM, de Haan RJ. Bacterial contamination of ready-to-use 1-L feeding bottles and administration sets in severely compromised intensive care patients. Critical Care Medicine. 2000;28(1):67-73.
11. Iversen C, Forsythe S. Isolation of Enterobacter sakazakii and other Enterobacteriaceae from powdered infant formula milk and related products. Food Microbiology. 2004;21(6):771-777.
12. Choi MJ, Kim SA, Lee NY, Rhee MS. New decontamination method based on caprylic acid in combination with citric acid or vanillin for eliminating Cronobacter sakazakii and Salmonella enterica serovar Typhimurium in reconstituted infant formula. International Journal of Food Microbiology. 2013;16;166(3):499-507.
13. Wang X, Meng J, Zhang J, Zhou T, Zhang Y, Yang B, et al. Characterization of Staphylococcus aureus isolated from powdered infant formula milk and infant rice cereal in China. International Journal of Food Microbiology. 2012;153(1-2):142-7.
14. Brouard C, Espié E, Weill FX, Kérouanton A, Brisabois A, Forgue AM, et al. Two consecutive large outbreaks of Salmonella enterica Serotype Agona infections in infants linked to the consumption of powdered infant formula. The Pediatric Infectious Disease Journal. 2007;26(2):148-52
15. Zanganeh M, Jordan M, Mistry H. A systematic review of economic evaluations for donor human milk versus standard feeding in infants. Maternal & Child Nutrition. 2021;17(2):e13151.
16. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014 17. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
18. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
19. Whānau Experiences Study Group, . Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
20. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
21. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
22. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
23. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
24. Harris S. Human milk donation in Aotearoa New Zealand. Masters Thesis dissertation, University of Auckland; 2023 [cited 2 February 2024]; Available from: https://researchspace.auckland.ac.nz/handle/2292/64703
25. Gelano TF, Bacha YD, Assefa N, Motumma A, Roba AA, Ayele Y, et al. Acceptability of donor breast milk banking, its use for feeding infants, and associated factors among mothers in eastern Ethiopia. International Breastfeeding Journal. 2018;26;13:23.
26. Jackson F, Obeng C. Perceptions of human milk banks as a response to the US infant formula shortage: a mixed methods study of US mothers. Women. 2022;2(3):218-230.
27. Meeks M, Franks A, McGregor H, Webb G, Lamb R. Supporting mothers, protecting babies for long-term health: establishing a pasteurised human milk bank. The New Zealand Medical Journal. 2019;8;132(1505):83-91.
28. Newborn Services Clinical Practice Committee, Starship Child Health. Hypoglycaemia in the neonate. 16 April 2024 [cited 2 September 2024]; Available from: https://starship.org.nz/guidelines/hypoglycaemia-in-the-neonate/
29. Levene I, Wilkinson D. Identification and management of neonatal hypoglycaemia in the full-term infant (British Association of Perinatal Medicine-Framework for Practice). Archives of disease in childhood - Education and Practice. 2019;104(1):29-32.

Question 9.

Should oral dextrose gel vs. placebo be used for preventing neonatal hypoglycaemia?	
POPULATION:	Newborn babies judged to be at risk of hypoglycaemia
INTERVENTION:	oral dextrose gel
COMPARISON:	placebo
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment

SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Current practice usually includes early identification of at-risk babies and prophylactic measures are advised. However, these measures usually involve use of formula milk or admission to the neonatal unit. Dextrose gel is non-invasive, inexpensive and effective for treatment of neonatal hypoglycaemia. If prophylactic dextrose gel reduced the incidence of neonatal hypoglycaemia, it potentially may reduce separation of mother and baby and support breastfeeding, as well as preventing brain injury.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Prophylactic oral dextrose compared to placebo gel or no gel results in** (1) : • Moderate reduction in hypoglycaemia (56 fewer per 1,000) [critical] • Little to no effect on neurodevelopmental impairment at ≥2 years [critical] • Moderate reduction in neurodevelopmental impairment at 6 to 7 years of age (84 fewer per 1,000) [critical] • Little to no effect on admission to special care nursery or neonatal intensive care nursery [critical] • Moderate reduction in fully breastfeeding at hospital discharge (84 fewer per 1,000) [critical] • Little to no effect on separation from mother for treatment of hypoglycaemia before discharge home [important] • Small increase in breastmilk feeding exclusively from birth to hospital discharge (30 more per 1,000) [important] • Little to no effect on duration of initial hospital stay [important]	**Prophylactic oral dextrose compared to placebo gel or no gel results in** (1): Little to no effect on major neurological disability at ≥2 years (There is substantial heterogeneity for major neurological disability at two years of age or older (I-square = 85%, p = 0.009), with the direction of effect suggesting benefit in one study (3) and possible harm in the other, larger study (2).

- No studies reported hypoglycaemic injury on brain injury, or cost

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with oral dextrose gel
Hypoglycaemia [critical]	2548 (2 RCTs)	⨁⨁⨁⨁ High	**RR 0.87** (0.79 to 0.95)	Study population	
				433 per 1,000	**56 fewer per 1,000** (91 fewer to 22 fewer)
Neurodevelopmental impairment at ≥2 years [critical]	1553 (2 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 1.03** (0.84 to 1.26)	Study population	
				193 per 1,000	**6 more per 1,000** (31 fewer to 50 more)
Neurodevelopmental impairment at 6 to 7 years of age [critical]	308 (1 RCT)	⨁◯◯◯ Very low[c]	**RR 0.85** (0.68 to 1.07)	Study population	
				559 per 1,000	**84 fewer per 1,000** (179 fewer to 39 more)
Admission to special care nursery or neonatal intensive care nursery [critical]	2548 (2 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 1.03** (0.81 to 1.31)	Study population	
				95 per 1,000	**3 more per 1,000** (18 fewer to 29 more)
Fully breastfeeding at hospital discharge [critical]	2523 (2 RCTs)	⨁◯◯◯ Very low[c]	**RR 1.09** (0.79 to 1.49)	Study population	
				928 per 1,000	**84 more per 1,000** (195 fewer to 455 more)
				Study population	

Uncertain effect on major neurological disability at six to seven years of age (85 fewer per 1,000).
May reduce receipt of treatment for hypoglycaemia during initial hospital stay slightly (35 fewer per 1,000)).
Little to no effect on the number of episodes of hypoglycaemia, and breastfeeding after hospital discharge (1).
Dextrose gel used for prophylaxis or treatment of neonatal hypoglycaemia does not alter the neonatal gut microbiome (4).

Separation from mother for treatment of hypoglycaemia before discharge home [important]	2548 (2 RCTs)	⊕⊕◯◯ Low[b,d]	**RR 1.12** (0.81 to 1.55)	50 per 1,000	**6 more per 1,000** (9 fewer to 27 more)
Hypoglycaemic injury on brain imaging [important] - not measured	-	-	-	-	-
Breastmilk feeding exclusively from birth to hospital discharge [important]	2525 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	**RR 1.06** (0.91 to 1.24)	Study population	
				500 per 1,000	**30 more per 1,000** (45 fewer to 120 more)
Duration of initial hospital stay [important]	2537 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	-	The mean duration of initial hospital stay [important] was **3.20** days	MD **0.06 days higher** (0.13 lower to 0.24 higher)
Cost [important] - not measured	-	-	-	-	-

a.Downgraded one level for serious inconsistency due to the substantial heterogeneity.
b.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
c.Downgraded three levels for extremely serious imprecision due to a very wide confidence interval suggesting markedly different inferences.
d.Downgraded two levels for very serious imprecision due to the wide confidence interval and low event rates.
*Absolute effects were calculated based on the control group risk

Considerations for Māori
In the hPOD trial of 2051 babies in Aotearoa New Zealand and Australia, the effects of prophylactic dextrose gel on the outcomes listed above were similar for the 116/238 Māori babies randomised (11.6%) compared to the findings for the whole cohort (unpublished data from (2)).
Considerations for Pacific

	In the hPOD trial of 2051 babies in Aotearoa New Zealandand Australia, the number of Pacific babies was very small, the effects of prophylactic dextrose gel on the outcomes listed above were similar for the 56/116 Pacific babies randomised (5.7%) compared to the findings for the whole cohort (unpublished data from (2)).	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Prophylactic oral dextrose compared to placebo gel or no gel results in:** (1) • Little to no difference in short-term adverse effects [critical]. a.Downgraded two levels for very serious imprecision due to the wide confidence interval and low event rates. *Absolute effects were calculated based on the control group risk **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	In a systematic review of buccal dextrose gel for the treatment of neonatal hypoglycaemia (5), no adverse events were reported in either the oral dextrose gel or the placebo gel group.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with oral dextrose gel
Adverse effects [critical]	2510 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 1.22** (0.64 to 2.33)	Study population	
				10 per 1,000	**2 more per 1,000** (4 fewer to 13 more)

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies		

Outcomes	Importance	Certainty of the evidence (GRADE)
Hypoglycaemia [critical]	CRITICAL	⊕⊕⊕⊕ High
Neurodevelopmental impairment at ≥2 years [critical]	CRITICAL	⊕⊕◯◯ Low[a,b]
Neurodevelopmental impairment at 6 to 7 years of age [critical]	CRITICAL	⊕◯◯◯ Very low[c]
Admission to special care nursery or neonatal intensive care nursery [critical]	CRITICAL	⊕⊕◯◯ Low[a,b]
Adverse effects [critical]	CRITICAL	⊕⊕⊕◯ Moderate[d]
Fully breastfeeding at hospital discharge [critical]	CRITICAL	⊕◯◯◯ Very low[c]
Separation from mother for treatment of hypoglycaemia before discharge home [important]	IMPORTANT	⊕⊕◯◯ Low[b,d]
Hypoglycaemic injury on brain imaging [important] - not measured	IMPORTANT	-
Breastmilk feeding exclusively from birth to hospital discharge [important]	IMPORTANT	⊕⊕⊕◯ Moderate[b]
Duration of initial hospital stay [important]	IMPORTANT	⊕⊕⊕◯ Moderate[b]
Cost [important] - not measured		-

a.Downgraded one level for serious inconsistency due to the substantial heterogeneity.
b.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
c.Downgraded three levels for extremely serious imprecision due to a very wide confidence interval suggesting markedly different inferences.
d.Downgraded two levels for very serious imprecision due to the wide confidence interval and low event rates.

Considerations for Māori

Because of the small numbers included in the available trials, the findings are less certain for Māori babies.

	Considerations for Pacific Because of the very small numbers included in the available trials, the findings are very uncertain for Pacific babies.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	***Excerpts from Values summary document*** ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Prophylactic oral dextrose compared to placebo gel or no gel: Moderate to low certainty evidence showed: • Moderate reduction in hypoglycaemia [critical] • Little to no effect on neurodevelopmental impairment at ≥ 2 years [critical] • Uncertain effect on neurodevelopmental impairment at 6 to 7 years of age [critical] • Little to no effect on admission to special care nursery or neonatal intensive care nursery [critical] • Uncertain effect on fully breastfeeding at hospital discharge [critical] • Little to no effect on separation from mother for treatment of hypoglycaemia before discharge home [important] • Small increase in breastmilk feeding exclusively from birth to hospital discharge [important] • Little to no effect on duration of initial hospital stay [important] **Considerations for Māori** Limited evidence suggests that the effects are similar for Māori babies. **Considerations for Pacific** No specific evidence about effects for Pacific babies, but baseline risk is likely to be similar to other babies studied	• Little to no effect on major neurological disability at ≥2 years • Uncertain effect on major neurological disability at 6 to 7 years of age • May reduce receipt of treatment for hypoglycaemia during initial hospital stay slightly • Little to no effect on the number of episodes of hypoglycaemia, and breastfeeding after hospital discharge
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Cost of dextrose gel: use of single-dose syringes, priced at NZ $15.00 each (Biomed Ltd., Auckland, NZ). Cost of dextrose gel administration: US $7.38 (6) Minimal training is required to administer gel Time of applying the gel: 5 minutes. Additional time is required for prescriptions, sourcing gel and documenting administration.	Regarding dextrose gel treatment, most practitioners reported that the gel was easily available and that guidelines for its use were easy to access and understand (7).
Certainty of evidence of required resources		

What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	High certainty about the cost of the gel There is no precise data on time; estimates are made based on experience.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Subjects who received prophylactic dextrose gel incurred costs to the health system of around United States US $14,000 over an 18 year time horizon, accruing 11.25 quality adjusted life years (QALYs), whereas those who did not receive prophylactic treatment incurred cost of around US $16,000 and experienced a utility of 11.10 QALYs (based on one study - early follow up showing benefits) (6).	

Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Dextrose gel does not require refrigeration, has a long shelf-life and is already being distributed around Aotearoa New Zealand. It can be used in any care setting and can be prescribed by a midwife. These factors are likely to favour equitable access in both rural and urban settings. ***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (9)*. However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (10)*.* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (9)*.* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (10)*.* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (9)*.* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori***	

	Effects of the intervention are likely to be similar in Māori babies to those reported above. *In the Whānau Experience study* (11*), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (12, 13, 14*).* *Additionally, a systematic literature review by Graham et al.* (15*) provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (15*).* ***Consideration for Pacific*** Effects of the intervention are likely to be similar in Pacific babies to those reported above. *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (11*).* ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (8*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (8*), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Many Aotearoa New Zealand practitioners would consider implementing dextrose gel prophylaxis even if the clinical benefits are relatively small (7). When considering introducing dextrose gel prophylaxis, outcomes most often considered important by practitioners included reduced hypoglycaemia-associated cognitive impairment, improved breastfeeding, reduced use of formula to treat hypoglycaemia, reduced neonatal unit admission and reduced incidence of hypoglycaemia (7). In the Pre-hPOD trial, most parents found the gel acceptable (364/402, 91%) (3).	The DESiGN trial (16) showed that it was feasible to give the gel for treatment of hypoglycaemia in Aotearoa New Zealand, as most sites were giving it prior to the guidelines being published and implemented.

	Considerations for Māori Evidence from Whānau Experience Study (11) found Whānau Māori had positive experiences with buccal dextrose gel. **Considerations for Pacific** Evidence from Whānau Experience Study found all Pacific mothers interviewed had either a positive or neutral perception of buccal dextrose gel.	Many studies in different countries have demonstrated the feasibility of implementing dextrose gel for treatment, and its implementation has resulted in reduced NICU admissions and increased breastfeeding rates (17, 18, 19, 20, 21, 22, 23, 24, 25).
Feasibility **Is the intervention feasible to implement?**		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Before administering the gel, practitioners need to weigh the babies to determine the appropriate dosage. The timing of applying the gel may be problematic. Considerations for Māori No additional data available Considerations for Pacific No additional data available	Similar to above

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			

BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

REFERENCES SUMMARY

1. Roberts L, Lin L, Alsweiler J, Edwards T, Liu G, Harding JE. Oral dextrose gel to prevent hypoglycaemia in at-risk neonates. Cochrane Database of Systematic Reviews. 2023;11(11):CD012152.
2. Harding JE, Hegarty JE, Crowther CA, Edlin RP, Gamble GD, Alsweiler JM; hPOD Study Group. Evaluation of oral dextrose gel for prevention of neonatal hypoglycemia (hPOD): A multicenter, double-blind randomized controlled trial. PLoS Medicine. 2021;18(1):e1003411.
3. Hegarty JE, Harding JE, Gamble GD, Crowther CA, Edlin R, Alsweiler JM. Prophylactic oral dextrose gel for newborn babies at risk of neonatal hypoglycaemia: a randomised controlled dose-finding trial (the Pre-hPOD Study). PLoS Medicine. 2016;13(10):e1002155.
4. St Clair SL, Harding JE, O'Sullivan JM, Gamble GD, Alsweiler JM, Vatanen T; hPOD Study Group. Effect of prophylactic dextrose gel on the neonatal gut microbiome. Archives of Disease in Childhood, Fetal and Neonatal Edition. 2022;107(5):501-507.
5. Edwards T, Liu G, Battin M, Harris DL, Hegarty JE, Weston PJ, et al. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. Cochrane Database of Systematic Reviews. 2022;3(3):CD011027.
6. Glasgow MJ, Edlin R, Harding JE. Cost-utility analysis of prophylactic dextrose gel vs standard care for neonatal hypoglycemia in at-risk infants. The Journal of Pediatrics. 2020;226:80-86.e1.
7. Liu GX, Grigg CP, Harding JE. New Zealand practitioners views about neonatal hypoglycaemia and its management. Journal of Paediatrics and Child Health. 2021;57(7):1150-1152.
8. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014

9. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
10. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
11. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
12. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
13. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
14. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
15. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
16. Alsweiler JM, Crowther CA, Harding JE. Midwife or doctor leader to implement a national guideline in babies on postnatal wards (DesIGN): a cluster-randomised, controlled, trial. PLoS ONE. 2023;28;18(9):e0291784.
17. Barber RL, Ekin AE, Sivakumar P, Howard K, O'Sullivan TA. Glucose gel as a potential alternative treatment to infant formula for neonatal hypoglycaemia in Australia. International Journal of Environmental Research and Public Health. 2018;15(5):876
18. Gregory K, Turner D, Benjamin CN, Monthe-Dreze C, Johnson L, Hurwitz S, et al. Incorporating dextrose gel and feeding in the treatment of neonatal hypoglycaemia. Archives of Disease in Childhood, Fetal and Neonatal Edition. 2020;105(1):45-49.
19. Makker K, Alissa R, Dudek C, Travers L, Smotherman C, Hudak ML. Glucose gel in infants at risk for transitional neonatal hypoglycemia. American Journal of Perinatology. 2018;35(11):1050-1056.
20. Meneghin F, Manzalini M, Acunzo M, Daniele I, Bastrenta P, Castoldi F, et al. Management of asymptomatic hypoglycemia with 40% oral dextrose gel in near term at-risk infants to reduce intensive care need and promote breastfeeding. Italian Journal of Pediatrics. 2021;47(1):201.
21. Rawat M, Chandrasekharan P, Turkovich S, Barclay N, Perry K, Schroeder E, et al. Oral dextrose gel reduces the need for intravenous dextrose therapy in neonatal hypoglycemia. Biomedicine Hub. 2016;1(3):1–9.
22. Scheans P, Bennett C, Harris D. Using dextrose (glucose) gel to reverse neonatal hypoglycemia. Neonatal Network. 2017;36(4):233-238
23. Stanzo K, Desai S, Chiruvolu A. Effects of dextrose gel in newborns at risk for neonatal hypoglycemia in a baby-friendly hospital. Journal of Obstetric, Gynecologic and Neonatal Nursing. 2020;49(1):55-64.
24. Stewart CE, Sage EL, Reynolds P. Supporting 'Baby Friendly': a quality improvement initiative for the management of transitional neonatal hypoglycaemia. Archives of Disease in Childhood Fetal and Neonatal Edition. 2016;101(4):F344-7.
25. Ter M, Halibullah I, Leung L, Jacobs S. Implementation of dextrose gel in the management of neonatal hypoglycaemia. Journal of Paediatrics and Child Health. 2017;53(4):408-411.

Question 10.

Should formula vs. control be used for prevention of neonatal hypoglycaemia?	
POPULATION:	Babies at risk of neonatal hypoglycaemia
INTERVENTION:	formula
COMPARISON:	control

MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Formula is sometimes used to prevent neonatal hypoglycaemia by providing an alternative source of glucose when breastfeeding is insufficient or not possible.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are authors of cited paper.

ASSESSMENT

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	None of the studies reported any desirable effects for formula feeding (1) **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	Tozier (2) conducted a chart review in the USA of 163 babies born to mothers with type 1 diabetes and reported that the first three blood glucose concentrations of babies fed colostrum (mothers' own milk) were no different from those of babies who received formula supplementation.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Formula compared to breastfeeding as first feed is associated with (1). • Large increase in neonatal hypoglycaemia (262 more er 1,000) [critical] • Large decrease in fully breastfeeding at hospital discharge (325 fewer per 1,000) [critical] • Moderate increase in the duration of hospital stay (1.2 days higher) [important]	Chertok 2009 (4) reported that among babies born to mothers with diabetes, breastfed babies had significantly higher mean blood glucose concentrations (3.20 mmol/L) compared to those who were formula fed for their first feed (2.68 mmol/L) (P = 0.002). Nicolas 2008 (5) reported that full-term babies without any risk factors who were breastfed presented much less hypoglycaemia than formula-fed neonates, with a statistically significant p-value of 0.0001 (numbers not provided).

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with control	Risk difference with formula
Hypoglycaemia [critical]	621 (2 non-randomised studies)	⨁◯◯◯ Very low[a,b,c]	**OR 3.01** (0.53 to 17.13)	Study population	
				293 per 1,000	**262 more per 1,000** (113 fewer to 584 more)
				Study population	

Fully breastfeeding at hospital discharge [critical]	554 (1 non-randomised study)	⨁◯◯◯ Very low[a,d]	**OR 0.20** (0.13 to 0.30)	483 per 1,000	**325 fewer per 1,000** (374 fewer to 264 fewer)
Duration of initial hospital stay [important]	554 (1 non-randomised study)	⨁◯◯◯ Very low[a]	-	The mean duration of initial hospital stay [important] was **4.8** days	MD **1.2 days higher** (0.34 higher to 2.06 higher)

a.Downgraded two levels for very serious risk of bias due to included studies being of low quality.
b.Downgraded two levels for very serious inconsistency due to substantial heterogeneity.
c.Downgraded one level for serious imprecision due to wide confidence interval and small sample size.
d.Upgraded one level for large effect.
*Absolute effects were calculated based on the control group risk

Note: One of the included studies reported all three outcomes (3), but 61% of the babies in the formula group were admitted to the NICU before the initiation of feeding due to respiratory distress syndrome, transient tachypnoea of the newborn, and prematurity (apnoea, severe hypotonia, perinatal depression, and birth trauma), compared to only 22% in the breastfeeding group. Among those admitted to the Well Baby Nursery, there was no difference between the formula and breastfeeding groups in the incidence of hypoglycaemia (40% vs. 30%) or the duration of the initial hospital stay.Additionally, in one of the included studies that reported on the hypoglycaemia outcome, the average time to initial feeding was half an hour for the breastfeeding group and 2.6 hours for the formula group (4).

Considerations for Māori
No additional data available
Considerations or Pacific
No additional data available

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	<table><tr><th>Outcomes</th><th>Importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Hypoglycaemia [critical]</td><td>CRITICAL</td><td>⊕◯◯◯ Very low[a,b,c]</td></tr><tr><td>Neurodevelopmental impairment [critical] - not measured</td><td>CRITICAL</td><td>-</td></tr><tr><td>Admission to special care nursery or neonatal intensive care nursery [critical] - not measured</td><td>CRITICAL</td><td>-</td></tr><tr><td>Adverse effects [critical] - not measured</td><td>CRITICAL</td><td>-</td></tr><tr><td>Fully breastfeeding at hospital discharge [critical]</td><td>CRITICAL</td><td>⊕◯◯◯ Very low[a,d]</td></tr></table> a.Downgraded two levels for very serious risk of bias due to included studies being of low quality. b.Downgraded two levels for very serious inconsistency due to substantial heterogeneity. c.Downgraded one level for serious imprecision due to wide confidence interval and small sample size. d.Upgraded one level for large effect.	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]*	

	High value, probably no important variability • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Formula compared to breastfeeding • Very low certainty evidence showed • Uncertain effect on neonatal hypoglycaemia [critical] • Uncertain effect on fully breastfeeding at hospital discharge [critical] • Uncertain effect on length of hospital stay [critical] **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	Vey low certainty evidence showed: No difference in early blood glucose concentrations between babies born to mothers with type 1 diabetes-fed colostrum and those given formula. Uncertain effect on blood glucose concentrations in breastfed babies compared to formula-fed babies born to diabetic mothers.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The costs can vary depending on the type of formula used and the quantity required. The typical price range for a 900g container of formula in a community setting in New Zealand is approximately NZD $20 to $50. The estimated cost per litre of prepared Stage 1 baby formula in New Zealand would be approximately NZD $3.19 to $7.96. Additionally, resource requirements may include staff time for preparation and feeding, potential costs for additional feeding equipment, and considerations for storage and handling of the formula.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	A formal assessment of the certainty of evidence of the cost of formula for the treatment of neonatal hypoglycaemia was not undertaken.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	There are no studies that assess the specific cost-effectiveness of formula particularly in the context of preventing neonatal hypoglycaemia. However, a few studies suggest that formula is generally more cost-effective than donor human milk in the short term. In the long term, exclusive breastfeeding might offer cost savings compared to formula. A study conducted in Germany (6) comparing the costs of feeding preterm infants donor human milk, mother's own milk, and formula found that DHM was significantly more expensive than formula or mother's milk. The cost per litre of DHM was €306.95, with a total cost of €82.88 per litre for production and use. In contrast, formula costs €10.28 per litre. This suggests that formula has much lower direct costs than donor human milk.	

	Formula typically ranges from NZ$20 to $50 for a 900g container, depending on the type and quantity used. Additional costs of formula include factors such as staff time for preparation and feeding, as well as potential expenses for feeding equipment and storage. For comparison, oral dextrose gel is priced at approximately NZ$15 per single-dose syringe. The administration of dextrose gel costs an additional NZ$15(7) and requires minimal training. Thus, the cost of using formula as a prevention option is likely to be similar to that of dextrose gel.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10). *However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (11). *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10).	

	In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%) (11). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (8), *participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (12)(13)(14)*Additionally, a systematic literature review by Graham et al.* (15) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (15). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (8). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (9). *Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (9) *71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	In the Whānau Experiences Study (8) , all Pacific mothers indicated a strong preference for breastfeeding their babies, with most favouring exclusive breastfeeding over formula feeding. Only 2 out of 10 participants in this group accepted formula. Similarly, among Asian mothers, some struggled with transitioning to formula feeding as they had initially planned to breastfeed exclusively. In the Growing Up in New Zealand cohort (16), exclusive breastfeeding was highly valued by many wāhine Māori due to its alignment with Tikanga Māori, indicating that formula use may be less acceptable, particularly when cultural traditions strongly emphasise breastfeeding. A survey in New Zealand (17) showed that health professionals viewed dextrose gel prophylaxis for neonatal hypoglycaemia positively because it can reduce the need for formula treatment. They preferred minimising formula use to support breastfeeding while ensuring effective treatment.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Formula is widely available and used in most neonatal care settings.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies

VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

REFERENCES SUMMARY

1. Iqbal A, Harding JE, Lin L. Infant formula for the prevention and treatment of neonatal hypoglycaemia – a systematic review and meta-analysis. Unpublished; 2024.
2. Tozier PK. Colostrum Versus Formula Supplementation for Glucose Stabilization in Newborns of Diabetic Mothers.Journal of Obstetric, Gynecologic & Neonatal Nursing. 2013 Nov-Dec;42(6):619-28.
3. Cordero L, Stenger MR, Landon MB, Nankervis CA. Early feeding, hypoglycemia and breastfeeding initiation in infants born to women with pregestational diabetes mellitus. Journal of Neonatal-Perinatal Medicine. 2018;11(4):357-364.
4. Chertok IR, Raz I, Shoham I, Haddad H, Wiznitzer. Effects of early breastfeeding on neonatal glucose levels of term infants born to women with gestational diabetes. Journal of Human Nutrition and Dietetics. 2009;22(2):166-9
5. Nicolas G, Chaaban R, Khalifeh MCF, Souaiby J, Salemeh Y. Neonatal hypoglycemia in newborns without risk factors. Cogent Medicine. 2018;5(1):40

6. Fengler J, Heckmann M, Lange A, Kramer A, Flessa S. Cost analysis showed that feeding preterm infants with donor human milk was significantly more expensive than mother's milk or formula. Acta Paediatrica. 2020;109(5):959-966.
7. Glasgow MJ, Edlin R, Harding JE. Cost-utility analysis of prophylactic dextrose gel vs standard care for neonatal hypoglycemia in at-risk infants. The Journal of Pediatrics. 2020;226:80-86.e1.
8. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
9. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
10. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
11. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
12. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
13. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
14. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
15. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
16. Bennett D, Gilchrist CA, Menzies RL, Harwood M, Kingi TK, Atatoa Carr P, et al. Determinants of exclusive breastfeeding for wāhine Māori. New Zealand Medical Journal. 2022;20;135(1555):73-87
17. Liu GX, Grigg CP, Harding JE. New Zealand practitioners views about neonatal hypoglycaemia and its management. Journal of Paediatrics and Child Health. 2021; 57(7):1150-1152.

Quetsion 11.

Should testing for neonatal hypoglycaemia vs. not testing be used for babies at risk of neonatal hypoglycaemia ?	
POPULATION:	Babies at risk of neonatal hypoglycaemia
INTERVENTION:	testing for neonatal hypoglycaemia
COMPARISON:	not testing
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies)

	3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	All birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment are recommended to reduce the risk of later developmental problems.* As neonatal hypoglycaemia is often asymptomatic unless severe, it is standard practice to screen babies considered to be at risk with repeated, painful blood tests over the first 12-24 hours after birth. There have been no studies that have compared the long-term neurodevelopmental outcomes of at-risk babies screened for neonatal hypoglycaemia and those not screened. The presumed benefit of screening babies at risk of neonatal hypoglycaemia is that treatment of hypoglycaemia may improve neurodevelopmental outcomes. However, there is currently no evidence from randomised controlled trials that treatment of neonatal hypoglycaemia improves long term outcomes, and there is recent evidence from a cohort study that babies at risk for neonatal hypoglycaemia, who were screened and found to have neonatal hypoglycaemia and received treatment to maintain a blood glucose concentration of ≥2.6 mmol/L, had worse neurodevelopmental outcomes than babies who were screened and did not have neonatal hypoglycaemia (1). It is possible that screening at-risk babies for hypoglycaemia may be harmful. Babies with hypoglycaemia who subsequently develop neurodevelopmental impairment are more likely to have had a rapid rise of their interstitial glucose concentration after hypoglycaemia, potentially due to treatment (2). Moreover, babies with risk factors for hypoglycaemia, such as babies of diabetic mothers and preterm babies, are less likely to be exclusively breastfed on discharge.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects

How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	There have been no trials of screening for neonatal hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	The desired anticipated effects are improved neurodevelopmental outcomes. However, there is no evidence that screening for hypoglycaemia or treatment of hypoglycaemia improves outcomes.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	There have been no trials of screening for neonatal hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	In addition to the pain that babies experience with heel prick blood tests, observational studies show that babies who are screened for neonatal hypoglycaemia are more likely to be given formula and less likely to be exclusively breastfed, even if their blood glucose concentrations were normal (3). However, babies with risk factors for neonatal hypoglycaemia such as those whose mothers had diabetes and those born by caesarean section are at higher risk of not being breastfed, independent of hypoglycaemia (4, 5), so it is difficult to determine if this association is causal (6).
Certainty of evidence		

What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There have been no trials of screening for neonatal hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	There have been no trials of screening for neonatal hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	A screening programme requires staff time, lancets and blood glucose analysers, see EtDs on timing of screening and types of analysers.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ○ Low ○ Moderate ○ High ● No included studies	We have not systematically searched for evidence of the resources required.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There is no evidence of the cost effectiveness of screening for neonatal hypoglycaemia.	
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education,*	

	employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions. ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10)*. However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (11)*.* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)*(10)*.* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (11)*.* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10)*.* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** In O'Brien's (8) retrospective observational single-centre study, babies from all non-European ethnic groups were more likely to be eligible for screening compared with babies of European mothers (29.7% v 22.3%; OR, 1.47; 95% CI, 1.43-1.51; p < .001). ***Consideration for Māori*** Babies of Māori wāhine were more likely to be eligible for screening for neonatal hypoglycaemia than babies of European women (26.4% v 22.3%) (8). *In the Whānau Experience study (Whānau Experiences Study Group., 2024), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (12)(13)(14)*.* *Additionally, a systematic literature review by Graham et al.* (7) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau*	

	Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming" (7). ***Consideration for Pacific*** Babies of Pacific women were more likely to be eligible for screening for neonatal hypoglycaemia than babies of European women (32.1% v 22.3%) (8). *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work (Whānau Experiences Study Group., 2024).* ***Considerations for Indian*** Babies of Indian women were more likely to be eligible for screening for neonatal hypoglycaemia than babies of European women (37.8.1% v 22.3%) (8). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (9). *Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (9)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	This practice is in widespread use.In the Whānau Experiences study (15) of whānau/families with diverse cultural backgrounds including Māori, Pacific and Asian ethnicities (studied because these groups have a higher likelihood of having a baby born at risk of neonatal hypoglycaemia), some parents reported negative views about blood testing, including being distressed by multiple testing, seeing their small child hurt, and not being offered the chance to help. **Consideration for Māori**	

	Whānau Māori want the very best health outcomes for their pēpi. Whānau felt empowered and disempowered by the healthcare team, and the health system, when health provision happened to them, rather than with them (e.g., testing). Whānau shared experiences of healthcare delivery that occurred without explanation, resulting in disempowerment, and others asked questions to enable enactment of mana motuhake, especially around tikanga. **Consideration for Pacific** Some Pacific mothers felt very distressed when their babies had to be tested multiple times.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	This practice is in widespread use, so it is feasible in Aotearoa New Zealand. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			

BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Edwards T, Liu G, Battin M, Harris DL, Hegarty JE, Weston PJ, et al. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. Cochrane Database of Systematic Reviews. 2022;3(3):CD011027.
2. McKinlay CJ, Alsweiler JM, Ansell JM, Anstice NS, Chase JG, Gamble GD, et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. New England Journal of Medicine. 2015;373(16):1507-18.
3. Napiórkowska-Orkisz M, Gutysz-Wojnicka A, Tanajewska M, Sadowska-Krawczenko I. Evaluation of methods to minimize pain in newborns during capillary blood sampling for screening: a randomized clinical trial. International Journal of Environmental Research and Public Health. 2022;19(2):870
4. Saginur M, Abdulnour J, Guérin E, Bancroft X, Corsi DJ, Zazzera VD, et al. Association between newborn hypoglycemia screening and breastfeeding success in an Ottawa, Ontario, hospital: a retrospective cohort study. Canadian Medical Association Journal Open. 2023;11(2):E381-E388.
5. Mukhopadhyay S, Wade KC, Dhudasia MB, Skerritt L, Chou JH, Dukhovny D, et al. Clinical impact of neonatal hypoglycemia screening in the well-baby care. Journal of Perinatology. 2020;40(9):1331-1338
6. Longmore DK, Barr ELM, Wilson AN, Barzi F, Kirkwood M, Simmonds A, et al. Associations of gestational diabetes and type 2 diabetes during pregnancy with breastfeeding at hospital discharge and up to 6 months: the PANDORA study. Diabetologia. 2020;63(12):2571-2581.
7. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
8. O'Brien M, Gilchrist C, Sadler L, Hegarty JE, Alsweiler JM. Infants eligible for neonatal hypoglycemia screening. JAMA Pediatrics. 2023;177(11):1187-1196

9. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
10. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
11. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
12. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
13. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
14. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
15. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.

Question 12.

Should expanded or restricted criteria vs. current criteria be used for screening for neonatal hypoglycaemia?	
POPULATION:	All newborn babies
INTERVENTION:	expanded or restricted criteria
COMPARISON:	current criteria
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention

	2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment are recommended to reduce the risk of later developmental problems.* Since neonatal hypoglycaemia is often asymptomatic, it is standard procedure to screen babies deemed at risk by measuring blood glucose concentrations at intervals after birth. Although there is a lack of evidence on the long-term neurodevelopmental outcomes of at-risk babies screened for neonatal hypoglycaemia versus those not screened, the evidence suggests that screening at-risk babies and managing hypoglycaemic episodes to maintain blood glucose concentrations ≥2.6 mmol/L may help preserve cognitive function. However, given that more than a quarter of all newborn babies may be eligible for screening, it is important to identify which babies would benefit from screening (1).
CONFLICT OF INTERESTS:	CC, DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We found no evidence for any critical or important outcomes. **Risk factors for neonatal hypoglycaemia** (2)	A review of 20 local guidelines from 18 hospitals in Australia and Aotearoa New Zealand (4) found that all guidelines recommended testing the blood glucose concentrations of at-risk babies rather than testing every baby. These guidelines typically include babies born to mothers with diabetes, and most also include stressed or

Risk factors	No. of studies	No. of participants	Odds ratio (OR) ranges	Pooled results OR (95%CI)
Maternal factors				
Diabetes (GDM, type 1, type 2)	53	214,766	1 – 65	4.45 (3.32, 5.97
Caesarean	5	2,195	1.18- 3.37	2.1 (1.57, 2.80)
Excess weight gain during pregnancy	3	30,004	1.12-1.83	1.36 (1.05, 1.77
Antidepressant medications used during pregnancy	2	75,219	1.37- 1.61	1.57 (1.12, 2.20
Alpha/beta blockers used during pregnancy	2	76,388	2.6-3.59	3.28 (2.47, 4.36
Obesity	3	5,971	1.2 (NS)- 5.59	2.03 (0.85, 4.89
Ritodrine used during pregnancy	2	1,073	1.58 (NS)-7.67	3.46 (0.73, 16.4
Hypertension	2	740	0.69 (NS)-1.14	0.92 (0.55, 1.56
Betamethasone	1	2,609	NA	1.69 (1.46, 1.96
Fever	1	348	NA	3.84 (1.56, 9.45
Prolonged labour	1	483	NA	9.07 (1.98, 41.5
Neonatal factors				
Preterm	19	11,234	1.33-19.32	2.82 (1.91, 4.15
SGA	13	5,623	1.32 – 23.17	1.98 (1.59, 2.47
LBW	8	4,285	1.13-6.07	2.21 (1.59, 3.08
LGA	7	2,242	1.52-34.36	2.0 (1.19, 3.36)
Macrosomia	5	6,495	1.49-6.25	2.37 (1.57, 3.57
Foetal distress	5	1,399	1.20-13.22	1.43 (1.12, 1.82
Hypothermia	3	1,098	1.50-3.40	2.09 (1.27, 3.44
Twin	3	5,412	2.0 – 13.95	3.63 (1.77, 7.44
Delayed feeding	2	5,72	1.56-2.07	1.73 (1.26, 2.37

* Abbreviations: GDM- gestational diabetes; SGA- small for gestational age; LBW: low birth weight; LGA: large for gestational age

Signs and symptoms of neonatal hypoglycaemia (2)

unwell babies, as well as those showing signs of hypoglycaemia. Other frequently mentioned risk factors were being small for gestational age (SGA, 16/18 guidelines), born preterm (16/18), and large for gestational age (LGA, 14/18). A systematic review of international guidelines on neonatal hypoglycaemia screening found that only half of them recommend screening for LGA (1). The most frequently identified risk factor reported in observational studies is babies born to diabetic mothers, with a pooled odds ratio (derived from meta-analysis, summarises the collective findings of multiple studies to gauge the strength and direction of association between exposure or intervention and an outcome) of 4.45 (95% CI: 3.32, 5.97), followed by preterm birth at 2.82 (95% CI: 1.91, 4.15), and being small for gestational age (SGA) at 1.98 (95% CI: 1.59, 4.15). Additional risk factors were low birth weight (LBW) associated with an odds ratio of 2.21 (95% CI: 1.59, 3.08), and large for gestational age (LGA) with an odds ratio of 1.98 (95% CI: 1.59, 2.47) (2).

The most commonly reported signs of neonatal hypoglycaemia include jitteriness, with percentages ranging from 1.0% to 62.7% of all babies with hypoglycaemia across studies, followed by seizures/convulsions, ranging from 0.6% to 38.9%, poor feeding or refusal to feed at 1.1% to 90.5%, lethargy at 1.0% to 69.4%, and irritability at 2.0% to 38.0% (2).

Signs and symptoms	No. of studies	No. of participants	Frequency ranges (among hypoglycaemia cases)
Jitteriness	15	1644	1.0% to 62.7%
Seizures/Convulsions	15	1500	0.6% to 38.9%
Poor feeding/refusal to feed	14	1315	1.1% to 90.5%
Lethargy	10	789	1.0% to 69.4%
Irritability	7	717	2.0% to 38.0%
Cyanosis	8	547	0.83% to 38.9%
Hypotonia	7	795	0.83% to 27.3%
Apnoea	6	870	0.80% to 37.88%
tachypnoea	5	569	0.45% to 29.0%
hypothermia	4	379	2.9% to 27.1%
Respiratory distress/ asphyxia	4	282	4.6% to 34.0%
Abnormal cry	3	349	0.91% to 22.3%
Pallor	3	395	0.91% to 7.0%
Vomiting	2	444	18.2% to 21.5%
Bradycardia	2	103	2.3% to 11.11%
Listlessness	1	85	69.4%
Tremor	1	22	4.55%
Tachycardia	1	30	1.0%

Consideration for Māori

Babies of Māori women were more likely to be eligible for screening for neonatal hypoglycaemia than babies of European women (26.4% v 22.3%) (1).

However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%) (3*).*

Consideration for Pacific

Babies of Pacific women were more likely to be eligible for screening for neonatal hypoglycaemia than babies of European women (32.1% v 22.3%) (1).

In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%) (3*).*

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We found no evidence for any critical or important outcomes. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	There have been no studies that have compared the long-term neurodevelopmental outcomes of babies screened for neonatal hypoglycaemia and those not screened. Screening for neonatal hypoglycaemia typically involves obtaining a heel-prick capillary blood sample, and then analysing the concentration of glucose. Heel-prick tests are likely to be painful for the baby. Babies who have hypoglycaemia but are not promptly screened may experience delays in treatment, potentially leading to neurological complications, particularly in severe cases. Moreover, if testing is not consistently continued, instances of delayed, recurrent or prolonged hypoglycaemia may go undetected.
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We found no evidence for any of the critical or important outcomes. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	The evidence comes exclusively from observational studies. We did not systematically evaluate the quality of the studies. Despite some substantial effect sizes, there is significant heterogeneity in the estimated size of effects across various studies.

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Neurodevelopmental impairment [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Considerations for Māori** Māori babies are more likely to be at risk of hypoglycaemia than New Zealand Europeans **Considerations for Pacific** Pacific babies are more likely to be at risk of hypoglycaemia than New Zealand Europeans	Panel to Consider: Expanding the screening criteria to encompass additional risk factors or symptoms is likely to increase the number of identified babies who are tested and likely receive treatment for hypoglycaemia. Consequently, initiating screening for these babies is likely to lead to the earlier detection and treatment of severe hypoglycaemia. However, some babies may receive unnecessary screening tests, and even unnecessary treatments and interventions. Restricted screening criteria may result in some babies with hypoglycaemia being incorrectly classified as not having the condition, potentially leading to delayed treatment and, in severe cases, neurological complications. Moreover, if testing is not consistently continued, instances of delayed, recurrent, or prolonged hypoglycaemia may go undetected.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Screening with an enzymatic glucometer costs NZ $ 86.94 per baby, while using a non-enzymatic glucometer costs NZ $ 97.08 per baby (5).	

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We have not systematically searched for evidence of the resources required.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The cost of testing is likely to be small compared to the cost of brain injury from undetected hypoglycaemia for an individual, but the evidence that prompt detection and treatment of hypoglycaemia alter neurodevelopmental outcomes is very uncertain. Screening more babies could potentially impose a greater financial burden on the healthcare system and require additional resources, particularly staff time.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?***	In the Whānau Experiences study, (6) one Pacific mother believed that the increased testing of their baby was primarily due to their race.

○ Increased ○ Varies ○ Don't know	*There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (8)*. However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (3)*.* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (8)*.* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (3)*.* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (8)*.* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (6)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (9)(10)(11)*.*	

	Additionally, a systematic literature review by Graham et al. (12) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (12). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (6). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (7). *Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (7)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	In the Whānau Experiences study (6) of parents with diverse cultural backgrounds including Pacific, Asian, and Māori ethnicities, some parents reported negative views about blood testing, including being distressed by multiple testing, seeing their small child hurt, and not being offered the chance to help. A few Asian participants reported that the heel prick testing felt transactional because few recalled being offered the opportunity to support their baby while being tested. **Considerations for Māori** Whānau Māori appreciated nursing staff providing additional cares during heel pricks to provide comfort during the painful procedure.	

	Considerations for Pacific A few Pacific mothers felt deeply distressed if their babies had to be tested.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Blood glucose screening is standard practice for babies at risk in Aotearoa New Zealand. Screening for all babies is likely to be feasible if additional resources were available. A substantial increase in staffing, training and equipment would be required. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know

RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

REFERENCES SUMMARY

1. O'Brien M, Gilchrist C, Sadler L, Hegarty JE, Alsweiler JM. Infants eligible for neonatal hypoglycemia screening. JAMA Pediatrics. 2023;1;177(11):1187-1196
2. Lin L, Ulyat, C, McClintock T, Harding J. Risk factors and clinical signs of neonatal hypoglycaemia: a scoping review. Unpublished; 2024.
3. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
4. Rajay AB, Harding JE; hPOD Study Group. Variations in New Zealand and Australian guidelines for the management of neonatal hypoglycaemia: A secondary analysis from the hypoglycaemia Prevention with Oral Dextrose gel Trial (hPOD). Journal of Paediatrics and Child Health; 2022;58(5):820-829.
5. Glasgow MJ, Harding JE, Edlin R. Cost analysis of cot-Side screening methods for neonatal hypoglycaemia .Neonatology. 2018;114(2):155-162.
6. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
7. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
8. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
9. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
10. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
11. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
12. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
13. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.

Quesiton 13.

Should other timings vs. start at 1-2 hours, intervals of 3-4 hours, finish after 12 hours of glucose concentrations above the threshold be used for testing neonatal hypoglycaemia?	
POPULATION:	Babies at risk of neonatal hypoglycaemia
INTERVENTION:	other timings
COMPARISON:	start at 1-2 hours, intervals of 3-4 hours, finish after 12 hours of glucose concentrations above the threshold
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings

PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn infants over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Hypoglycaemia is commonly asymptomatic, so at-risk babies usually undergo blood testing to detect low glucose concentrations. This usually involves obtaining a heel-prick capillary blood sample, although other types of blood samples are sometimes tested. The timing of these screening tests is important, as heel-prick tests may be painful for the baby (1), distressing for their whānau, and require staff time and other resources.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are all authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We found no evidence for any of the critical or important outcomes. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Start Time A review of 20 local guidelines from 18 hospitals in Australia and Aotearoa New Zealand (11) found that the most commonly recommended start time for testing was 1-2 hours after birth (56%), including 7 guidelines from Aotearoa New Zealand (5 recommendations of 1-2 hours and 2 of 1 hour). A survey of 59 practitioners caring for babies at risk of hypoglycaemia in Aotearoa New Zealand found that 44 (75%) reported the first blood sample was taken 1-2 hours after birth, but 5 (8%) reported this was at <1 hour, 3 (5%) before 2 hours, and 4 (7%) at 2-4 hours (12). Data from three observational studies that started testing at 1-2 hours after birth in at-risk babies showed that the frequency of detected hypoglycaemia was higher at 1 hour than at 2 hour -32% at 1h to 12% at 2h, n = 1570 (2), -6% at 1h to 3% at 2h , n = 190 (13) -10% at 1h to 2% at 2h , n = 690 (14) and decreased further thereafter. However, there are

		insufficient data to determine the timing of recurrent hypoglycaemia (since earlier detected hypoglycaemia was likely to have been treated), or the proportion of infants with hypoglycaemia on early testing who would have recovered without treatment by the next time of testing. Testing Interval In the review of 20 local guidelines, the most commonly recommended screening interval was 3-4 hourly (10 guidelines, 7 from Aotearoa New Zealand), with an additional 3 guidelines recommending 3-hourly and one recommending 4-hourly (11). Data from three observational studies (total of 417 at-risk babies) reporting regular blood glucose testing suggest that 10-17% of detected hypoglycaemia occurred between the initial test at 1-2 hours and the second test 3-4 hours later (13, 15, 16). However, there is a lack of clarity about whether the same babies were tested at every time point, and the proportion of new versus recurrent cases. There are also insufficient data to determine the proportion of cases that might occur during 3 – 4-hourly intervals between testing in older babies (3 to 4 hours). Timing in Relation to Feeds In a study of 227 babies (64 (28%) Māori) in Aotearoa New Zealand who were ≥ 35 weeks gestation and developed hypoglycaemia in the first 48 hours after birth, there was no significant change in glucose concentrations within 90 minutes after feeding by breastfeeding or mother's expressed breastmilk (whether expressed before or after the birth). However, blood glucose concentrations did increase slightly after a formula feed (mean increase 0.2mmol/L, 95% CI 0.004 to 0.04 mmol/L) (17). Another study of 62 well, term babies in Aotearoa New Zealand (2 (3%) Māori) found that there was very little change in interstitial glucose concentrations in response to breastfeeds in the first 48 hours, but the response increased after this age to 0.41-0.44 mmol/L on days 3-4 (18).

		Stop Time In the review of 20 local guidelines, six recommended screening for a minimum of 12 hours (all from Aotearoa New Zealand), three recommended 9–12 hours and one 24 hours (11). The survey of 59 practitioners caring for babies at risk of hypoglycaemia in Aotearoa New Zealand found that 41 (71%) reported that in at-risk but well babies 3 tests were taken; (3%) reported 4 tests; 4 (7%) reported 7 tests (likely to equate to 3-4 hourly testing for 24 hours); and 3 (5%) reported testing for 24 hours if the baby had a mother with diabetes, but only for 3 consecutive tests for other risk groups (12). Two studies that continued screening at-risk babies for 24 hours after birth found that relatively few new cases were identified after 12 hours (i.e., 0.3% of 1570 babies (2); and 2% of 160 babies (3). Similarly, two studies that continued screening for 48 hours after birth found that a relatively small proportion of cases were identified after 12 hours (1.1% of 177 babies (4); 0.6% of 502 babies, (5). However, using a testing protocol that continued for 72 hours, Kushwaha and Sahni identified 7/125 (5.6%) new cases after 24 hours and 3/125 (2.4%) after 48 hours (6). In the Sugar Babies study, Harris et al. used a testing protocol that continued for a minimum of 24 hours (1 hour after birth, then 3-4 hours for 24 hours, then 3-8 hourly for the next 24 hours) in 514 at-risk babies (150, 29% Māori, 16, 3% Pacific) in Aotearoa New Zealand, with treatment of detected hypoglycaemia intended to keep glucose concentrations >2.6 mmol/L (7). In this study, 260 babies developed hypoglycaemia, 187/390 (48%) of hypoglycaemic episodes occurred in the first 6 hours, and 315/390 (81%) in the first 24 hours, but 95/260 babies (37%) had their first episode after 3 normal blood glucose measurements, and 15 (6%) had their first episode >24 hours after birth. Of severe hypoglycaemic episodes (< 2.0 mmol/L), 106/143 (74%) occurred within 6 hours and 130/143 (90%) in the first 12 hours.

		In the hPOD trial of 2,133 at-risk babies from Aotearoa New Zealand and Australia (238 (11%) Māori, 116 (5%) Pacific) (8), hypoglycaemia occurred after 12 hours in 213/1,207 (18%) of babies with measurements after this time. In an American study of 830 at-risk babies who were tested for neonatal hypoglycaemia, it first occurred on the initial measurement for 202 babies (63.1%), the second measurement for 68 babies (21.3%), and the third measurement for 50 babies (15.6%). (9). In the babies not at risk of neonatal hypoglycaemia from the GLOW study (10), 12% had a low plasma glucose between 12-24 hours.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We found no evidence for the critical or important outcomes. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Screening for neonatal hypoglycaemia typically involves obtaining a heel-prick capillary blood sample, and then analysing the concentration of glucose. Heel-prick tests are likely to be painful for the neonate. In the Sugar Babies study of 514 at-risk babies screened for hypoglycaemia for at least 24 hours in Aotearoa New Zealand (229 (45%) Māori, 22 (4%) Pacific) (7), the median number of blood glucose measurements per baby was 9 (range 1-21). In the hPOD trial of 2,13 at-risk babies in Aotearoa New Zealand and Australia (238 (11%) Māori, 116 (5%) Pacific) (8) the mean (SD) number of glucose measurements per baby was 7.8 (4.0) in those who became hypoglycaemic and 3.8 (1.5) in those who did not.
Certainty of evidence What is the overall certainty of the evidence of effects?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We found no evidence for the critical or important outcomes. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Estimates of frequency of hypoglycaemia at different times are very uncertain.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Starting time of 1 hour vs other times: Where data are available, it appears that the frequency of hypoglycaemia is higher at 1 hour than at 2 hours and decreases thereafter. Finishing time of 12 hours vs other times: Available data suggests that a relatively small proportion of cases of neonatal hypoglycaemia could be missed (i.e., 0.3 – 1.1%) if screening tests were to conclude at 12 hours. Intervals between tests of 3-4 hourly: There is limited evidence to suggest that a small proportion of cases or episodes (i.e., 10 – 17%) may occur between the initial test at 1–2 hours and the second test, approximately 3–4 hours later. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Panel to Consider: Start Time Earlier age at start of screening (1 hour vs 2+ hours) is likely to result in a higher proportion of babies receiving treatment for hypoglycaemia. It is uncertain what proportion of these babies would have had higher glucose concentrations later without treatment. However, earlier screening is likely to detect severe hypoglycaemia earlier and therefore allow earlier treatment. Testing Interval Approximately 10-17% of hypoglycaemia may occur between initial testing at 1-2 hours and the next test 3-4 hours later. There is no evidence about the risks and benefits of more or less frequent testing. Glucose concentrations may not change in relation to feeds in the first 48 hours. Stop Time There is wide variability in the reported incidence of later hypoglycaemia in at-risk babies, ranging from 0.3% to 18% after 12 hours and 5-6% after 24 hours.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Each heel-prick test requires at least one heel lancet and blood collection device and approximately 5-6 minutes of staff time. The average cost of enzymatic glucometer per test is NZ $11.49. The average cost of non-enzymatic glucometer per test is NZ $4.25 (19). Cost for analysis of the sample depends on the device used (see EtD on that topic).	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We have not systematically searched for evidence of the resources required.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The cost of additional testing is likely to be small compared to the cost of brain injury from undetected hypoglycaemia, but the evidence that prompt detection and treatment of hypoglycaemia alters neurodevelopmental outcome is very uncertain (see EtD on that topic).	

Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (21*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (7*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (21*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific*	

	babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%) (7*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (21*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (22*), participants expressed appreciation for the inclusion of prayer or tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (23, 24, 25*). Additionally, a systematic literature review by Graham et al.* (26*) provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (26*).* ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (22*).* ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (20*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that*	

	are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey (20)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Number of tests In a qualitative study of 16 parents (5 Māori, 1 Pacific) interviewed 9–13 years after their baby was born at risk of hypoglycaemia, four specifically recalled blood tests for glucose measurement as stressful or traumatic and a negative aspect of participating in the follow-up study (CHYLD), even though the blood tests were part of routine care and not the research study (27). In the Whānau Experiences study (22) of whānau/families with diverse cultural backgrounds including Māori, Pacific and Asian ethnicities (studied because these groups have a higher likelihood of having a baby born at risk of neonatal hypoglycaemia), some parents reported negative views about blood testing, including being distressed by multiple testing, seeing their small child hurt, and not being offered the chance to help. Consideration for Māori Whānau Māori want the very best health outcomes for their pēpi. Whānau felt empowered and disempowered by the healthcare team, and the health system, when health provision happened to them, rather than with them (e.g., testing). Whānau shared experiences of healthcare delivery that occurred without explanation, resulting in disempowerment, and others asked questions to enable enactment of mana motuhake, especially around tikanga. Consideration for Pacific	Start Time The protocol for the hPOD trial (8) of well, at-risk babies specified giving prophylactic dextrose or placebo gel 1 hour after birth and the first blood glucose measurement at 2 hours. There was consistent feedback from almost all of the 18 participating hospitals that at the time of administration of the gel (1 hour), many babies were receiving skin-to-skin contact and/or their first feed. Staff expressed reluctance to interrupt this time to administer other procedures.

	Some Pacific mothers felt very distressed when their baby had to be tested multiple times.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Blood glucose screening is standard practice for babies at risk in Aotearoa New Zealand. An increase in frequency or duration of screening is likely to be feasible but would potentially require additional resources, particularly staff time, in most settings. Consideration for Māori Whānau Māori want the very best health outcomes for their pēpi. Whānau felt empowered and disempowered by the healthcare team, and the health system, when health provision happened to them, rather than with them (e.g., testing). Whānau shared experiences of healthcare delivery that occurred without explanation, resulting in disempowerment, and others asked questions to enable enactment of mana motuhake, especially around tikanga. Consideration for Pacific Some Pacific mothers felt very distressed when their baby had to be tested multiple times.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies

VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

REFERENCES SUMMARY

1. Barker DP, Rutter N. Exposure to invasive procedures in neonatal intensive care unit admissions. Archives of Disease in Childhood. 1995;72(1):F47-8.
2. Blank C, van Dillen J, Hogeveen M. Primum non nocere: earlier cessation of glucose monitoring is possible. European Journal of Pediatrics. 2018;177(8):1239-1245.
3. Bandika VL, Were FN, Simiyu ED, Oyatsi DP. Hypoglycaemia and hypocalcaemia as determinants of admission birth weight criteria for term stable low risk macrosomic neonates. African Health Sciences. 2014;14(3):510-6.
4. Hamborg-Petersen B, Hansen KN, Hansen US, Lund HT. Hypoglykaemi i neonatalperioden. Behov for blodsukkerkontrol [Hypoglycemia in the neonatal period. The need for blood sugar control]. Ugeskrift for Laeger. 1990;29;152(5):327-9. Danish.
5. Holtrop PC. The Frequency of hypoglycemia in full-term large and small for gestational age newborns.American Journal of Perinatology. 1993;10(2):150-4
6. Kushwaha J, Sahni GS. Study of blood glucose level in newborns at SKMCH, Muzaffarpur, Bihar. International Journal of Pharmaceutical and Clinical Research Original Research Article. 2023;15:952-7.

7. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
8. Harding JE, Hegarty JE, Crowther CA, Edlin RP, Gamble GD, Alsweiler JM; hPOD Study Group. Evaluation of oral dextrose gel for prevention of neonatal hypoglycemia (hPOD): A multicenter, double-blind randomized controlled trial. PLoS Medicine. 2021;28;18(1):e1003411.
9. Cummings CT, Ritter V, LeBlanc S, Sutton AG. Evaluation of risk factors and approach to screening for asymptomatic neonatal hypoglycemia. Neonatology. 2022;119(1):77-83.
10. Harris DL, Weston PJ, Gamble GD, Harding JE. Glucose profiles in healthy term infants in the first 5 days: The Glucose in Well Babies (GLOW) Study. The Journal of Pediatrics. 2020;223:34-41.e4
11. Rajay AB, Harding JE; hPOD Study Group. Variations in New Zealand and Australian guidelines for the management of neonatal hypoglycaemia: A secondary analysis from the hypoglycaemia Prevention with Oral Dextrose gel Trial (hPOD). Journal of Paediatrics and Child Health. 2022;58(5):820-829.
12. Ulyatt C, Harding JE, Alsweiler J, Clapham V, Lin L. Current practice for testing for neonatal hypoglycaemia in Aotearoa New Zealand care settings. Unpublished. 2024.
13. Pillai SK, Fhausiya VK. A cross-sectional study on the frequency and risk factors for neonatal hypoglycemia in babies born in rural Kerala. Journal of Family Medicine and Primary Care. 2022;11(11):6949-6954. .
14. Wang LY, Wang LY, Wang YL, Ho CH. Early neonatal hypoglycemia in term and late preterm small for gestational age newborns. Pediatrics and Neonatology. 2023;64(5):538-546.
15. Khandare J, Ds M, Ananthan A, Nanavati R. Is routine monitoring for hypoglycemia required in intramural asymptomatic infant of diabetic mother? An audit in a tertiary care hospital. Journal of Tropical Pediatrics. 2020;66(2):194-200.
16. Karahasanoğlu O, Karatekin G, Köse R, Nuhoğlu A. Hypoglycemia in small-for-gestational-age neonates. The Turkish Journal of Pediatrics. 1997;39(2):159-64
17. Harris DL, Gamble GD, Weston PJ, Harding JE. What happens to blood glucose concentrations after oral treatment for neonatal hypoglycemia?. The Journal of Pediatrics. 2017;190:136-141.
18. Harris DL, Weston PJ, Harding JE. Relationships between feeding and glucose concentrations in healthy term infants during the first five days after birth—the Glucose in Well Babies Study (GLOW). Frontiers in Pediatrics; 2023;24;11:1147659.
19. Glasgow MJ, Harding JE, Edlin R; Children with Hypoglycemia and Their Later Development (CHYLD) Study Team. Cost analysis of treating neonatal hypoglycemia with dextrose gel. The Journal of Pediatrics. 2018;198:151-155.e1.
20. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
21. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
22. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
23. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
24. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
25. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
26. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
27. Franke N, Rogers J, Wouldes T, Ward K, Brown G, Jonas M, Keegan P, Harding J. Experiences of parents whose children participated in a longitudinal follow-up study. Health Expectations. 2022.;25(4):1352-1362.

Question 14.

Should specific pain management strategies vs. control/ placebo/ no intervention be used for pain management during blood sampling for neonatal hypoglycaemia?	
POPULATION:	Newborn babies having blood sampling for screening for and treatment of neonatal hypoglycaemia
INTERVENTION:	specific pain management strategies
COMPARISON:	control/ placebo/ no intervention

MAIN OUTCOMES:	Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau Validated pain scores Pain reactivity Adverse effects
SETTING:	Any care settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Standard clinical practice is to monitor at-risk babies to determine need for treatment to prevent long term consequences of hypoglycaemia (1). This involves collecting a blood sample to test glucose concentration, most commonly using a heel prick (1). However, blood sampling is a painful procedure (2) and pain has also been suggested to have detrimental effects on neurodevelopment in very preterm babies (3). Because using painful procedures to collect blood to test for neonatal hypoglycaemia is currently unavoidable, it is crucial to identify effective pain management strategies that can be used during blood testing. The Premature Infant Pain Profile (PIPP) is a tool designed for assessing pain in neonates, particularly preterm babies. It considers physiological and behavioral indicators, with a scale ranging from 0 to 21, with higher scores indicating more pain (4, 5). The Neonatal Infant Pain Scale (NIPS) evaluates pain based on facial expression, crying, breathing, and limb movements. Scores range from 0 to 7, with higher scores indicating more pain (6). The Douleur Aiguë Nouveau-né (DAN) scale rates acute pain in term and preterm neonates, scoring from 0 to 10. It assesses facial expressions, limb movements, and vocal expression (7). The Neonatal Facial Coding System (NFCS) assesses pain through facial expressions on a scale of 0 to 10, where 0 is no pain and 10 is the most pain (8).
CONFLICT OF INTERESTS:	CC, DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The desirable effect of different pain management methods are shown below (18): **Sucrose** (administration of oral sucrose with or without non-nutritive sucking (e.g. pacifiers) and other sweet solutions (e.g. glucose) prior to or during painful procedures) Preterm and term babies: • Reduces the Pain Profile of Premature Infants (PIPP) score at 30 seconds after heel lance (MD -1.74 (-2.11 to -1.37), 7 randomised controlled trials (RCTs), 547 babies; the mean PIPP scores at 30 seconds after heel lance ranged from 4.9 to 13.3 in the control group) (19). • Reduces the Neonatal Infant Pain Scale (NIPS) score for venipuncture (MD -0.90 (-1.81 to 0.01), 1 RCT, 111 babies; the mean NIPS score was 3.8 in the control group) (20). Preterm babies: • Little to no effect on the PIPP score at 30 seconds after heel lancing (MD -1.88 (-2.32 to 1.44), 3 RCTs, 192 babies; the mean PIPP scores at 30 seconds after heel lancing ranged from 6.3 to 13.3 in the control group) (19). Term babies: • Reduces the NIPS score after heel lancing (MD -2 (-2.42 to -1.58), 1 RCT, 56 babies; the mean NIPS score immediately after heel lancing was 3 in the control group) (19). • Reduces the PIPP score at 30 seconds after heel lancing (MD -0.87 (-1.8 to 0.06), 3 RCTs, 227 babies; the mean PIPP scores at 30 seconds ranged from 4.9 to 8.5 in the control group) (19). • Uncertain effect on the Douleur Aiguë Nouveau-né behavioural pain scale (DAN) score in term babies at 30 seconds after heel lancing (MD -1.9 (-8.58 to 4.78), 1 RCT, 32 babies; the mean DAN score at 30 seconds was 9.5 in the control group) (19). • Reduces the PIPP score during venipuncture (weighted MD 2.79 (-3.76 to -1.83), 1 RCT, 213 babies; the mean PIPP scores ranged from 8.9 to 9.2 in the control group) (20). Results reported narratively Sucrose compared to water was reported to lower NIPS scores one minute after heel lance or blood sampling (21, 22) and two minutes after heel lance (22). Sucrose plus non-nutritive sucking was also reported to lower PIPP scores one minute after heel lance compared to standard care (positioning and swaddling) (24) or compared to no intervention, sucrose only or non-nutritive sucking only (9). **Skin-to-skin contact (with mothers or Whānau)**	

	• Large reduction in PIPP at 30 seconds after heel lance (MD -3.47 (-5.55 to -1.38), 4 RCTs, 191 babies; the mean PIPP scores ranged from 10.9 to 13.2 in the control group) ((11, 12) our additional analysis). • Reduced Neonatal Facial Coding System (NFCS) score during heel lancing (MD -0.89 (-1.16 to -0.61), 2 RCTs, 362 babies; the mean NFCS score was 3 in the control group at 30 seconds after heel lancing (MD -0.78 (-0.95 to -0.60), 2 RCTs, 362 babies; the mean NFCS score was 1.78 in the control group) ((11, 12) our additional analysis). • Uncertain effect on the proportion of babies with low or no pain during the procedure as measured by the Neonatal Infant Pain Scale (NIPS) score (RD -0.03 (-0.08 to 0.01), 3 RCTs, 480 babies) (11). • Reduces the proportion of infants in severe pain measured by NIPS (RD −0.23 (−0.31 to −0.15), 3 RCTs, 480 babies) and increases the proportion with no pain (0.35 (0.26 to 0.44), 3 RCTs, 480 babies) during recovery (11). Results reported narratively Skin-to-skin contact compared to control was reported to lower PIPP score at 30 seconds (14) and two minutes (15)(16) after the procedure. Skin-to-skin contact compared to control was also reported to lower NFCS score in preterm babies during heel lance and recovery (17). **Breastfeeding (23)** • Large reduction in NIPS score compared to no intervention (MD -2.53 (-3.46 to -1.60), 5 RCTs, 459 babies; the mean NIPS scores ranged from 3.45 to 6.43 in the control group). • Large reduction in NFCS score compared to no intervention (MD -4.20 (-5.14 to -3.26), 1 RCT, 60 babies; the mean NFCS score was 7.1 in the control group). • Reduction in DAN score compared to no intervention (MD -1.87 (-4.61 to 0.86), 2 RCTs, 250 babies; the mean DAN score was 5.9 in the control group). • Little to no difference in PIPP score compared to no intervention (MD -0.49 (-2.39 to 1.41), 1 RCT, 29 babies). • Large reduction in PIPP score compared to placebo (MD -5.95 (-7.42 to -4.48), 1 RCT, 29 babies; the mean PPIP score was 11.13 in the control group). • Reduction in DAN score compared to placebo (MD -6.24 (-7.38 to -5.10), 1 RCT, 89 babies; the mean DAN score was 8.49 in the control group). **Supplemental breast milk** (breast milk placed on the tongue or in mouth) (23)	

	• Little to no effect on the NIPS score compared to no intervention (MD -0.30 (-1.60 to 1.00), 1 RCT, 60 babies; the mean NIPS score was 5.1 in the control group). • Reduction in DAN score compared to no intervention (MD -1.00 (-2.15 to 0.15), 1 RCT, 60 babies; the mean DAN score was 6.48 in the control group). • Reduction in NFCS score at two minutes after heel lance compared to one dose of water (MD -0.84 (-1.09 to -0.59), 1 RCT, 45 babies; the mean NFCS score was 5.64 in the control group) and compared to two doses of water (MD -0.59 (-0.83 to -0.35), 1 RCT, 44 babies; the mean NFCS score was 6.23 in the control group). • Little to no effect on body pain score compared to placebo (MD 0.48 (-0.38 to 1.34)). **Opioids** (10) This review includes babies receiving opioids for pain during procedures such as dialysis, extracorporeal membrane oxygenation treatment, before screening for retinopathy of prematurity, placement of Broviac catheter, air leak drainage, insertion of a central line, heel lance, lumbar puncture, venipuncture, arterial line placement, and any other painful procedures. • Large reduction in PIPP/PIPP-R scores during the painful procedure (MD -2.58 (95% CI -3.12 to -2.03), 3 RCTs, 199 babies; the mean PIPP/PIPP-R during the procedure ranged from 8 to 11 in the control group). • Reduction in NIPS score during the procedure (MD -1.97 (-2.46 to -1.48), 2 RCTs, 102 babies; the mean NIPS during the procedure ranged from 5 to 6 in the control group). • Little to no effect on the DAN score 1-2 hours after the procedure (MD -0.20 (-2.21 to 1.81), 1 RCT, 42 babies). **Other non-pharmacological strategies** (13) Pain reactivity: babies' response or sensitivity to painful stimuli within the first 30 seconds after the painful stimulus Pain regulation: babies' response or sensitivity to painful stimuli after the initial pain response period (i.e., after the first 30 seconds following the painful stimulus) Standard mean difference (SMD): Different measures of pain intensity (coded by either trained nurses or research staff) were converted into a standard scale to help readers interpret the findings. The standard scale ranges from 0 to 21, with 0 being no pain and 21 being very severe pain. **Non-nutritive sucking compared to control**	

	• In preterm babies, moderate reduction in pain reactivity (SMD -0.57 (-1.03 to -0.11), 7 RCTs, 597 babies) and moderate improvement in pain regulation (SMD 0.61 (0.95 to 0.27), 6 RCTs, 379 babies). • In term babies, large reduction in pain reactivity (SMD -1.13 (-1.57 to -0.68), 8 RCTs, 545 babies), and large improvement in pain regulation (SMD -1.49 (-2.20 to -0.78), 9 RCTs, 536 babies). **Facilitated tucking** • In preterm babies, large reduction in pain reactivity (SMD -1.01 (-1.44 to -0.58), 12 RCTs, 733 babies) and moderate improvement in pain regulation (SMD -0.59 (-0.92 to -0.26), 10 RCTs, 557 babies). **Light reduction** (minimising the amount of light the baby is exposed to, either directly (e.g., covering their eyes) or indirectly (e.g., placing a blanket over the babies' incubator). • In preterm babies, light reduction likely reduces pain reactivity (SMD -0.71 (-1.08 to -0.34), 2 RCTs, 125 babies) and improves immediate pain regulation compared to a no-treatment control (SMD -1.16 (-1.53 to -0.78), 2 RCTs, 125 babies). **Other methods of pain management** • In term babies, cold addition (cooling the site of the painful procedure using a non-pharmacological method, such as the application of an ice pack to the procedure site) may reduce pain reactivity compared to a no-treatment control (SMD -0.85 (-1.48 to -0.23), 2 RCTs, 142 babies). • Little to no effect of paracetamol or topical anaesthetics on pain scores. • Little to no effect of heat addition on pain reactivities. • Very uncertain effects of swaddling, swallowing water, rocking or holding, touch/massage, sound reduction, sound addition, smell addition, therapeutic touch (holding hands over the babies without direct contact), co-bedding or music on pain scores or pain reactivities. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Undesirable Effects How substantial are the undesirable anticipated effects?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	**Sucrose** Of several studies that reported adverse effects, none reported a difference between the sucrose and placebo groups. One study reported that there was no difference in blood glucose concentrations between the sucrose and water groups. The review authors concluded that there is a very low proportion of minor adverse events with sucrose. **Breastfeeding** One study reported that there was no difference in the number of babies with effective sucking between the breastfeeding and control groups. **Supplemental breast milk** One study found no difference in adverse events (oxygen saturation <80%, nausea, regurgitation or vomiting, heart rate <100 beats per minute) between supplemental breast milk and placebo groups. **Opioids** Increase in episodes of apnoea compared to placebo (RR 3.15, 95% CI 1.08 to 9.16; 3 RCTs, 199 babies; low-certainty evidence). **Non-nutritive sucking compared to control** For preterm babies, one study reported that one of the 22 participants receiving the non-nutritive sucking intervention vomited. Six studies explicitly mentioned that no adverse events occurred. For term babies, one study reported that one participant in the treatment group and two participants in the control group were desaturated during the study. The remaining eight studies did not report any adverse events. **Facilitated tucking** Of the ten studies, one reported that a participant developed septicaemia after receiving experimental care. The other nine studies did not observe any adverse effects. **Light reduction** No data **Cold addition** No data **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	Sucrose In preclinical studies, repetitive sucrose during the first week of life in mice negatively impacts the development of important brain structures (25) and did not prevent or ameliorate effects of pain (heel prick) exposure on memory in adulthood (26) Moreover, these adverse effects of sucrose in adult mice were seen regardless of whether sucrose was given for pain or not (25)(26). The limited observational research conducted in very preterm babies suggests sucrose may not ameliorate negative long-term outcomes related to neonatal pain-related stress exposure. Studies have shown that cumulative sucrose exposure may be associated with poorer neurobehaviour at term equivalent age (27) and at 18 months corrected age (CA), perhaps more so for girls (28). Recent work by researchers in Canada demonstrated that cumulative sucrose exposure exacerbated the relationship between neonatal pain-stress (number of painful procedures) and infant cognition and language at 18 months corrected age (CA)(29). To date, no RCT has reported on long-term neurodevelopmental outcomes of repetitive sucrose for acute painful procedures (19).

Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low
● Low
○ Moderate
○ High
○ No included studies

Outcomes	Certainty of Evidence
Sucrose	
PIPP scores at 30 seconds after heel lance in preterm and term infants	Moderate
NIPS score for venipuncture in preterm and term infants	Moderate
PIPP scores at 30 seconds after heel lancing in preterm infants	Low
NIPS score after heel lancing in term infants	Moderate
PIPP scores at 30 second after lancing in term infants	Low
DAN scores at 30 seconds after heel lancing in term infants	Very low
NIPS score immediately after heel lance in term infants	Moderate
PIPP score during venipuncture in term infants	High
Adverse event – not estimated	Very low
Skin-to-skin contact	
PIPP during heel prick compared to control	High
NFCS during heel lance and recovery	Moderate
proportion of infants in low or no pain during the procedure	Very low
proportion of infants in severe pain measured by NIPS and proportion in no pain	Moderate
Adverse event – not reported	-
Breastfeeding	
Compared to no intervention: NIPS score	Moderate
Compared to no intervention: NFCS score	Low
Compared to no intervention: DAN score	Low
Compared to no intervention: PIPP score	Low
Compared to placebo: PIPP score	Low
Compared to placebo DAN score	Low
Adverse event – not estimated	Very low
Supplemental breastmilk	
Compared to no intervention: NIPS score	Low
Compared to no intervention: DAN score	Low
Compared to one dose of water: NFCS score at two minutes after heel lance	Low
Compared to two doses of water: NFCS score at two minutes after heel lance	Low
body pain score compared to placebo	Low
Adverse event – not estimated	Very low
Opioids	
PIPP/PIPP-R scores during the painful procedure	Moderate
NIPS score during the procedure	Low
DAN score 1-2 hours after the procedure	Low
Adverse event – not estimated	Very low
Non-nutritive sucking compared to control	
pain reactivity and pain regulation in preterm and term infants	Very low
Adverse events in preterm and term infants	Very low
Facilitated tucking	
Pain reactivity and pain regulation in preterm infants	Very low
Adverse events in preterm infants	Very low
Light reduction	
Pain reactivity and pain regulation in preterm infants	Moderate
Adverse events – not reported	-
Cold addition	
Pain reactivity in term infants	Low
Adverse events – not reported	-

	Considerations for Māori No additional data available **Considerations for Pacific** No additional data available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In the Whānau Experiences study (30) of whānau/families with diverse cultural backgrounds, including Māori, Pacific, and Asian ethnicities (studied because these groups have a higher likelihood of having a baby born at risk of neonatal hypoglycaemia), some parents reported negative views about blood testing, including being distressed by multiple tests, seeing their small child hurt, and not being offered the chance to help. *Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects		

Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Desirable effects • Sucrose compared to control probably results in a reduction of pain after single heel lances. • Skin-to-skin contact, breastfeeding or supplemental breast milk, opiods, light reduction, or cold addition may reduce pain in babies undergoing painful procedures. • Non-nutritive sucking or facilitated tucking may reduce pain in babies, but the evidence is very uncertain. Undesirable effects • Very uncertain undesirable effects for sucrose, breastfeeding, supplemental breastmilk, non-nutritive sucking, or facilitated tucking. • Opioids may result in an increase in episodes of apnoea. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Sucrose cost NZ$13.91 per 25 ml (Biomed, NZ) Skin-to-skin contact, breastfeeding, supplemental breastmilk, non-nutritive sucking, facilitated tucking, light reduction or cold addition do not have a per unit cost, but time must be spent training health professionals and their supporting the interventions and educating parents. These non-pharmacological methods require minimal financial resources but necessitate dedicated time and effort for training and education.	
Certainty of evidence of required resources		

What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We are reasonably certain of the cost of sucrose, but uncertain about the cost of staff time and training.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No evidence on the cost-effectiveness. As the comparator of standard care or no intervention does not have a cost, cost-effectiveness is likely to favour the comparator. However, since pain has been suggested to have detrimental effects on neurodevelopment in very preterm babies (3), adequately treating pain in the NICU may have beneficial effects on later neurodevelopment, which have not yet been quantified.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?***	It is important that education for parents around pain management strategies occurs consistently, as a Finnish study of

○ Probably increased ○ Increased ○ Varies ○ Don't know	*There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (32). *However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (33). *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (32). *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* ((33). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (32). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** Whānau Māori are highly tuned to notice when healthcare professionals appear to be both desensitised to providing care versus caring for their pēpi. Whānau noticed when staff provided comfort and care for painful procedures, which made them feel like the staff cared for their pēpi. In some situations, this was their pēpi first experience of pain. When staff had made a connection with the whānau through whanaungatanga, whānau had an opportunity to establish a relationship, which enabled the opportunity to ask questions, and be fully informed about the painful procedure.	178 NICU parents found that the non-pharmacological strategies used by parents varied in different hospitals (38). The authors suggested this may be due to differing levels of family-centred care practised between the hospitals. Providing a range of different pain strategies will help ensure sufficient pain management is available to all babies, including those whose parents face barriers to being present for all painful procedures. These barriers may be present for a variety of reasons including continued need to work, living further from the hospital or having other young children.

	In the Whānau Experience study (30)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (34)(35)(36)*. Additionally, a systematic literature review by Graham et al.* (37) *provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (37). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (30) ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (31)*. Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (31)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A study of smell addition with mother's breastmilk to manage pain during heel pricks found this intervention acceptable for more than 80% of mothers (n=11) and nurses (n=20) (39). In a questionnaire completed by 81 parents in a surgical NICU in Australia, most parents used non-nutritive sucking and strategies involving touch nearly always or always during painful procedures (including touching, holding, positioning, swaddling, and facilitated tucking), suggesting that these strategies are acceptable to parents and clinicians (40). Breastfeeding, breastmilk scent, sucrose, skin-to-skin and music were not as frequently used, with 12%, 22%, 33%, 34% and 40% of parents using these nearly always or always during painful procedures.	

	This study also reported that 80% of parents wanted to be present during painful procedures (40). Researchers who interviewed 12 parents suggested that pain management strategies involving parents decreased parental stress by providing a way for parents to contribute to reducing their babies' pain (41). However, this is not true for all parents, with some preferring to leave the room during painful procedures to avoid seeing their baby in pain (42). Because parental presence is necessary for some pain management strategies like skin-to-skin and breastfeeding, it is important to offer a range of strategies so parents can decide what is best for their whānau. **Considerations for Māori** In the whānau experience study (30), Whānau Māori valued being offered skin to skin and then supported to breastfeed their pēpi during testing. **Considerations for Pacific** In the whānau experience study (30), 50% of Pacific women were offered skin-to-skin contact during hypoglycaemia testing. All the women who were offered this, expressed they believe skin-to-skin contact is very important for the care of their baby. One woman interviewed said that in a case where a mother cannot provide skin-to-skin contact, a father should. **Consideration for Asian** In the whānau experience study (30), few Asian participants remembered being offered the opportunity to provide skin-to-skin contact. A few participants expressed that they would have appreciated being offered the choice.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	By 2007, sucrose was already used in most Aotearoa New Zealand neonatal units, indicating feasibility in the Aotearoa New Zealand context (43). It is recommended for consideration in the Starship guidelines for neonates and babies undergoing painful procedures, alongside ensuring the babies is "calm, relaxed, warm and fed" (44). Sucrose is feasible as it provides pain relief only 1-2 minutes after administration, meaning it can be applied immediately before a painful procedure. Although the Australian study above (40) noted that breastfeeding and skin-to-skin contact were used by some parents during painful procedures, these interventions do pose logistical challenges as the breastfeeding parent or another caregiver needs to be present at the time of	

	the painful procedure (45). Breastfeeding is also not as feasible for some babies who have difficulty sucking (45). The need for different strategies to suit different situations was highlighted in a study of 178 parents in NICUs across Finland (38). They found that the non-pharmacological interventions used by parents were related to the gestational and postnatal age of babies, their length of hospitalisation, condition, and pain intensity. For example, babies with a lower gestational age were more likely to receive comforting touch methods, including kangaroo care, whilst those with a higher gestational age were more likely to receive sucrose or breastfeeding. Lack of information about feasibility in relation to other methods not currently used (i.e. facilitated tucking). **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Committee on Fetus and Newborn; Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics. 2011;127(3):575-9.
2. Devi R, Priyadarshi M, Singh P, Chaurasia S, Basu S. Neonatal pain response to various heel prick devices: a randomized controlled trial. Indian Pediatrics. 2023;15;60(11):893-898.
3. Grunau RE, Whitfield MF, Petrie-Thomas J, Synnes AR, Cepeda IL, Keidar A, et al. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. Pain. 2009;143(1-2):138-46.
4. Gibbins S, Stevens BJ, Yamada J, Dionne K, Campbell-Yeo M, Lee G, et al. Validation of the Premature Infant Pain Profile-Revised (PIPP-R). Early Human Development. 2014;90(4):189-93.
5. Stevens BJ, Gibbins S, Yamada J, Dionne K, Lee G, Johnston C, et al. The Premature Infant Pain Profile-Revised (PIPP-R): initial validation and feasibility. The Clinical Journal of Pain. 2014;30(3):238-43.
6. Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. Neonatal Network. 1993;12(6):59-66.
7. Carbajal R, Paupe A, Hoenn E, Lenclen R, Olivier Martin M. DAN une échelle comportementale d'évaluation de la douleur aiguë du nouveau-né. Archives Pediatrie. 1997;4(7), 623-628.
8. Grunau RVE, Craig KD. P. Pain expression in neonates: facial action and cry. Pain. 1987;28(3):395-410.
9. Thakkar P, Arora K, Goyal K, Das RR, Javadekar B, Aiyer S, et al. To evaluate and compare the efficacy of combined sucrose and non-nutritive sucking for analgesia in newborns undergoing minor painful procedure: a randomized controlled trial. Journal of Perinatology. 2016;36(1):67-70.
10. Kinoshita M, Olsson E, Borys F, Bruschettini M. Opioids for procedural pain in neonates. Cochrane Database of Systematic Reviews. 2023;11;2021(12):CD015056
11. Johnston C, Campbell-Yeo M, Disher T, Benoit B, Fernandes A, Streiner D, et al. Skin-to-skin care for procedural pain in neonates. Cochrane Database of Systematic Reviews. 2017;2(2):CD008435.
12. Shukla VV, Bansal S, Nimbalkar A, Chapla A, Phatak A, Patel D, Nimbalkar S. Pain control interventions in preterm neonates: a randomized controlled trial. Indian Pediatrics. 2018;55(4):292-296
13. Pillai Riddell RR, Bucsea O, Shiff I, Chow C, Gennis HG, Badovinac S, et al. Non-pharmacological management of infant and young child procedural pain. Cochrane Database of Systematic Reviews. 2023;6(6):CD006275
14. Mosayebi Z, Javidpour M, Rahmati M, Hagani H, Movahedian A H. The effect of kangaroo mother care on pain from heel lance in preterm newborns admitted to neonatal intensive care unit: a crossover randomized clinical trial.Journal of Comprehensive Pediatrics. 2014;5(4):e22214.
15. Akcan E, Yiğit R, Atici A. The effect of kangaroo care on pain in premature infants during invasive procedures. The Turkish Journal of Pediatrics. 2009;51(1):14-8.
16. Cong X, Ludington-Hoe SM, Walsh S. Randomized crossover trial of kangaroo care to reduce biobehavioral pain responses in preterm infants: a pilot study. Biological Research For Nursing. 2011;13(2):204-16.
17. Castral TC, Warnock F, Leite AM, Haas VJ, Scochi CG. The effects of skin-to-skin contact during acute pain in preterm newborns. European Journal of Pain. 2008;12(4):464-71.

18. Lord L, Harding JE, Crowther CA, Lin L. Pain management strategies for babies during blood sampling for neonatal hypoglycaemia: an overview of reviews. Unpublished. 2024.
19. Yamada J, Bueno M, Santos L, Haliburton S, Campbell-Yeo M, Stevens B. Sucrose analgesia for heel-lance procedures in neonates. Cochrane Database of Systematic Reviews. 2023;30;8(8):CD014806.
20. Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database of Systematic Reviews. 2016;16;7(7):CD001069
21. Overgaard C, Knudsen A. Pain-relieving effect of sucrose in newborns during heel prick. Biology of the Neonate. 1999;75(5):279-84.
22 Ramenghi LA, Griffith GC, Wood CM, Levene MI. Effect of non-sucrose sweet tasting solution on neonatal heel prick responses. Archives of Disease in Childhood. 1996;74(2):F129-31
23 Shah PS, Torgalkar R, Shah VS. Breastfeeding or breast milk for procedural pain in neonates. Cochrane Database of Systematic Reviews. 2023;29;8(8):CD004950.
24. Stevens B, Yamada J, Beyene J, Gibbins S, Petryshen P, Stinson J, et al. Consistent management of repeated procedural pain with sucrose in preterm neonates: is it effective and safe for repeated use over time?. The Clinical Journal of Pain. 2005;21(6):543-8.
25. Tremblay S, Ranger M, Chau CMY, Ellegood J, Lerch JP, Holsti, et al. Repeated exposure to sucrose for procedural pain in mouse pups leads to long-term widespread brain alterations. PAIN. 2017;158(8):1586-1598.
26. Ranger M, Tremblay S, Chau CMY, Holsti L, Grunau RE, Goldowitz D. Adverse behavioral changes in adult mice following neonatal repeated exposure to pain and sucrose. Frontiers in Psychology. 2019;9:2394
27. Johnston CC, Filion F, Snider L, Majnemer A, Limperopoulos C, Walker CD, et al. Routine Sucrose Analgesia During the First Week of Life in Neonates Younger Than 31 Weeks' Postconceptional Age. Pediatrics. 2002;110(3):523-8.
28. Schneider, Juliane, Duerden, Emma G., Guo, Ting, Ng, Karin, Hagmann, Patric, Bickle Graz, Myriam, Grunau, Ruth E., Chakravarty, M. Mallar, Hüppi, Petra S., Truttmann, Anita C., Miller, Steven P. Procedural pain and oral glucose in preterm neonates: brain development and sex-specific effects. PAIN. 2018;159(3):p 515-525.
29. Selvanathan T, Zaki P, McLean MA, Au-Young SH, Chau CMY, Chau V, et al.. Early-life exposure to analgesia and 18-month neurodevelopmental outcomes in very preterm infants. Pediatric Research. 2023;94(2):738-746.
30. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
31. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
32. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
33. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
34. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
35. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
36. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
37. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
38. Pölkki T, Korhonen A, Laukkala H. Parents use of nonpharmacologic methods to manage procedural pain in infants. Journal of Obstetric, Gynecologic and Neonatal Nursing. 2018;47(1):43-51.
39. De Clifford-Faugère G, Aita M, Héon M, Le May S. Management of procedural pain in preterm infants through olfactive stimulation with mothers' milk: A pilot study. Science of Nursing and Health Practices. 2019;2(1):1–13.
40. Jyoti J, Spence K, Laing S, Griffiths N, Popat H. Parents awareness and use of nonpharmacological methods to manage their babys procedural pain in a surgical neonatal intensive care unit. Journal of Neonatal Nursing. 2023; 29(1):60-67.
41. Gale G, Franck LS, Kools S, Lynch M. Parents' perceptions of their infants pain experience in the NICU.International Journal of Nursing Studies. 2004;41(1):51-8.
42. Hassankhani H, Negarandeh R, Abbaszadeh M, Jabraeili M. The role of mothers during painful procedures on neonates: a focused ethnography. Journal of Neonatal Nursing. 2020;26(6):340-3.
43. Heaton P, Herd D, Fernando A. Pain relief for simple procedures in New Zealand neonatal units: practice change over six years. Journal of Paediatrics and Child Health. 2007;43(5):394-7
44. Paediatric Pain, Starship Child Health. Sucrose analgesia. 21 August 2023 [cited 2 February 2024]. Available from: https://starship.org.nz/guidelines/sucrose-analgesia/ .
45. McNair C, Campbell-Yeo M, Johnston C, Taddio A. Nonpharmacological management of pain during common needle puncture procedures in infants. Clinics in Perinatology; 2019;46(4):709-730.

Question 15.

Should a point-of-care testing method be used to diagnose hypoglycaemia in neonates ?	
POPULATION:	Neonates
INTERVENTION:	a point-of-care testing method
PURPOSE OF THE TEST:	Screening for neonatal hypoglycaemia
LINKED TREATMENTS:	Milk feedings (either breastmilk or breastmilk substitute); buccal dextrose gel; glucagon; intravenous glucose
ANTICIPATED OUTCOMES:	Critical outcomes True positive True negative False positive False negative
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendations
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* The difficulty with detecting hypoglycaemic episodes is that they are usually asymptomatic or babies may have non-specific signs, so regular blood testing to measure glucose concentrations is recommended, particularly for at-risk babies. While laboratory methods are the diagnostic standard and have a high degree of accuracy, the requirement to send blood to the lab and wait for the results means that there can be delays in providing timely treatment for low blood glucose concentrations. Point-of-care (also called cot-side) testing methods allow for rapid results and immediate management decisions, but concerns have been raised about their inaccuracies, leading to missed cases where hypoglycaemia remains undetected, or unnecessary treatment of those with normal blood glucose concentrations (1).

	There are a number of different types of point-of-care devices and they use several different methods for detecting glucose concentrations. We have grouped studies together based on the modality of each device (reaction enzyme used, photometric or electrochemical measurement). These are (the devices currently used in Aotearoa New Zealand are bolded): Enzymatic (glucose oxidase, GO) + photometry: Reflotest, BM-Reflolux, Reflolux II, Accu-chek III, One Touch II, Ames Glucometer, SureStep, **Dextrostix** Enzymatic (glucose dehydrogenase, GDH) + photometry: **HemoCue; Accu-chek Active** Enzymatic (GO) + electrochemistry: **Elite XL** , Precision PCx , ABL 735, EasyGluco, GlucoTest Plus, StatStrip, **iSTAT, Freestyle NeoH** Enzymatic (GDH) + electrochemistry: Advantage Boeh , Accu-chek Advantage, Accu-chek Inform, Precision Xceed, Precision Xceed Pro, Optium Xceed, Contour, Accu-chek Aviva Nano, Accu-chek Performa Enzymatic (hexokinase): Encore QA+, **ABL 800** These are metrics commonly used in medical diagnostics and binary classification tasks to evaluate the performance of a model or a test. 1. Sensitivity (True Positive Rate): Sensitivity measures the proportion of actual positive cases that are correctly identified by a diagnostic test or a model. Sensitivity = True Positives / (True Positives + False Negatives) 2. Specificity (True Negative Rate): Specificity measures the proportion of actual negative cases that are correctly identified by a diagnostic test or a model. Specificity = True Negatives / (True Negatives + False Positives) 3. Positive Predictive Value (PPV): PPV measures the probability that subjects with a positive test result truly have the disease. PPV = True Positives / (True Positives + False Positive) 4. Negative Predictive Value (NPV): NPV measures the probability that subjects with a negative test result truly don't have the disease. NPV = True Negatives / (True Negatives + False Negatives) 5. Accuracy: Accuracy measures the overall correctness of the diagnostic test or model across all classes. Accuracy = (True Positives + True Negatives) / (True Positives + True Negatives + False Positives + False Negatives)
CONFLICT OF INTERESTS:	CC, DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Test accuracy How accurate is the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ Varies ○ Don't know	**Different point-of-care testing methods have different sensitivities and specificities for detecting hypoglycaemia in at-risk babies (2).** **Enzymatic (GO) + photometry (Dextrostix)** Low sensitivity:0.72 (95% CI: 0.64 to 0.76)| High specificity:0.95 (95% CI: 0.87 to 0.98) **Enzymatic (GDH) + photometry (HemoCue, Accu-chek Active)** Low sensitivity:0.64 (95% CI: 0.13 to 0.95)| High specificity:0.99 (95% CI: 0.88 to 1.00) **Enzymatic (GO) + electrochemistry (Elite XL, iSTAT, Freestyle NeoH)** Moderate to high sensitivity:0.82 (95% CI: 0.70 to 0.89)| High specificity:0.94 (95% CI: 0.83 to 0.98) **Enzymatic (GDH) + electrochemistry (Optium Xceed, Accu-chek Advantage)** Moderate to high sensitivity: 0.81 (95% CI: 0.62 to 0.91)| High specificity:0.96 (95% CI: 0.88 to 0.99) **Enzymatic (hexokinase) (ABL 800)** Moderate to high sensitivity: 0.84 (95% CI: 0.73 to 0.91) | High specificity: 0.93 (95% CI: 0.88 to 0.96) **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Threshold (mmol/L) to classify positive or negative results: **Enzymatic (GO) + photometry:** 7 studies used 2.2, 1 study used 2.1, 1 study 2.0 and 1 study used 1.9 **Enzymatic (GDH) + photometry:** 4 studies used 2.5/2.6, 2 studies used 2.2, and 1 study used 2.0 **Enzymatic (GO) + electrochemistry:** 8 studies used 2.5/2.6, 4 studies used 2.2/2.1, and 1 study used 2.0 **Enzymatic (GDH) + electrochemistry:** 10 studies used 2.5/2.6, 2 studies used 2.2 **Enzymatic (hexokinase):** 2 studies used 2.6
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We assumed a pre-test probability (prevalence) of 50% in at-risk babies (4). Among 1000 at-risk babies, of whom 500 babies (50%) will develop hypoglycaemia and 500 will not, using the following point-of-care testing methods: **Enzymatic (GO) + photometry (Dextrostix)** 360 (320 to 380) babies with hypoglycaemia will be correctly identified; 475 (435 to 490) babies without hypoglycaemia will be correctly identified. **Enzymatic (GDH) + photometry (HemoCue, Accu-chek Active)** 320 (65 to 475) babies with hypoglycaemia will be correctly identified; 495 (440 to 500) babies without hypoglycaemia will be correctly identified. **Enzymatic (GO) + electrochemistry (Elite XL, iSTAT, Freestyle NeoH)** 410 (350 to 445) babies with hypoglycaemia will be correctly identified;	Babies with positive results will usually be treated and undergo further testing. For babies with negative results, testing may cease, alleviating any burden for the baby and whānau/family and reducing the use of resources (3).

	470 (415 to 490) babies without hypoglycaemia will be correctly identified. **Enzymatic (GDH) + electrochemistry (Optium Xceed, Accu-chek Advantage)** 405 (310 to 455) babies with hypoglycaemia will be correctly identified; 480 (440 to 495) babies without hypoglycaemia will be correctly identified. **Enzymatic (hexokinase) (ABL 800)** 420 (365 to 455) babies with hypoglycaemia will be correctly identified; 465 (440 to 480) babies without hypoglycaemia will be correctly identified. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We assumed a pre-test probability (prevalence) of 50% in at-risk babies (4), among 1000 at-risk babies, of whom 500 babies (50%) will develop hypoglycaemia and 500 will not, using the following point-of-care testing methods: **Enzymatic (GO) + photometry (Dextrostix)** 140 (120 to 180) babies with hypoglycaemia will be incorrectly classified as not having hypoglycaemia; 25 (10 to 65) babies without hypoglycaemia will be incorrectly classified as having hypoglycaemia . **Enzymatic (GDH) + photometry (HemoCue, Accu-chek Active)** 320 (65 to 475) babies with hypoglycaemia will be incorrectly classified as not having hypoglycaemia; 5 (0 to 60) babies without hypoglycaemia will be incorrectly classified as having hypoglycaemia. **Enzymatic (GO) + electrochemistry (Elite XL, iSTAT, Freestyle NeoH)** 90 (55 to 145) babies with hypoglycaemia will be incorrectly classified as not having hypoglycaemia; 25 (10 to 85) babies without hypoglycaemia will be incorrectly classified as having hypoglycaemia.	Babies incorrectly classified as having hypoglycaemia will potentially undergo unnecessary treatment and additional testing. This places an unnecessary burden on the whānau/family in terms of both time and anxiety. Moreover, it entails the wasteful expenditure of time and resources. Babies with hypoglycaemia incorrectly classified as not having hypoglycaemia may not be treated promptly, and in severe cases this may result in neurological complications (5). Testing may not be continued so that delayed or prolonged hypoglycaemia may not be detected.

	Enzymatic (GDH) + electrochemistry (Optium Xceed, Accu-chek Advantage) 90 (55 to 150) babies with hypoglycaemia will be incorrectly classified as not having hypoglycaemia; 30 (10 to 85) babies without hypoglycaemia will be incorrectly classified as having hypoglycaemia. **Enzymatic (hexokinase) (ABL 800)** 80 (45 to 135) babies with hypoglycaemia will be incorrectly classified as not having hypoglycaemia; 35 (20 to 60) babies without hypoglycaemia will be incorrectly classified as having hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low
○ Low
○ Moderate
○ High
○ No included studies

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence50%		
Enzymatic (GO) + photometry: Pooled sensitivity:0.72 (95% CI: 0.64 to 0.76)| **Pooled specificity**:0.95 (95% CI: 0.87 to 0.98)			
True positives	**360** (320 to 380)	3614 (10)	⊕⊕⊕◯ Moderate[a]
False negatives	**140** (120 to 180)		
True negatives	**475** (435 to 490)	3614 (10)	⊕⊕◯◯ Low[a,b]
False positives	**25** (10 to 65)		
Enzymatic (GDH) + photometry: Pooled sensitivity:0.64 (95% CI: 0.13 to 0.95)| **Pooled specificity**:0.99 (95% CI: 0.88 to 1.00)			
True positives	**320** (65 to 475)	952 (6)	⊕◯◯◯ Very low[b,c]
False negatives	**180** (25 to 435)		
True negatives	**495** (440 to 500)	952 (6)	⊕⊕⊕⊕ High
False positives	**5** (0 to 60)		
Enzymatic (GO) + electrochemistry: Pooled sensitivity:0.82 (95% CI: 0.70 to 0.89)|**Pooled specificity**:0.94 (95% CI: 0.83 to 0.98)			
True positives	**410** (350 to 445)	5791 (14)	⊕⊕⊕◯ Moderate[b]
False negatives	**90** (55 to 150)		
True negatives	**470** (415 to 490)	5791 (14)	⊕⊕⊕◯ Moderate[b]
False positives	**30** (10 to 85)		
Enzymatic (GDH) + electrochemistry: Pooled sensitivity:0.81 (95% CI: 0.62 to 0.91)|**Pooled specificity**:0.96 (95% CI: 0.88 to 0.99)			
True positives	**405** (310 to 455)	3862 (12)	⊕◯◯◯ Very low[a,b,d]
False negatives	**95** (45 to 190)		
True negatives	**480** (440 to 495)	3862 (12)	⊕⊕◯◯ Low[a,b]
False positives	**20** (5 to 60)		
Enzymatic (hexokinase): Pooled sensitivity: 0.84 (95% CI: 0.73 to 0.91) |**Pooled specificity**: 0.93 (95% CI: 0.88 to 0.96)			
True positives	420 (365 to 455)	201 (2)	⊕⊕⊕◯ Moderate[a]
False negatives	80 (45 to 135)		
True negatives	465 (440 to 480)	201 (2)	⊕⊕⊕◯ Moderate[a]
False positives	35 (20 to 60)		

CI: confidence interval. ***Explanations:*** a. Downgraded one level of risk of bias due to overall unclear risk of bias. b. Downgraded one

	Considerations for Māori No additional evidence available **Considerations for Pacific** No additional evidence available	

Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We did not find any research evaluating the direct impact of tests on outcomes for babies.	The mean number of blood glucose tests was 6.0 in at-risk babies who did not have hypoglycaemia, 7.0 in babies with an initial measurement below the threshold, and 11.1 in babies whose first measurement was above the threshold but who had a subsequent measurement below the threshold (3). Inaccurate measurement was cited as a contributing factor in almost all cases of litigation related to neonatal hypoglycaemia in the UK (6).

Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No direct evidence was found.	In otherwise healthy newborn babies with asymptomatic moderate hypoglycaemia, using a lower glucose treatment threshold (1.9 mmol/L) was found to be as effective as a conventional threshold (2.6mmol/L) in terms of psychomotor development at 18 months (7).

Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No direct evidence was found.	
Certainty of effects What is the overall certainty of the evidence of effects of the test?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	We are reasonably confident about the effects of the test, as these are routine practices throughout Aotearoa New Zealand. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty	Increased accuracy is associated with a decreased number of tests because if testing methods are known to be inaccurate, it is usual to recommend that any positive test (i.e. blood glucose concentration measured below the threshold) is repeated using a more accurate laboratory method (3). In the Whānau Experiences study (8) of whānau/families with diverse cultural backgrounds including Māori, Pacific and Asian ethnicities (studied because these groups have a higher likelihood of having a baby born at risk of neonatal hypoglycaemia), some parents reported	

or variability	negative views about blood testing, including being distressed by multiple testing, seeing their small child hurt, and not being offered the chance to help. *Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention	A guideline panel needs to evaluate whether the benefits of a correct classification (True Positive and True Negative) outweigh the potential harms of an incorrect classification (False Positive and False Negative). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

○ Varies ○ Don't know		
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost usually includes cost of inital decice, supplies and staff timing. Cost data were available from a study of babies at risk of hypoglycaemia who had blood glucose concentrations measured 1 hour after birth, then every 3–4 hours before feeds for the first 24 hours, and every 6–8 hours for the subsequent 24 hours. The authors reported that screening using an enzymatic + electrochemical glucometer (i-STAT) cost NZ$86.94, whereas using a photometric glucometer (Accu-CHEK, HemoCue) with positive tests repeated cost NZ$97.08 per baby in 2016/2017 (3).	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	High certainty about the cost of nzymatic + electrochemical glucometer (i-STAT) and a photometric glucometer (Accu-CHEK, HemoCue).	
Cost effectiveness		

Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The cost-effectiveness analyses showed that using an enzymatic + electrochemical glucometer is cost-saving with wide variations in staff time and costs, irrespective of the false-positive level of photometric glucometers, and where ≥78% of low values are laboratory confirmed. Where photometric glucometers may be less costly (e.g., a false-negative rate exceeding 15%), instances of hypoglycaemia will be missed (3).	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?***	

	Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%) (10*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (4*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (4*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (8*), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (11, 12, 13). *Additionally, a systematic literature review by Graham et al.* (14*) provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (14*).* ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (8*).* ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (9*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist*	

	services. In the 2014 Maternity Consumer Survey, (9)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	A national survey (15) of directors/managers of neonatal units, midwives, registered nurses, and neonatal/paediatric consultants (n=84) spanned all district health boards (DHBs) in Aotearoa New Zealand except Te Whatu Ora Whanganui. Respondents were asked which device they preferred for neonatal blood glucose testing. The majority of midwives preferred iStat (7/24), Blood gas analsyer (5/24) and Accuchek (4/24). The majority of doctors preferred blood gas analyser (8/16) followed by iSTAT (5/16). Managers of care units preferred iStat (6/19), Blood gas analsyer (5/19) and Accuchek (5/19). Lead maternity carer (LMC) midwives mainly preferred iSTAT (4/8). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Point-of-care devices are readily accessible throughout Aotearoa New Zealand. A national survey in Aotearoa New Zealand (15), encompassing directors/managers of neonatal units, midwives, registered nurses, and neonatal/paediatric consultants (n=84), spanned all DHBs except Te Whatu Ora Whanganui. Nearly all respondents (69 out of 70) indicated that capillary heel-prick blood sampling was their preferred method for screening neonates for hypoglycaemia. The technique for analysing capillary blood samples were blood gas analyser (19/59), Accu-chek (10/59), i-STAT (9/58), HemoCue (10/59), FreeStyle NeoH (3/59), Dextrostix (1/59), lab analysis (unknown instrument) (4/59)	

	Considerations for Māori No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	Low	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			No included studies
CERTAINTY OF EFFECTS	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know

RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Sirkin A, Jalloh T, Lee L. Selecting an accurate point-of-care testing system: clinical and technical issues and implications in neonatal blood glucose monitoring. Journal for Specialists in Pediatric Nursing. 2002;7(3):104-12.
2. St Clair S, Ulyatt C, Harding J, Crowther C, Lin L. Glucose testing methods: A systematic review and meta-analysis of diagnostic accuracy of point-of-care devices for neonatal hypoglycaemia. Unpublished. 2024.
3. Glasgow MJ, Harding JE, Edlin R; for the CHYLD Study Team. Cost analysis of cot-Side screening methods for neonatal hypoglycaemia. Neonatology. 2018;114(2):155-162.
4. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
5. Shah R, Harding J, Brown J, McKinlay C. Neonatal glycaemia and neurodevelopmental outcomes: a systematic review and meta-analysis. Neonatology. 2019;115(2):116-126
6. Hawdon, Jane M., Beer, Jeanette, Sharp, Deborah, Upton, Michele. Neonatal hypoglycaemia: learning from claims.Archives of Disease in Childhood. Fetal and Neonatal Edition; 2017.
7. van Kempen AA, Ackermans MT, Endert E, Kok JH, Sauerwein HP. Glucose production in response to glucagon is comparable in preterm AGA and SGA infants. Clinical Nutrition. 2005;24(5):727-36.
8. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
9. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]. Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
10. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
11. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
12. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
13. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
14. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.

15. Ulyatt C, Harding JE, Alsweiler J, Clapham V, Lin L. Current practice for testing for neonatal hypoglycaemia in Aotearoa New Zealand care settings. Unpublished. 2024.

Question 16.

Should higher or lower blood glucose concentrations vs. blood glucose concentration of 2.6 mmol/L be used for defining of neonatal hypoglycaemia?	
POPULATION:	Newborn babies
INTERVENTION:	higher or lower blood glucose concentrations
COMPARISON:	blood glucose concentration of 2.6 mmol/L
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment

SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* However, the definition of neonatal hypoglycaemia remains controversial and has changed over time (1). Recommended thresholds for defining hypoglycaemia in published guidance vary between 2.0 and 4.0 mmol/L. The most common threshold in primary studies was 2.6 mmol/L (2).
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are all authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Lower threshold** Would result in fewer babies being identified as having hypoglycaemia and therefore being treated and having further testing. This would potentially: • reduce testing • avoid overtreatment, including NICU admission [critical] • increase breastfeeding [critical] In a single randomised controlled trial (RCT) conducted in the Netherlands (3), 689 at-risk babies ≥35 weeks' gestation with asymptomatic moderate hypoglycaemia (blood glucose 1.9 to <2.6 mmol/L) at 3–24 hours of age were randomised to treatment to maintain glucose concentrations of ≥2.0 mmol/L (intervention group) or ≥2.6 mmol/L. They found little to no difference in: • Neurodevelopmental impairment at ≥18 months of age [critical] • Bayley cognitive or motor scores at ≥18 months of age • Duration of initial hospital stay [important]	**Reasons for threshold of 2.6mmol/L:** There are at least three methods for determining an appropriate threshold for identifying neonatal hypoglycaemia. One is the statistical approach, which defines hypoglycaemia as a blood or plasma glucose level that is more than two standard deviations below the mean in healthy low-risk babies, i.e., below the 95th centile. In the GLOW study, a prospective observational study of healthy-term appropriate-for-gestational age babies, the mean glucose concentrations rose throughout the first 18 hours, remained stable to 48 hours (3.3 ± 0.6 mmol/L), and then rose to a new plateau after 72 hours (4.6 ± 0.7 mmol/L). In this study, a blood glucose

- Cost [important]

There were no data for admission to special care nursery or neonatal intensive care nursery, fully breastfeeding at hospital discharge, separation from the mother for treatment of hypoglycaemia before discharge home, hypoglycaemic injury on brain imaging, time to blood glucose normalisation after intervention, receipt of treatment for hypoglycaemia during initial hospital stay, number of episodes of hypoglycaemia, breastmilk feeding exclusively from birth to hospital discharge, or duration of treatment.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 2.6 mmol/L blood glucose concentrations	Risk difference with lower blood glucose concentrations
Neurodevelopment impairment at ≥18 months	582 (1 RCT)	⨁⨁◯◯ Low[a,b]	-	No differences between groups of the neurodevelopment impairment at ≥18 months measured by either Bayley cognitive scores or motors < -2 standard deviation.	
Admission to special care nursery or neonatal intensive care nursery - not measured	-	-	-	-	-
Fully breastfeeding at hospital discharge - not measured	-	-	-	-	-
Separation from the mother for treatment of hypoglycaemia before discharge home - not measured	-	-	-	-	-

concentration <2.6 mmol/L was approximately the 10th percentile from 2 hours to 48 hours of age (8).

The second approach to defining neonatal hypoglycaemia is to consider the glucose concentration at which there is evidence of triggering counter-regulatory mechanisms or the neurophysiological definition.

Koh 1988 measured evoked potentials (electrical potentials produced after stimulation of specific neural tracts) during hypoglycaemia in 17 babies (only 5 were neonates) and found that abnormal sensory evoked potentials occurred only in those with blood glucose concentrations <2.6 mmol/L, although this did not occur in all babies. Importantly, recovery of evoked potentials took up to 24 hours in the neonates (9).

Pryds 1990 found that when blood glucose concentrations were <1.7 to 2.5 mmol/L in babies <34 weeks of gestational age (n = 25, mean gestational age 30.4 weeks), cerebral blood flow and plasma epinephrine concentrations increased (10).

A third approach to defining neonatal hypoglycaemia is to determine the glucose concentration below which there is evidence of brain injury.

Lucas 1988 studied 661 preterm babies <1850g birthweight and examined the relationship between developmental scores at 18 months and the number of days on which blood glucose was measured below concentrations varying from 0.4 to 4 mmol/L. They reported that the strongest association was seen using a cut-off of <2.5 mmol/L, i.e., babies who had blood glucose concentrations <2.5 mmol/L on more days had

Hypoglycaemic injury on brain imaging - not measured	-	-	-	-	-
Breastmilk feeding exclusively from birth to hospital discharge - not measured	-	-	-	-	-
Duration of initial hospital stay	686 (1 RCT)	⊕⊕◯◯ Low[a,b]	-	The mean duration of initial hospital stay was **4.7** days	MD **0.1 days lower** (0.6 lower to 0.4 higher)
Cost	686 (1 RCT)	⊕⊕◯◯ Low[a,b]	-	No differences between groups on the cost of hospital stay for the babies and the costs after the neonatal period.	

a.Downgraded one level for serious risk of bias due to lack of blinding.
b.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
*Absolute effects were calculated based on the control group risk

A retrospective cohort study conducted in Ottawa, Canada including 10,965 babies consistently observed decreases in the initial rate of exclusive breastfeeding with hypoglycaemia screening (4).
Using data from the Sugar Babies study (5), which focused on babies at risk of hypoglycaemia, it was estimated that reducing the blood glucose concentration threshold to 1.94 mmol/L would decrease the incidence of hypoglycaemia from 52% to 13% and the cost of screening using a non-enzymatic glucometer from NZ $97.08 to NZ $47.71 (6).

Higher threshold
Would result in more babies being identified as having hypoglycaemia and therefore being treated and having further testing. This would potentially lead to:

lower developmental scores. Abnormalities in arithmetic and motor scores persisted at 8 years (11).
An Aotearoa New Zealand prospective cohort study (CHYLD) of children at risk of hypoglycaemia found that children who had experienced blood glucose concentrations <2.6 mmol/L (n = 477, 38% Māori, 4% Pacific) had poorer scores on executive function and visual-motor function at 4.5 years (12), but not 2 years, with worse scores if the hypoglycaemia was recurrent or severe (<2.0 mmol/L) (13). There were no differences in school achievement between those who did and did not have glucose concentrations <2.6 mmol/L at 9–10 years (n = 480, 31% Māori, 2% Pacific) (14), but there were small differences in specific aspects of executive function, behaviour and brain imaging (15)(16).
All babies were screened and treated with the intention of maintaining blood glucose concentrations >2.6 mmol/L.
Lower Threshold
In the RCT of lower versus higher thresholds (3), babies randomised to the lower threshold group experienced a large decrease in receipt of IV dextrose: 21/348 (6%) vs. 70/341 (21%), mean difference -14.5% (-19.5 to -9.5) (146 fewer per 1,000), and a large decrease in supplemental oral feeding, although the rate of supplemental feeding was high in both groups: 275/348 (79%) vs. 332/341 (97%), mean difference -18.3% (-23.1 to -13.8) (185 per 1000). The number of babies who needed to be treated to prevent one instance of intravenous glucose administration was 7, to prevent one instance of tube feeding was 12, and to prevent one instance of

	• fewer recurrent and severe episodes of hypoglycaemia • better long-term neurological outcomes for some babies [critical] **Consideration for Māori** Using a threshold of 2.6 mmol/L for neonatal hypoglycaemia, the Sugar Babies study (7) reported that the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%). **Consideration for Pacific** Using a threshold of 2.6 mmol/L for neonatal hypoglycaemia, the Sugar Babies study (7) reported that the proportion of babies who developed hypoglycaemia was similar in Pacific babies (6/16, 38%) to that in the whole cohort (260/514, 51%).	supplemental oral feeding was 5. The duration of breastfeeding was similar in both groups. Babies randomised to the lower threshold group also had a small decrease in the number of glucose measurements, mean 6.4 (SE 0.1), n = 345 vs. 7.0 (0.2), n = 337, mean difference -0.7 (-1.0 to -0.3). These numbers are similar to those found in a single study conducted in Aotearoa New Zealand (n = 481, 31% Māori), where the mean number of blood glucose tests was 6.0 in at-risk babies who did not have hypoglycaemia, 7.0 in babies with an initial measurement below the threshold, and 11.1 in babies whose first measurement was above the threshold but who had a subsequent measurement below the threshold (6). **Higher Threshold** No additional studies
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Lower Threshold** May result in: • Some at-risk babies not being identified • Delayed diagnosis and treatment • More recurrent or severe episodes of hypoglycaemia • Increased risk of neurological complications [critical] In the RCT (3) there were two serious adverse effects [critical]; one convulsions and one death, both in the lower threshold group and considered not likely related to treatment. Severity of hypoglycaemia [less important]—more in lower threshold group Lower threshold results in:	**Lower Threshold** In the RCT (3) the low threshold group had a large increase in episodes of hypoglycaemia (<2.6 mmol/L) (57% vs. 47%, mean difference 10%, 95% CI 2-17) (225 more per 1,000) . **Higher Threshold** No additional studies

- Large increase in moderate hypoglycaemia (104 more per 1,000) [critical]
- Moderate increase in severe hypoglycaemia (46 more per 1,000) [critical]
- Uncertain effect on serious adverse effects [critical]; both in the lower threshold group (1 convulsions and 1 death) and considered not likely related to treatment.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with blood glucose concentration of 2.6 mmol/L	Risk difference with lower blood glucose concentrations
Adverse effects-serious	689 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 4.93** (0.24 to 103.02)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Adverse effects - severe hypoglycaemia (< 2.0 mmol/L)	689 (1 RCT)	⨁⨁⨁◯ Moderate[a]	**RR 1.88** (1.04 to 3.41)	Study population	
				53 per 1,000	**46 more per 1,000** (2 more to 127 more)
Adverse effect-moderate hypoglycaemia (2.0-2.6mmol/L)	689 (1 RCT)	⨁⨁◯◯ Low[a,c]	**RR 1.25** (0.92 to 1.69)	Study population	
				416 per 1,000	**104 more per 1,000** (33 fewer to 287 more)

a.Downgraded one level for serious risk of bias due to lack of blinding.
b.Downgraded two levels for serious imprecision due to wide confidence intervals and zero events in the control group.
c.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
*Absolute effects were calculated based on the control group risk

	Higher Threshold Would result in more babies being identified as having hypoglycaemia and therefore being treated and having further testing. This would potentially lead to: • increased testing • increased treatment • more NICU admission, formula use • decrease in the initial rate of exclusive breastfeeding **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence is mostly based on observational studies and expert opinions. While there was one high-quality randomised trial examining different treatment thresholds (3), the developmental outcomes in this study were assessed at 18 months of age. However, cognitive and social functioning problems that have been associated with neonatal hypoglycaemia typically emerge in later developmental stages than this age. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	In the Whānau Experiences study (17) of whānau/families with diverse cultural backgrounds including Māori, Pacific and Asian ethnicities (studied because these groups have a higher likelihood of having a baby born at risk of neonatal hypoglycaemia), some parents reported negative views about blood testing, including being distressed by multiple testing, seeing their small child hurt, and not being offered the chance to help. **Consideration for Māori** Whānau Māori want the very best health outcomes for their pēpi. Whānau felt empowered and disempowered by the healthcare team, and the health system, when health provision happened to them, rather than with them (e.g., testing). Whānau shared experiences of healthcare delivery that occurred without explanation, resulting in disempowerment, and others asked questions to enable enactment of mana motuhake, especially around tikanga. **Consideration for Pacific** Some Pacific mothers also felt very distressed when their baby had to be tested multiple times.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Lower threshold** compared to 2.6 mmol/L: Very low certainty evidence showed: • Little to no effect on neurodevelopmental impairment at ≥18 months of age [critical], duration of initial hospital stay [important], cost [important]. • Large increase in moderate hypoglycaemia • Moderate increase in severe hypoglycaemia • Uncertain effect on serious adverse effects [critical] **Higher threshold** compared to 2.6 mmol/L: No additional studies. **Considerations for Māori** Limited evidence suggests that the effects are similar for Māori babies. **Considerations or Pacific** No specific evidence about the effects on Pacific babies, but the baseline risk is likely to be similar to other babies studied.	**Lower threshold** compared to 2.6 mmol/L: May result in • a large decrease in receipt of IV dextrose • a large decrease in supplemental oral feeding, although the rate of supplemental feeding was high in both groups • small decrease in the number of glucose measurements Operational thresholds should be set at a level that is intended to achieve the best balance of benefits for the least harm for all babies, even if only a proportion of them would be at risk below this level since it is currently not possible to identify individual risk. In addition, operational thresholds need to include a "margin of safety", to allow for intervention to prevent glucose concentrations falling to a potentially brain-threatening level. The need for this margin of safety was demonstrated in data from the CHYLD study (13). Despite all babies being screened and treated to maintain blood glucose concentrations ≥2.6 mmol/L, 24% had glucose concentrations below this level that were not detected by routine blood glucose measurements, and 25% of those treated for hypoglycaemia had glucose concentrations <2.6 mmol/L for >5 hours in the first 48 hours.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	Cost: Screening using an enzymatic glucometer cost NZ$86.94 (US $63.47) (6). Costs of treatment for a baby with hypoglycaemia estimated at NZ $7-8,000 Time: Staff time for testing with an enzymatic glucometer is around 6 to 8 minutes. Additional time is needed for informing the family, preparing the meter, and documenting the results. **Lower Threshold:** In the randomised trial, reducing the intervention threshold to 2.0 mmol/L meant the number of newborns that needed to be treated to prevent one instance of intravenous glucose administration was 7, and the number needing to be treated to prevent one instance of tube feeding was 12 (3). Reducing the blood glucose concentration threshold to 1.94 mmol/L was estimated to decrease the incidence of hypoglycaemia from 52% to 13%. Additionally, the cost of screening decreased from NZ $87-97 to NZ $48-87 per baby (6). These are likely to result in substantial cost savings.	

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not do a systematic search for evidence about resource requirements.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	We did not do a systematic search for evidence about cost-effectiveness.	
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	A consistent definition of neonatal hypoglycaemia can improve equity by ensuring fair and equal access to diagnosis, treatment, and care for all babies. This consistency helps to minimise potential biases or disparities that may arise from different interpretations or thresholds used by different healthcare professionals or institutions. ***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism,*	

	income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions. ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (19*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (7*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (19*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (7*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (19*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (17*), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (20, 21, 22). *Additionally, a systematic literature review by Graham et al.* (23*) provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (23). ***Consideration for Pacific***	

	Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work (17). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (18*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (18*), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We found no evidence about acceptability to whānau/families. A survey conducted within Australia and Aotearoa New Zealand Neonatal Network in 2014 showed that doctors were consistent about the definition of neonatal hypoglycaemia and would treat babies with a blood glucose level <2.6 mmol/L (24). A more recent review of guidelines for the management of neonatal hypoglycaemia in 9 Aotearoa New Zealand and 9 Australian hospitals from 2015–19 reported that 11 of the 12 Aotearoa New Zealand guidelines used a definition of <2.6 mmol/L, as did 4 of the 7 Australian guidelines. The other 4 guidelines used <2.0 mmol/L (2 guidelines), <2.1 mmol/L (1 guideline), and <2.2 mmol/L (1 guideline) (25). Thus, a threshold of 2.6 mmol/L or lower is likely to be acceptable to practitioners. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Since 11 out of the 12 Aotearoa New Zealand guidelines employed a definition of <2.6 mmol/L, it is feasible to use this definition (25). Considerations for Māori No additional evidence available Considerations for Pacific No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**

COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

REFERENCES SUMMARY

1. Tin W. Defining neonatal hypoglycaemia: a continuing debate. Seminars in Fetal and Neonatal Medicine. 2014;19(1):27-32
2. Horwitz J, Mardiros L, Musa A, Welch VA, Hodgson A, Narvey M, et al. Scoping review of evidence for managing postnatal hypoglycaemia. BMJ Open. 2022;12(2):e053047.
3. van Kempen AAMW, Eskes PF, Nuytemans DHGM, van der Lee JH, Dijksman LM, van Veenendaal NR, et al. Lower versus traditional treatment threshold for neonatal hypoglycemia. The New England Journal of Medicine. 2020;382(6):534-544.
4. Saginur M, Abdulnour J, Guérin E, Bancroft X, Corsi DJ, Zazzera VD, et al. Association between newborn hypoglycemia screening and breastfeeding success in an Ottawa, Ontario, hospital: a retrospective cohort study. CMAJ Open. 2023;11(2):E381-E388.
5. Harris DL, Weston PJ, Signal M, Chase JG, Harding JE. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. The Lancet. 2013;382(9910):2077-83.
6. Glasgow MJ, Harding JE, Edlin R; for the CHYLD Study Team. Cost analysis of cot-Side screening methods for neonatal hypoglycaemia. Neonatology. 2018;114(2):155-162.
7. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
8. Harris DL, Weston PJ, Harding JE. Relationships between feeding and glucose concentrations in healthy term infants during the first five days after birth—the Glucose in Well Babies Study (GLOW). Frontiers in Pediatrics; 2023;24;11:1147659.
9. Koh TH, Aynsley-Green A, Tarbit M, Eyre JA. Neural dysfunction during hypoglycaemia. Archives of Disease in Childhood. 1988;63(11):1353-8.
10. Pryds O, Christensen NJ, Friis-Hansen B. Increased cerebral blood flow and plasma epinephrine in hypoglycemic, preterm neonates. Pediatrics. 1990;85(2):172-6.
11. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycemia. The British Medical Journal. 1988;297(6659):1304-8.
12. McKinlay CJD, Alsweiler JM, Anstice NS, Burakevych N, Chakraborty A, Chase JG, et al. Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years. JAMA Pediatrics. 2017;171(10):972-983.
13. McKinlay CJ, Alsweiler JM, Ansell JM, Anstice NS, Chase JG, Gamble GD, et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. New England Journal of Medicine. 2015;373(16):1507-18.
14. Shah R, Dai DWT, Alsweiler JM, Brown GTL, Chase JG, Gamble GD, et al. Association of neonatal hypoglycemia with academic performance in mid-childhood. JAMA. 2022;327(12):1158-1170.
15. Dai DWT, Franke N, McKinlay CJD, Wouldes TA, Brown GTL, Shah R, et al. Executive function and behaviour problems in school-age children born at risk of neonatal hypoglycaemia. Developmental Medicine and Child Neurology. 2023;65(9):1226–1237.
16. Nivins S, Kennedy E, Thompson B, Gamble GD, Alsweiler JM, Metcalfe R, et al. Associations between neonatal hypoglycaemia and brain volumes, cortical thickness and white matter microstructure in mid-childhood: An MRI study. Neuroimage Clinical. 2022;33:102943.
17. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished. 2024.
18. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014

19. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
20. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
21. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
22. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
23. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
24. Harris DL, Weston PJ, Battin MR, Harding JE. A survey of the management of neonatal hypoglycaemia within the Australian and New Zealand Neonatal Network. Journal of Paediatrics and Child Health.2014;50(10):E55-62.
25. Rajay AB, Harding JE; hPOD Study Group. Variations in New Zealand and Australian guidelines for the management of neonatal hypoglycaemia: A secondary analysis from the hypoglycaemia Prevention with Oral Dextrose gel Trial (hPOD). Journal of Paediatrics and Child Health. 2022;58(5):820-829.

Question 17.

Should clinical observations vs. other/no clinical observations be used for monitoring babies with neonatal hypoglycaemia?	
POPULATION:	Babies with neonatal hypoglycaemia
INTERVENTION:	clinical observations
COMPARISON:	other/no clinical observations
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:**

	1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in babies over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* There are no evidence-based recommendations regarding whether clinical observations should be used for monitoring babies with neonatal hypoglycaemia.
CONFLICT OF INTERESTS:	JA, DH, JH, JR and LL are authors of a cited paper.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Symptomatic neonatal hypoglycaemia was associated with poorer neurodevelopmental outcomes compared to asymptomatic hypoglycaemia in a study of 110 hypoglycaemic neonates (1). At follow up when infants were at least 6 months of age, symptomatic infants were more likely to have cerebral palsy or cerebral palsy and epilepsy, compared to asymptomatic infants (21/42, 50% and 29/68, 42.5% respectively, p <0.05). Similarly, a study of 70 hypoglycaemic neonates found increased rates of neurological problems in those with symptomatic hypoglycaemia compared to those who were asymptomatic (2) followed up for a mean of 8.3 months.	According to Rozance and Hay, the signs and symptoms of neonatal hypoglycaemia are abnormal cry, poor feeding, hypothermia, diaphoresis, tremors and jitteriness, hypotonia, irritability, lethargy, seizures, cyanosis, pallor, tachypnoea, apnoea and cardiac arrest (5). However, these are non-specific and not present in all babies with hypoglycaemia, even when hypoglycaemia is severe (6).

	Seizures during symptomatic neonatal hypoglycaemia have been associated with poorer clinical outcomes at 5-7 years, although in this study only 8 hypoglycaemic infants had seizures (3). Another study found convulsions during neonatal hypoglycaemia were associated with poorer neurodevelopmental outcomes at 1-4 years, but the 8 babies who had convulsions were also diagnosed and treated later which may also contribute to poor neurodevelopmental outcomes (4). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	A study of 220 babies (32 hypoglycaemic) examined all the above signs and symptoms except for diaphoresis, lethargy, cyanosis, and cardiac arrest (7). They found that only jitteriness and tachypnoea were predictive of low blood glucose levels within 2 hours of birth. A study of 190 babies in rural India found that, of those with neonatal hypoglycaemia, only 5% of had seizures 35% were jittery, 30% had poor activity, 10% poor sucking and 15% poor crying (8). Another Indian study of 100 hypoglycaemic babies found that jitteriness, lethargy and cyanosis were the most common clinical signs (38%, 35%, 23% respectively) (9). Fewer than 10% of hypoglycaemic babies demonstrated hypotonia, apnoea, seizures or tachypnoea (9). In Aotearoa New Zealand, of 514 babies at risk of neonatal hypoglycaemia (150 Māori, 16 Pacific), 79% of those who developed hypoglycaemia had no clinical signs, 15% were too sleepy to feed and 7% were jittery (10). Of all hypoglycaemic episodes in this group, 81% occurred within the first 24 hours, with episodes continuing to at least 48 hours. This suggests that the first 48 hours may be an important window for monitoring babies for hypoglycaemia.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	The studies identified did not report on undesirable effects of monitoring infants for symptoms or seizures. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence is very low as it comes from observational studies with small sample sizes. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]*	

	• *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	Clinical observations to identify signs of hypoglycaemia may aid in detection and treatment, including in babies who are not considered at risk, and this may improve neurodevelopmental outcomes. There is no information about undesirable effects. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings	Clinical observations require staff time, depending on the specific observations and their frequency.	

● Varies ○ Don't know		
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not do a systematic search for evidence about resource requirements.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	Clinical observation of babies with neonatal hypoglycaemia will increase costs. However, recognising which babies have hypoglycaemia, and particularly severe hypoglycaemia, may allow treatment and improve neurodevelopmental outcomes and result in substantial cost savings. We found no evidence assessing this.	
Equity		

What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (13). *However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (10). *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (13). *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (10). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (13). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?***	

	Consideration for Māori *In the Whānau Experience study* (11)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions. Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (14)(15)(16)*. Additionally, a systematic literature review by Graham et al.* (17) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst Whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (17)*.* Whānau Māori requested that they be fully informed of what to expect following hypoglycaemia testing, and what follow-up they should receive, when they should receive follow up, and what both the short-term, medium-term, and long-term best practice monitoring plan is. Whānau Māori thought about the future, and any involvement in providing feedback was seen in a service mindset. ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (11)*.* ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (12)*. Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (12)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	A systematic search was not carried out for evidence investigating acceptability of clinical observations for babies with hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Regular clinical observation of newborn babies is recommended standard practice and therefore likely to be feasible in all newborn care settings, although increased frequency may require additional staffing resources. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	In Aotearoa New Zealand, the Newborn Observation Chart is used in many facilities to assess babies >35 weeks of gestational age in the first two hours and at 24 hours (18). It involves observing respiratory rate, work of breathing, temperature, heart rate, colour, behaviour and feeding. Monitoring for babies at risk of hypoglycaemia will involve making the same observations, but specifically looking for abnormal cries, tremors, jitteriness, hypotonia, irritability, lethargy and seizures when assessing behaviour. However, monitoring for hypoglycaemia would need to be done regularly over the first 24-48 hours, which would require increased staffing resources and is impossible in the home birth setting.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**

UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Caksen H, Güven AS, Yilmaz C, Unal O, Basaranoglu M, Sal E, et al. Clinical outcome and magnetic resonance imaging findings in infants with hypoglycemia. Journal of Child Neurology. 2011;26(1):25-30.
2. Gurbuz G, Gur S, Tufekci S, Halis H. A retrospective analysis of the neurological evaluation of cases with neonatal hypoglycemia. Cureus. 2022;14(11):e31088.
3. Pildes RS, Cornblath M, Warren I, Page-El E, Di Menza S, Merritt DM, et al. A prospective controlled study of neonatal hypoglycemia. Pediatrics. 1974;54(1):5-14.
4. Koivisto M, Blanco-Sequeiros M, Krause U. Neonatal symptomatic and asymptomatic hypoglycaemia: a follow-up study of 151 children. Developmental Medicine and Child Neurology. 1972;14(5):603-14.
5. Rozance PJ, Hay WW. Hypoglycemia in newborn infants: features associated with adverse outcomes. Biology of the Neonate. 2006;90(2):74-86.
6. Cowett RM, Loughead JL. Neonatal glucose metabolism: differential diagnoses, evaluation, and treatment of hypoglycemia. Neonatal Network. 2002;21(4):9-19..
7. Hoops D, Roberts P, Van Winkle E, Trauschke K, Mauton N, DeGhelder .. Should routine peripheral blood glucose testing be done for all newborns at birth?. The American Journal of Maternal/Child Nursing. 2010;35: 264-70.
8. Pillai SK, Fhausiya VK. A cross-sectional study on the frequency and risk factors for neonatal hypoglycemia in babies born in rural Kerala. Journal of Family Medicine and Primary Care. 2022;11(11):6949-6954.
9. Bhand SA, Sheikh F Siyal A, Nizamani M, Saeed M. Neonatal hypoglycemia: presenting pattern and risk factors of neonatal hypoglycemia. The Professional Medical Journal. 2014;21:04.
10. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
11. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished. 2024.
12. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
13. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
14. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
15. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
16. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
17. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
18. Auckland District Health Board, . Newborn assessment: observation chart and early warning score.2021.

Question 18.

Should continuous glucose monitoring vs. intermittent blood glucose testing be used for babies at risk of or diagnosed with neonatal hypoglycaemia?	
POPULATION:	Babies at risk of or diagnosed with neonatal hypoglycaemia
INTERVENTION:	continuous glucose monitoring
COMPARISON:	intermittent blood glucose testing

MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment at ≥18 months of age (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	All birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn infants over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Diagnosis and monitoring or treatment of neonatal hypoglycaemia routinely involve intermittent measurement of blood or plasma glucose concentrations. However, this is invasive, and the likelihood of detecting changes in glucose concentrations depends on the frequency of measurement, so rapid changes may be missed with infrequent testing. For adults and children, particularly those with diabetes, there are a range of continuous interstitial glucose monitoring devices available. These comprise of a filament sensor placed under the skin, which generates a small electric current by oxidation of glucose in the interstitial fluid when a voltage is applied. The current is recorded by a transmitter device on the skin and converted to a glucose concentration using the algorithm built into each device. The glucose concentration is then displayed in real time on a nearby monitor. Measurements are usually averaged every 5 minutes to give 12 “continuous” readings each hour, or 288 each day. The devices can be set to trigger an alarm when the measured glucose concentration is outside the target range set. The sensors can remain in place for 5–14 days,

	depending on the device, but most need calibration with blood glucose measurements every 12 hours. No commercially available devices have regulatory approval for children younger than two years.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are all authors of cited papers.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	We found no studies of the use of continuous glucose monitoring (CGM) in babies already diagnosed with hypoglycaemia. Continuous glucose monitoring compared to intermittent blood glucose testing in very preterm or very low birthweight (VLBW) babies results in (1) • Little to no effect on hypoglycaemia episode [critical] and duration of initial hospital stay [important] • No studies reported on the other critical or important outcomes.	In one of the RCTs contributing to this review (2), there were fewer hypoglycaemic events in the CGM group (1.4 ±2 vs 4.7 ± 6.2 events per subject, P = .01, MD −3.30, 95% CI −5.85 to −0.75; 1 study, 50 participants). In the other RCT in this review (3) there were fewer events in the control group (MD 0.80, 95% CI 0.62 to 0.98; 1 study, 48 participants). In an RCT (2) of 50 preterm babies (<= 32 weeks or <1500g), babies randomised to CGM compared to those randomised to blinded CGM (not available to clinicians) spent more time in the euglycaemic range (4–8 mmol/L) (median 84% vs 68%, *P* <.001) and less time in the "severe" (<2.6 mmol/L) hypoglycaemia range (0.6% (95% CI, 0.3 to 1.4) vs 2.2% (95% CI, 1.4 to 3.3), P = .007) and with severe hyperglycaemia (>10 mmol/L, 0.0% (IQR 0.0 to 0.3) vs 0.3% (IQR 0.0 to 1.6), P =.14). The CGM

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with intermittent blood glucose testing	Risk difference with continuous glucose monitoring
Hypoglycaemia episode [critical]	200 (2 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 1.02** (0.49 to 2.12)	Study population	
				124 per 1,000	**2 more per 1,000** (63 fewer to 139 more)
Neurodevelopmental impairment [critical] - not measured	-	-	-	-	-

Admission to special care nursery or neonatal intensive care nursery [critical] - not measured	-	-	-	-	-	
Fully breastfeeding at hospital discharge [critical] - not measured	-	-	-	-	-	
Separation from the mother for treatment of hypoglycaemia before discharge home [important] - not measured	-	-	-	-	-	
Hypoglycaemic injury on brain imaging [important] - not measured	-	-	-	-	-	
Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	-	-	-	-	-	
Duration of initial hospital stay	50 (1 RCT)	⨁◯◯◯ Very low[a,c]	-	The median duration was 46 days (interquartile range 40 to 74) in the CGM group and 51 days (37 to 63) in the control group (P = 0.59).		
Cost - not measured	-	-	-	-	-	

a.Downgraded one level for serious risk of bias due to moderate to low quality of the included studies (study).
b.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
c.Downgraded two levels for very serious imprecision due to small sample size.

Considerations for Māori
No additional evidence available
Considerations for Pacific
No additional evidence available

group also had decreased glycaemic variability (SD: 1.2 ± 0.3 vs 1.5 ± 0.4 mmol/L, *P* =.01; coefficient of variation: 22.8% ± 4.2% vs 27.9% ± 5.0%; *P* <.001).

In an RCT (3) of 43 very low birth weight preterm babies (<=1500g), the number of blood samples per baby was lower in the CGM group (16.9 ± 1.0 vs 21.9 ± 1.0, P <0.001).

One study reported on pain scores during CGM device insertion and blood sampling for glucose monitoring (4). Median Premature Infant Pain Profile (PIPP) was 5 (interquartile range 4 to 6) in the CGM group and 8 (7 to 9) in the heel prick control group (P <0.001).

Undesirable Effects

How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Studies of CGM use in babies reported no adverse effects over seven days in 188 VLBW babies (5) and in 102 babies ≥ 32 weeks at risk of hypoglycaemia (6). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	One study reported detachment of the device more than once in 2/50 VLBW babies (2). One study reported failure of the device in 4/48 babies due to technical problems with insertion (3). No study reported skin problems with CGM. Characteristics of current CGM devices include a relatively long initial stabilisation period (usually 1-2 hours) before a reading is available, and a lag between any change in glucose concentration and a change in the reading (likely to be up to 30 minutes). They are also susceptible to drift between calibrations, and will usually report a low glucose concentration as <2.2 mmol/L without giving the actual value (7). This combination of drift, physiological lag and the inherent noise of the sensor results in poor point accuracy, with 95% limits of agreement of at least ± 1 mmol/L (6, 8). CGM also detects many episodes of low glucose concentrations that are not detected clinically using intermittent blood sampling. In one study of 102 babies (ethnicity not reported) ≥32 weeks at risk of hypoglycaemia , low glucose concentrations (<2.6mmol/L)

		were detected in 32 babies with blood sampling and 45 babies with CGM (6). Of 265 episodes of low glucose concentrations on CGM, 215 (81%) were not detected with blood glucose concentrations (6). In normal term babies not considered at risk of hypoglycaemia, CGM detected low glucose concentrations in 30/41 (73%) compared to 26/67 (39%) using blood glucose concentrations (9).

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		The certainty of the evidence was very low due to the overall limited number of studies, with few babies enrolled (2).

Outcomes	Importance	Certainty of the evidence (GRADE)
Hypoglycaemia episode [critical]	CRITICAL	⊕⊕◯◯ Low[a,b]
Neurodevelopmental impairment [critical] - not measured	CRITICAL	-
Admission to special care nursery or neonatal intensive care nursery [critical] - not measured	CRITICAL	-
Adverse effects [critical]	CRITICAL	⊕◯◯◯ Very low[c]
Fully breastfeeding at hospital discharge [critical] - not measured	CRITICAL	-
Separation from the mother for treatment of hypoglycaemia before discharge home [important] - not measured	IMPORTANT	-

Hypoglycaemic injury on brain imaging [important] - not measured	IMPORTANT	-	
Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	IMPORTANT	-	
Duration of initial hospital stay	IMPORTANT	⨁◯◯◯ Very low[a,d]	
Cost - not measured	IMPORTANT	-	

a.Downgraded one level for serious risk of bias due to moderate to low quality of the included studies (study).
b.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
c.Downgraded two levels for very serious imprecision due to small sample size and zero event.
d.Downgraded two levels for very serious imprecision due to small sample size.

Considerations for Māori
No additional evidence available
Considerations for Pacific
No additional evidence available

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]*	

	High value, probably no important variability • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Continuous glucose monitoring compared to intermittent blood glucose testing Very low certainty evidence showed • Little to no effect on hypoglycaemic episode [critical] • Uncertain effect on adverse effect [critical] • Uncertain effect on duration of initial hospital stay [important] **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Use of CGM may reduce the number of hypoglycaemic events in VLBW babies, reduce the number of heel-prick blood tests, and reduce pain, but the evidence is very uncertain. Further, point glucose measurements on CGM are very inaccurate, potentially leading to over- and under-detection and therefore potential mistreatment of hypoglycaemia. CGM also detects many episodes of low interstitial glucose concentrations that are not detected using intermittent blood sampling, including in well term babies not considered at risk of neonatal hypoglycaemia, and it is uncertain what these episodes mean and whether they should be treated.
Resources required		

How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The costs of the devices vary widely but are likely to be several thousand NZD. The cost of the sensor and transmitter, whether supplied separately or as a single unit, is $1–200 per patient (for up to 7-10 days). Sensor insertion takes a few minutes. Connection of the device and regular calibration also take a few minutes. Training is required to place and connect the sensors, and to troubleshoot the resulting signal on the monitor.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The cost estimates are from recent use in research settings in Aotearoa New Zealand, but specific quotes have not been obtained. The costs of staff training and time have not been estimated. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Given that most CGM devices necessitate intermittent blood tests for calibration, it is improbable that the intervention would be cost-effective over the relatively brief monitoring period typically needed for most babies with hypoglycaemia. However, for babies experiencing prolonged or severe hypoglycaemia, or those requiring extended monitoring such as low birth weight babies, CGM may approach cost-effectiveness.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (11*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (12*).*	

	Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%) (11*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (12*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (11*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study (*(13*), participants expressed appreciation for the inclusion of prayer or tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (14, 15, 16*).* *Additionally, a systematic literature review by Graham et al.* (17*) provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (17*).* ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work (*(13*).* ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (10*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (10*), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Harris et al reported that parents of 102 babies at risk of hypoglycaemia at ≥32 weeks tolerated CGM well and that nursing staff found the CGM easy to use (6). In another study of 67 (9 (14%) Māori) well term babies, no parents reported that they disliked the CGM device (18). Both studies were undertaken in Aotearoa New Zealand but Māori data were not reported separately. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The devices are widely used in older children and adults so are potentially available in secondary and tertiary care settings, as is the expertise needed to use them. However, they have rarely been used outside a research setting for babies in Aotearoa New Zealand. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies

VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

REFERENCES SUMMARY

1. Galderisi A, Trevisanuto D, Russo C, Hall R, Bruschettini M. Continuous glucose monitoring for the prevention of morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews. 2021;12(12):CD013309.
2. Galderisi A, Facchinetti A, Steil GM, Ortiz-Rubio P, Cavallin F, Tamborlane WV, et al. Continuous glucose monitoring in very preterm infants: a randomized controlled trial. Pediatrics. 2017;140(4):e20171162.
3. Uettwiller F, Chemin A, Bonnemaison E, Favrais G, Saliba E, Labarthe F. Real-time continuous glucose monitoring reduces the duration of hypoglycemia episodes: a randomized trial in very low birth weight neonates. PLoS ONE. 2015;10(1):e0116255.
4. Galderisi A, Lago P, Steil GM, Ghirardo M, Cobelli C, Baraldi E, et al. Procedural pain during insertion of a continuous glucose monitoring device in preterm infants. The Journal of Pediatrics. 2018;200:261-264.e1.
5. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, VanWeissenbruch M, Midgley P. Validation of the continuous glucose monitoring sensor in preterm infants.Archives of Disease in Childhood. Fetal and Neonatal Edition. 2013;98(2):F136-40.

6. Harris DL, Battin MR, Weston PJ, Harding JE. Continuous glucose monitoring in newborn babies at risk of hypoglycemia. The Journal of Pediatrics. 2010;157(2):198-202.e1.
7. Harding JE, Alsweiler JM, Edwards TE, McKinlay CJ. Neonatal hypoglycaemia. BMJ Medicine. 2024;3(1):e000544.
8. Tiberi E, Cota F, Barone G, Perri A, Romano V, Iannotta R, et al. Continuous glucose monitoring in preterm infants: evaluation by a modified Clarke error grid. Italian Journal of Pediatrics. 2016;9;42:29.
9. Harris DL, Weston PJ, Harding JE. Relationships between feeding and glucose concentrations in healthy term infants during the first five days after birth—the Glucose in Well Babies Study (GLOW). Frontiers in Pediatrics; 2023;24;11:1147659.
10. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
11. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
12. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
13. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished. 2024.
14. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
15. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
16. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
17. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
18. Cumberpatch AR, Weston PJ, Harding JE, Harris DL. Parents of babies who participated in an invasive clinical study report a positive experience: the Glucose in Well Babies (GLOW) study. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2020;105(1):4-7.

Question 19.

Should measurement of other metabolites in addition to glucose vs. measurement of glucose alone be used for diagnosing and monitoring of neonatal hypoglycaemia?	
POPULATION:	Babies at risk of or diagnosed with neonatal hypoglycaemia
INTERVENTION:	measurement of other metabolites in addition to glucose
COMPARISON:	measurement of glucose alone
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies)

	Important but not critical: 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any settings where newborn babies are tested
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment are recommended to reduce the risk of later developmental problems.* Glucose is the primary fuel for the brain. Alternative brain fuels include lactate, ketones (beta-hydroxybutyrate, acetoacetate), and some amino acids, with lactate and ketones being the most substantive. Lactate is continually produced by many tissues including the brain, but increased production and therefore blood concentrations occurs particularly when oxygen supply is limited. Ketones are produced in the liver by breakdown of fatty acids in response to insufficient glucose supply, usually caused by fasting. The brain availability and utilisation of both ketones (1) and lactate (2) is related to the blood concentrations. The newborn brain is able to extract and utilise ketones for brain fuel at a rate 4 to 5-fold greater than that of an adult (1). The availability of these alternative fuels to sustain brain metabolism has long been proposed as an important mechanism to prevent injury when glucose availability is reduced (3)(4)(5). Thus, it has been proposed that measuring these fuels in addition to glucose might help identify which babies are at risk of brain injury, and which might not be and thus not need treatment to increase glucose concentrations. In older babies and children, measuring alternative fuels as well as glucose can also help to identify the likely cause of the hypoglycaemia, but it is not clear if these tests are helpful in newborn babies, and if so, when they should be done.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	We found no evidence for any of the critical or important outcomes. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	Although most neonatal hypoglycaemia occurs in the first few days after birth due to delayed transition from continuous glucose supply from the mother to intermittent feeding, a small proportion can be due to serious and potentially life-threatening conditions such as genetic causes, congenital anomalies and excessive insulin production (hyperinsulinaemia). These babies may be at particularly high risk of hypoglycaemic brain injury (8) and early diagnosis and treatment may therefore be particularly important in these babies. Measurement of lactate and beta-hydroxybutyrate, along with glucose and insulin, may help detect these rarer causes of hypoglycaemia. Blood lactate concentrations are variable in well term newborns and fall quickly after the first day (9)(10). There is minimal synthesis of ketones (ketogenesis) in the first 6 to 12 hours after birth, even in healthy babies (11)(12). Ketone concentrations are low on the first day, and rise slowly over the next 2-4 days (13). The GLOW study showed in 67 healthy breastfed newborns in Aotearoa New Zealand (2 (3%) Māori) glucose provided 72-84% of estimated potential brain fuels in the first 5 days, with lactate providing a maximum of 25% on day 1 and bet-hydroxybutyrate up to 7% on days 2-3. However, when blood glucose concentrations were low (below the median of 3.7 mmol/L, over the first 5 days) an increase in beta-hydroxybutyrate concentrations was slow and only seen

		after the first postnatal day. The blood lactate concentration did not increase when the blood glucose concentrations were low (11). Babies with hypoglycaemia (< 2.6 mmol/L) in the first 2-3 days have very low blood ketone concentrations during hypoglycaemic episodes (9) (13)(14). Data from the GLOW study suggests that there are two phases of low glucose concentrations in healthy newborns: an initial phase in which ketone concentrations are low; and a second phase in which low glucose concentrations are accompanied by elevated ketone concentrations (11)(6). Preliminary findings suggest that it may be useful to measure the combination of blood glucose and BHB concentrations after 72 hours to help distinguish between those babies with congenital hyperinsulinemia and those who remain hypoglycaemic for other reasons, such as failure to establish breastfeeding (fasting) (7). Preliminary evidence suggests that measuring ketones at approximately 72 hours may help distinguish the cause of the hypoglycaemia (8). **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	We found no evidence for any of the critical or important outcomes. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	Additional measurements incur additional costs and require additional blood, sometimes resulting in more than one heel prick per measurement. One study reviewing case records of babies born at Auckland and Middlemore hospitals over five years (67,965 babies) identified 39 babies (7 (18%) Māori, 19 (49%) Pacific) ≥36 week's gestation with prolonged (>72 hours) hypoglycaemia, or approximately 5.7 per 10,000 births (15). An additional two babies with prolonged hypoglycaemia due to congenital hyperinsulinism were identified. This suggests that approximately 4 per 1,000 babies would be potentially eligible for additional testing if this occurred at or after 72 hours of age.
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	We found no evidence for any of the critical or important outcomes.	Additional evidence is very uncertain.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]*	

○ Probably no important uncertainty or variability ○ No important uncertainty or variability	• *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	We found no evidence about the balance of desirable and undesirable effects for the outcomes of interest. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	Additional measurements, particularly of lactate, ketones and insulin in addition to glucose, may help identify more serious causes of hypoglycaemia. However, these are very uncommon.

Resources required

How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Costs of measuring (LabPlus NZ) lactate NZ $18.69 ketones NZ $18.81 insulin NZ $29.43 Blood volume needed lactate 0.5 mL ketones 0.5 mL insulin 0.5 mL Additional cost of staff time and storage of sample.	While reliable point-of-care analysers are available, the analysis of the alternative brain fuels often requires a separate analyser and may necessitate a second heel prick.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	We are confident in our estimates for the cost of measuring test and blood volume, but uncertain about the additional costs related to staff time or storage.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	We did not conduct a systematic cost-effectiveness analysis. The laboratory cost for measuring glucose is NZ$3.19 (Labplus, NZ).	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing)) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (18). *However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (19).	

	Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%) (18). *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (19). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (18). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (16)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (20)(21)(22). *Additionally, a systematic literature review by Graham et al.* (23) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (23). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (16) ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (17)*. Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with*	

	limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey (18)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	We found no evidence about the acceptability of measuring other metabolites for diagnosing or monitoring neonatal hypoglycaemia. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Most clinical laboratories can analyse lactate and ketone concentrations, but some may only be able to do this on relatively large volumes of blood, and require samples to be transported on ice. Many birthing units have access to point-of-care lactate analysers (used for measuring fetal scalp samples) but few, if any, have point-of-care ketone analysers. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

○	●	○	○	○

REFERENCES SUMMARY

1. Kraus H, Schlenker S, Schwedesky D. Developmental changes of cerebral ketone body utilization in human infants. Biological Chemistry. 1974;355(2):164-70.
2. Wyss MT, Jolivet R, Buck A, Magistretti PJ, Weber B. In vivo evidence for lactate as a neuronal energy source. The Journal of Neuroscience. 2011;18;31(20):7477-85
3. de L Costello AM, Pal DK, Manandhar DS, Rajbhandari S, Land JM, Patel N. Neonatal hypoglycaemia in Nepal 2. Availability of alternative fuels.Archives of Disease in Childhood - Fetal and Neonatal Edition. 2000;82(1):F52-8
4. Hawdon JM, Ward Platt MP, Aynsley-Green A. Patterns of metabolic adaptation for preterm and term infants in the first neonatal week. Archives of Disease in Childhood. 1992;67(4 Spec No):357-65.
5. de Rooy L, Johns A. Management of the vulnerable baby on the postnatal ward and transitional care unit. Early Human Development. 2010;86(5):281-5.
6. Harris DL, Weston PJ, Gamble GD, Harding JE. Glucose profiles in healthy term infants in the first 5 days: The Glucose in Well Babies (GLOW) Study. The Journal of Pediatrics. 2020;223:34-41.e4
7. Stanley CA, Weston PJ, Harris DL, De León DD, Harding JE. The role of beta-hydroxybutyrate measurement in the evaluation of plasma glucose concentrations in newborn infants. Archives of Disease in Childhood Fetal and Neonatal Edition. 2024 Mar 1:fetalneonatal-2024-326865.
8. Steinkrauss L, Lipman TH, Hendell CD, Gerdes M, Thornton PS, Stanley CA. Effects of hypoglycemia on developmental outcome in children with congenital hyperinsulinism. Journal of Pediatric Nursing. 2005;20(2):109-18.
9. Harris DL, Weston PJ, Harding JE. Lactate, rather than ketones, may provide alternative cerebral fuel in hypoglycaemic newborns. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2015;100(2):F161-4.
10. Rabinowitz JD, Enerbäck S. Lactate: the ugly duckling of energy metabolism. Nature Metabolism. 202;2(7):566-571.
11. Harris DL, Weston PJ, Harding JE. Alternative cerebral fuels in the first five days in healthy term infants: the Glucose in Well Babies (GLOW) Study. The Journal of Pediatrics. 202;231:81-86.e2.
12 Futatani T, Ina S, Shimao A, Higashiyama H, Fujita S, Igarashi N, et al. Exclusive breast-feeding and postnatal changes in blood sodium, ketone, and glucose levels. Pediatrics International. 2019;61: 471-474
13. Stanley CA, Rozance PJ, Thornton PS, De Leon DD, Harris D, et al. Re-evaluating transitional neonatal hypoglycemia: mechanism and implications for management. The Journal of Pediatrics. 2015;166(6):1520-5.e1
14. Stanley CA, Anday EK, Baker L, Delivoria-Papadopolous M. Metabolic fuel and hormone responses to fasting in newborn infants. Pediatrics. 1979;64:613–9
15. Bailey MJ, Rout A, Harding JE, Alsweiler JM, Cutfield WS, McKinlay CJD. Prolonged transitional neonatal hypoglycaemia: characterisation of a clinical syndrome. Journal of Perinatology. 2021;41(5):1149-1157
16. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished. 2024.
17. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
18. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
19. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
20. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
21. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
22. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
23. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.

Question 20.

Should neurological monitoring/ imaging vs. no neurological monitoring/ imaging be used for monitoring babies with neonatal hypoglycaemia?	
POPULATION:	Babies with neonatal hypoglycaemia

INTERVENTION:	neurological monitoring/ imaging
COMPARISON:	no neurological monitoring/ imaging
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn infants over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* It is unclear which, if any, neurological monitoring or imaging techniques should be recommended for monitoring of babies with neonatal hypoglycaemia.

CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are authors of cited paper.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	A study of 264 term babies (35 cases with symptomatic hypoglycaemia, 229 controls) was conducted, excluding babies with hypoxic-ischemic encephalopathy, major congenital malformations, multiple dysmorphic features, congenital infections and chromosomal abnormalities (1). Using T1- weighted transverse and sagittal MRI and T2 weighted transverse MRI before six weeks postnatal age was found to be moderately predictive for abnormal neurodevelopmental outcomes at a minimum of 18 months of age (positive predictive value (PPV) for any white matter injury predicting any abnormal neurodevelopmental outcome = 26/33, 79%, PPV for severe injury predicting any abnormal neurodevelopmental outcome = 13/15, 87%). In a study of 45 late preterm or term babies with neonatal hypoglycaemia, including babies with comorbid conditions (44% had hypoxic-ischaemic-encephalopathy) (2), MRI scanning within six days of the onset of neonatal hypoglycaemia allowed diffusion restriction to be visualised. At follow up when babies were 4-8 months, low mesial occipital apparent diffusion coefficient was associated with cortical visual defects, but this was based on only two participants with cortical visual loss i.e., a PPV of 2/6, 33% and did not reach statistical significance (p=0.1). Participants with cortical visual loss had significantly lower occipital diffusion coefficients than gestational-age matched control subjects, whilst those without cortical visual loss did not have significantly different occipital diffusion compared to gestational-age matched controls. In a study of 86 late preterm or term babies with hypoglycaemic brain injury (not due to asphyxia, infection or congenital disease) (3), using conventional and diffusion-weighted MRI imaging within 23 days of the onset of neonatal hypoglycaemia, extensive brain injury was found to be moderately predictive of death and any neurodevelopmental impairment (PPV = 10/14, 71%). This rate was higher than for participants with focal injury on MRI (35/62, 56%). A study of 75 term babies with hypoglycaemic encephalopathy, excluding babies with congenital dysplasia of the brain, bilirubin encephalopathy, hypoxic-ischemic encephalopathy, intracranial infection and septicaemia or poor MRI quality (4) undertook T1, T2 and diffusion-weighted imaging at a mean of 6 days of age. 40 participants had normal neurodevelopment or mild developmental	

	disability and 35 had severe developmental disability at 9-12 months. Increased T1 and T2 values of the occipital lobe, T1 value of the corpus callosum or T1 value of the thalamus predicted increased risk of severe developmental disability with a sensitivity and specificity of above 75%. A combination of these parameters with clinical features (duration of hypoglycaemia and neonatal behavioural neurological assessment) had the highest sensitivity and specificity (89.1% and 90.6% respectively). In 24 babies without major congenital abnormalities who were moderate preterm, late preterm or term, changes in amplitude-integrated EEG were not found to be associated with hypoglycaemic episodes (5). The authors concluded there was no clinical utility of cot-side amplitude-integrated EEG for monitoring brain function in relation to hypoglycaemia. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No undesirable effects were explored in the studies found. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence is all from observational studies, meaning that the certainty of evidence is low or very low. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not conduct a systematic search to assess how people value the main outcomes, but caregivers may have different perspectives as to whether they want to know the neurodevelopmental prognosis of their baby. For example, parents of an extremely preterm baby who received a routine MRI before discharge described receiving an abnormal result as traumatic (6). They found no changes to their follow-up care based on the MRI and the prognosis provided was not in line with their toddler's neurodevelopmental trajectory. They state in retrospect, if they had the opportunity to make a fully informed choice, they would not have agreed to the MRI. However, in a qualitative study of caregivers of moderate to late preterm babies who were taking part in an MRI study in Aotearoa New Zealand (n = 12, 1 Māori) 7/12 reported initial anxiety due to abnormal findings, but all 12 expressed a preference for early detection of potential developmental risks, all reported reassurance from study participation, and none voiced any safety concerns for MRI (7). *Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability***	

	• *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know	MRI is moderately predictive of neurodevelopmental outcome in some groups of babies, particularly those with severe hypoglycaemia. Amplitude-integrated EEG does not appear to have any desirable effects. There is no information about other kinds of neurological monitoring, or about undesirable effects. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not conduct a systematic search to evaluate the resources required. An economic analysis of the installation and use of a specialised MRI machine in the neonatal intensive care unit was conducted in the UK in 2003 (8). The cost of each scan was estimated at £60 and the cost of the machine and set up £150,000. The time taken per scan was 30-40 minutes. However, this study did not specifically include infants with neonatal hypoglycaemia and only involved T1 and T2 weighted imaging, not diffusion weighted imaging. In a research study of babies in Auckland, New Zealand, using MRI sequences that would be suitable for studying babies with hypoglycaemia, each MRI costs approximately NZ$900, excluding staffing and transport costs. Costs for MRI for clinical purposes are likely to be higher. No information could be found about the cost of EEG monitoring.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The resources required for MRI scanning are uncertain. The resources required for EEG monitoring are very uncertain. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	The cost of MRI scans mean that cost-effectiveness is unlikely to favour the intervention. However, it is unclear whether resources may be saved from potential earlier diagnosis of neurodevelopmental impairment when MRI scans are used to indicate prognosis. It is unclear whether resource requirements favour the intervention or comparison for EEG as no information has been found regarding costs.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (11*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10*).*	

	In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%) (11*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (10*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (12*), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (13, 14, 15*).* *Additionally, a systematic literature review by Graham et al.* (16*) provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (16*).* ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (12*).* ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (9*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (9*), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	We did not do a systematic search for evidence on acceptability and could not find any evidence on the acceptability of using MRI or EEG on babies for caregivers or clinicians. However, a study investigating the use of MRI for preterm babies at term equivalent age found that MRI reduced maternal anxiety, suggesting it is likely acceptable to caregivers (17). Recruitment of moderate-to-late preterm babies to an MRI study (MoPED) suggests that MRI is acceptable to a proportion of parents in Aotearoa New Zealand, but this is very variable. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

Feasibility
Is the intervention feasible to implement?

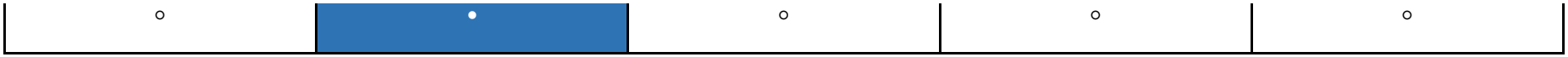
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	MRI imaging of babies with hypoglycaemia may be feasible to help predict later outcomes as MRI is currently used to assess babies with encephalopathy in Aotearoa New Zealand to provide diagnostic and prognostic information (18). However, a survey of neonatologists in New Zealand and Australia identified that resource limitations and logistics would prevent 17/95 (18%) of clinicians from conducting an MRI scan in a term infant with encephalopathy (18). The use of amplitude-integrated EEG monitoring may be feasible in an Aotearoa New Zealand context as it was used in the study discussed above conducted in Waikato Hospital (5). According to Starship Guidelines, video amplitude-integrated EEG brain monitoring should be considered for infants with perinatal asphyxia, further suggesting feasibility in infants with hypoglycaemia in Aotearoa (19). For some secondary and all primary services, babies would need to be transported to another centre to access MRI and EEG facilities. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention



REFERENCES SUMMARY

1. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics. 2008;122(1):65-74.
2. Tam EW, Widjaja E, Blaser SI, Macgregor DL, Satodia P, Moore AM. Occipital lobe injury and cortical visual outcomes after neonatal hypoglycemia. Pediatrics. 2008;122(3):507-12
3. Zhang Y, Chen D, Ji Y, Yu W, Mao J. Dynamic magnetic resonance imaging findings in the early stages of neonatal hypoglycemic brain injury. European Journal of Pediatrics. 2022;181(12):4167-4174.
4. Tian Z, Zhu Q, Wang R, Xi Y, Tang W, Yang M. The advantages of the magnetic resonance image compilation (MAGiC) method for the prognosis of neonatal hypoglycemic encephalopathy. Frontiers in Neuroscience; 2023;17:1179535.
5. Harris DL, Weston PJ, Williams CE, Pleasants AB, Battin MR, Spooner CG, et al.. Cot-side electroencephalography monitoring is not clinically useful in the detection of mild neonatal hypoglycemia. The Journal of Pediatrics; 2011;159(5):755-760.e1.
6. Pearce R, Baardsnes J. Term MRI for small preterm babies: do parents really want to know and why has nobody asked them?. Acta Paediatrica. 2012;101(10):1013-5.
7. Williams S, Harding JE, Battin M, Rogers J, Franke N. Parent experiences of MRI and early neurodevelopment follow-up for infants born moderate-to-late preterm: a qualitative study as part of the MoPED study. In Press. 2024.
8. Whitby EH, Paley MN, Smith MF, Sprigg A, Woodhouse N, Griffiths PD... Low field strength magnetic resonance imaging of the neonatal brain. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2003;88(3):F203-8.
9. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
10. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
11 Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012
12. Whānau Experiences Study Group, . Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished. 2024.
13. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
14. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
15. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
16. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
17. Edwards AD, Redshaw ME, Kennea N, Rivero-Arias O, Gonzales-Cinca N, Nongena P, et al. Effect of MRI on preterm infants and their families: a randomised trial with nested diagnostic and economic evaluation. Archives of Disease in Childhood, Fetal and Neonatal Edition. 2018;103(1):F15-F21
18. Filan PM, Inder TE, Anderson PJ, Doyle LW, Hunt RW. Monitoring the neonatal brain: A survey of current practice among Australian and New Zealand neonatologists .Journal of Paediatrics and Child Health. 2007;43(7-8):557-9.
19. Newborn Services Clinical Practice Committee, Starship Child Health. Brain monitoring in the neonate - Cadwell video aEEG.18 May 2023 [cited 2 February 2024]; Available from: https://starship.org.nz/guidelines/brain-monitoring-in-the-neonate-video-aeeg/

Question 21.

Should higher minimum target blood glucose concentration vs. most common minimum target during treatment (2.6mmol/L) be used for babies being treated for neonatal hypoglycaemia?

POPULATION:	Babies being treated for neonatal hypoglycaemia

INTERVENTION:	higher minimum target blood glucose concentration
COMPARISON:	most common minimum target during treatment (2.6mmol/L)
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	All settings where babies are treated for neonatal hypoglycaemia
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factor (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* The most widely accepted threshold for diagnosis and therefore initiating treatment for neonatal hypoglycaemia is 2.6 mmol/L, although some guidelines use lower thresholds, particularly in the first few hours after birth (see definitions EtD). Once treatment is initiated, some guidelines recommend targeting a higher glucose concentration, and one RCT has tested a lower glucose concentration, while most consider a target glucose

	concentration ≥2.6mmol/L is adequate. We reviewed the evidence for use of a minimum target glucose concentration higher or lower than 2.6 mmol/L compared with ≥2.6mmol/L.
CONFLICT OF INTERESTS:	DM, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Higher Thresholds** We found no evidence for any of the critical or important outcomes. **Lower Thresholds** In a single randomised control trial (RCT) conducted in the Netherlands (1), 689 at-risk babies ≥35 weeks' gestation with asymptomatic moderate hypoglycaemia (blood glucose 1.9 to <2.6mmol/L) at 3-24 hours of age were randomised to treatment to maintain glucose concentrations ≥2.0mmol/L (intervention group) or ≥2.6 mmol/L. They found: • Large increase in the recurrent hypoglycaemia after randomisation • Little to no difference in: • Neurodevelopmental impairment at ≥18 months of age [critical] • Bayley cognitive or motor scores at ≥18 months of age • Duration of initial hospital stay [important] • Cost [important] There were no data for admission to special care nursery or neonatal intensive care nursery, fully breastfeeding at hospital discharge, separation from the mother for treatment of hypoglycaemia before discharge home, hypoglycaemic injury on brain imaging, time to blood glucose normalisation after intervention, receipt of treatment for hypoglycaemia during initial hospital stay, number of episodes of hypoglycaemia, breastmilk feeding exclusively from birth to hospital discharge, or duration of treatment.	**Higher Thresholds** Most international guidelines recommend that hypoglycaemic babies should be treated to maintain blood glucose concentrations >2.6 mmol/L, even if the recommended threshold for intervention is <2.6 mmol/L (2, 3). Some guidelines recommend a higher target glucose concentration (>3.3 mmol/L) for babies >48 hours (4) or >72 hours (5) of age. The main reasons given for this are: 1. In some babies, prolonged hypoglycaemia will be due to congenital hyperinsulinism, and an estimated one third of these babies have neurological damage (6). Damage is more likely in babies who have hypoglycaemia in the first week after birth. 2. The recommended lower limit of normal blood glucose concentrations in older children and adults is 3.9 mmol/L (7). This is similar to the 10th centile for blood glucose concentrations in well term babies after 72 hours of age (8). 3. In adult volunteers, as blood glucose concentrations fall, secretion of counter-regulatory

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with most common minimum target during treatment (2.6mmol/l)	Risk difference with higher minimum target blood glucose concentration
Recurrent hypoglycaemia after randomisation	689 (1 RCT)	⊕⊕⊕◯ Moderate[a]	**RR 1.48** (1.09 to 1.99)	Study population	
				469 per 1,000	**225 more per 1,000** (42 more to 465 more)
Neurodevelopment impairment at ≥18 months	582 (1 RCT)	⊕⊕◯◯ Low[a,b]	-	No differences between groups of the neurodevelopment impairment at ≥18 months measured by either Bayley cognitive scores or motors < -2 standard deviation.	
Admission to special care nursery - not measured	-	-	-	-	-
Fully breastfeeding at hospital discharge - not measured	-	-	-	-	-
Separation from the mother for treatment of hypoglycaemia before discharge home - not measured	-	-	-	-	-
Hypoglycaemic injury on brain imaging - not measured	-	-	-	-	-
Breastmilk feeding exclusively from birth	-	-	-	-	-

hormones (cortisol, glucagon, adrenaline, nor-adrenaline and growth hormone) were activated at glucose concentrations of approximately 3.9 mmol/L; autonomic symptoms (anxiety, palpitations, tremor, sweating and irritability) at 3.3 mmol/L; and neuroglycopaenic symptoms (hunger, dizziness, tingling, blurred vision, difficulty thinking, and faintness) and deterioration in cognitive function occurred at approximately 2.8 mmol/L (9).

Lower Threshold

In the RCT of lower vs higher thresholds (1), babies randomised to the lower threshold group experienced a large decrease in receipt of IV dextrose, 21/348 (6%) vs 70/341 (21%), mean difference -14.5% (-19.5 to -9.5) (146 fewer per 1,000), and a large decrease in supplemental oral feeding, although the rate of supplemental feeding was high in both groups 275/348 (79%) vs 332/341(97%), mean difference -18.3% (-23.1 to -13.8) (185 per 1000). The number of babies who needed to be treated to prevent one instance of intravenous glucose administration was 7, to prevent one instance of tube feeding was 12, and to prevent one instance of supplemental oral feeding was 5. The duration of breastfeeding was similar in both groups.

Babies randomised to the lower threshold group also had a small decrease in the number of glucose measurements, mean 6.4 (SE 0.1), n = 345 vs 7.0 (0.2), n = 337, mean difference – 0.7 (-1.0 to -0.3).

to hospital discharge - not measured					
Duration of initial hospital stay	686 (1 RCT)	⊕⊕◯◯ Low[a,b]	-	The mean duration of initial hospital stay was **0** days	MD **0.1 days lower** (0.6 lower to 0.4 higher)
Cost	689 (1 RCT)	⊕⊕◯◯ Low[a,b]	-	No differences between groups on the cost of hospital stay for the babies and the costs after the neonatal period.	

a.Downgraded one level for serious risk of bias due to lack of blinding.
b.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
*Absolute effects were calculated based on the control group risk

Considerations for Māori
No additional evidence available
Considerations for Pacific
No additional evidence available

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	**Higher Thresholds** We found no evidence for any of the critical or important outcomes. **Lower Threshold** May result in: Some at-risk babies not being identified; delayed diagnosis and treatment; more recurrent or severe episodes of hypoglycaemia; increased risk of neurological complications [critical] Lower threshold results in: (1), • Large increase in moderate hypoglycaemia (104 more per 1,000) [critical]; • Moderate increase in severe hypoglycaemia (46 more per 1,000) [critical]; • Uncertain effect on serious adverse effects [critical]: both in the lower threshold group (1 convulsions and 1 death) and considered not likely related to treatment.	**Higher Thresholds** Higher target glucose concentrations are likely to result in more testing and treatment. It is uncertain which babies might benefit from this and which may experience escalated treatment without benefit. One study reviewing case records of babies born at Auckland and Middlemore hospitals over five years (67,965 babies) identified 39 (7 (18%) Māori, 19 (49%) Pacific) babies with prolonged (>72 hours) hypoglycaemia, or approximately 5.7 per 10,000 births (10). An additional two hypoglycaemic babies with congenital hyperinsulinism were identified. This suggests that approximately 4 per 1,000 babies with hypoglycaemia would potentially be eligible for a higher treatment target after 72 hours of age. **Lower Thresholds** In the RCT (1), the low threshold group had a large increase in episodes of hypoglycaemia (< 2.6 mmol/L) (57% vs 47%, mean difference 10%, 95% CI 2-17) (225 more per 1,000). The duration of breastfeeding was similar in both groups.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with most common minimum target during treatment (2.6mmol/l)	Risk difference with higher minimum target blood glucose concentration
Adverse effects-serious	689 (1 RCT)	⨁◯◯◯ Very low[a,b]	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Adverse effects - severe hypoglycaemia (< 2.0 mmol/L)	689 (1 RCT)	⨁⨁⨁◯ Moderate[a]	**RR 1.88** (1.04 to 3.41)	Study population	
				53 per 1,000	**46 more per 1,000** (2 more to 127 more)
Adverse effect-moderate hypoglycaemia (2.0-2.6mmol/L)	689 (1 RCT)	⨁⨁◯◯ Low[a,c]	**RR 1.25** (0.92 to 1.69)	Study population	
				416 per 1,000	**104 more per 1,000** (33 fewer to 287 more)

	a.Downgraded one level for serious risk of bias due to lack of blinding. b.Downgraded two levels for very serious imprecision due to wide confidence intervals and zero events in the control group. c.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm. *Absolute effects were calculated based on the control group risk **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Higher Thresholds** We found no evidence for any of the critical or important outcomes. **Lower Thresholds** While there was one high-quality randomised trial examining different treatment thresholds (1), the developmental outcomes in this study were assessed at 18 months of age. However, cognitive and social functioning problems that have been associated with neonatal hypoglycaemia typically emerge in later developmental stages than this age. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability***	

● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	• *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Higher Thresholds** We found no evidence for any of the critical or important outcomes. **Lower threshold** compared to 2.6 mmol/L: • Very low certainty evidence showed: • Little to no effect on neurodevelopmental impairment at ≥18 months of age [critical], duration of initial hospital stay [important], cost [important] • Large increase in moderate hypoglycaemia • Moderate increase in severe hypoglycaemia • Uncertain effect on serious adverse effects [critical] **Considerations for Māori** No additional evidence available **Considerations for Pacific**	**Higher Thresholds** Desirable: possible decrease in the risk of brain injury. Undesirable: Potential harm of more intensive and prolonged testing and treatment. **Lower Thresholds** Desirable: A large decrease in use of supplemental feeding and IV dextrose, and a small decrease in number of blood tests. Undesirable: A large increase in the number of episodes of hypoglycaemia (<2.6 mmol/L) and in severe hypoglycaemia. No difference in duration of breastfeeding.

	No additional evidence available	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	Higher Thresholds Babies being treated for hypoglycaemia beyond 48 or 72 hours of age are likely to be in NICU. Higher targets are likely to result in longer NICU stays. The estimated cost of NICU care in Aotearoa New Zealand is NZ $2200 per day.The cost of brain injury due to hypoglycaemia is uncertain but potentially high.Lower Thresholds A 500mL preparation of glucose 10% IV solution costs approximately NZ$26.65(11) and the initial infusion level for hypoglycaemic neonates recommended by Starship is 60 mL/kg/day (12).	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	Very uncertain	
Cost effectiveness		

Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There is no study on the cost-effectiveness.	

Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?***	

	Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%) (15*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (16*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (15*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (16*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (15*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (13*), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (17)(18)(19). *Additionally, a systematic literature review by Graham et al.* (20) *provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (20*).* ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (13*).* ***Other considerations*** *The Ministry of Health* (14*) identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (14*).*	

	Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey (Ministry of Health, 2015), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence was found regarding the acceptability of higher minimum target blood glucose concentration. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	A higher treatment target is likely to be feasible because it would require an extension of existing practice. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

JUDGEMENT

DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

REFERENCES SUMMARY

1. van Kempen AAMW, Eskes PF, Nuytemans DHGM, van der Lee JH, Dijksman LM, van Veenendaal NR, et al. Lower versus traditional treatment threshold for neonatal hypoglycemia. The New England Journal of Medicine. 2020;382(6):534-544.
2. Committee on Fetus and Newborn; Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics. 2011;127(3):575-9.
3. Hawdon JM. Identification and management of neonatal hypoglycemia in the full-term Infant. British Association of Perinatal Medicine Framework for Practice, 2017. Journal of Human Lactation. 2019;35(3):521-523.
4. Queensland Clinical Guidelines. Hypoglycaemia-newborn. Guideline No.MN23.8-V13-R28. Queensland Health. 2023. Available from: https://www.health.qld.gov.au/qcg
5. Narvey MR, Marks SD. T. The screening and management of newborns at risk for low blood glucose. Paediatrics and Child Health. 2019;24(8):536-554
6. Steinkrauss L, Lipman TH, Hendell CD, Gerdes M, Thornton PS, Stanley CA. Effects of hypoglycemia on developmental outcome in children with congenital hyperinsulinism. Journal of Pediatric Nursing. 2005;20(2):109-18
7. Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, et al. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. The Journal of Pediatrics. 2015;167(2):238-45.
8. Harris DL, Weston PJ, Gamble GD, Harding JE. Glucose profiles in healthy term infants in the first 5 days: The Glucose in Well Babies (GLOW) Study. The Journal of Pediatrics. 2020;223:34-41.e4.
9. Mitrakou A, Ryan C, Veneman T, Mokan M, Jenssen T, Kiss I, et al. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. American Journal of Physiology. 1991;260(1 Pt 1):E67-74.
10. Bailey MJ, Rout A, Harding JE, Alsweiler JM, Cutfield WS, McKinlay CJD. Prolonged transitional neonatal hypoglycaemia: characterisation of a clinical syndrome. Journal of Perinatology. 2021;41(5):1149-1157.
11. CapesMedical. IV fluids. 2023 [cited 2 February 2024]; Available from: https://www.capesmedical.co.nz/shop/Intravenous++Administration/IV+Fluids.html; 2023.
12. Newborn Services Clinical Practice Committee, Starship Child Health. Hypoglycaemia in the neonate. Starship Child Health; 6 April 2024 [cited 6 September 2024]; Available from: https://starship.org.nz/guidelines/hypoglycaemia-in-the-neonate/
13. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished. 2024.
14. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
15. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
16. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
17. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
18. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
19. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
20. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.

Question 22.

Should buccal dextrose gel vs. placebo gel or no gel be used for babies with neonatal hypoglycaemia?	
POPULATION:	Babies with neonatal hypoglycaemia
INTERVENTION:	buccal dextrose gel
COMPARISON:	placebo gel or no gel

MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision :** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Treatment frequently involves the use of formula milk and/or admission to the neonatal intensive care unit to receive intravenous dextrose (sugar) infusion into the veins (a “drip” or “IV”), resulting in potential temporary separation from the mother. Sugar gel applied to the inside of the mouth is a simple and low-cost option for the initial care of infants with low blood glucose levels. We need to determine whether oral dextrose is more effective than no treatment or other treatments.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are all authors of cited papers.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
○ Moderate
● Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Buccal dextrose compared to placebo gel or no gel results in (1)(2)(3):

- Large increase in correction of hypoglycaemia (275 more per 1,000) [critical]
- Moderate decrease in admission to neonatal intensive care nursery (79 fewer per 1,000) [critical]
- Moderate increase in fully breastfeeding at hospital discharge (51 more per 1,000) [critical]
- Large reduction in separation from mother for treatment of hypoglycaemia before discharge home (116 fewer per 1,000) [important]
- No studies reported the following outcomes: hypoglycaemic injury on brain imaging, duration of initial hospital stay, cost

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo gel or no gel	Risk difference with buccal dextrose gel
Correction of hypoglycaemia [critical]	553 (2 RCTs)	⊕⊕⊕⊕ High[a,b]	**RR 1.46** (1.32 to 1.63)	Study population	
				597 per 1,000	**275 more per 1,000** (191 more to 376 more)
Admission to special care nursery or neonatal intensive care nursery [critical]	237 (1 RCT)	⊕⊕⊕◯ Moderate[c]	**RR 0.83** (0.61 to 1.11)	Study population	
				462 per 1,000	**79 fewer per 1,000** (180 fewer to 51 more)
Fully breastfeeding at discharge [critical]	291 (1 RCT)	⊕⊕◯◯ Low[a,c]	**RR 1.06** (0.97 to 1.16)	Study population	
				847 per 1,000	**51 more per 1,000**

ADDITIONAL CONSIDERATIONS

Buccal dextrose compared to placebo gel or no gel results in (1):

- Moderate increase in correction of hypoglycaemia for each hypoglycaemic episode (66 more per 1,000)
- Moderate reduction in major neurological disability at 4.5 years (24 fewer per 1,000)
- Small reduction in the low educational achievement at 9 to 10 years (27 fewer per 1,000) (5)
- Moderate increase in exclusive breastfeeding after discharge (87 more per 1,000)
- Little to no effect on time to blood glucose normalisation after intervention and receipt of intravenous treatment for hypoglycaemia before discharge home

An RCT conducted in India reported a reduction in receipt of intravenous treatment for hypoglycaemia within 0 to 4 hours (RR 0.25, 95% 0.11 to 0.56), and 4 to 24 hours (RR 0.34, 95% 0.18 to 0.61) (3).
The Sugar Babies Study of 237 babies in Aotearoa New Zealand (71, 30% Māori) reported that 68/118 [58%] in the

					(25 fewer to 136 more)
Separation from mother for treatment of hypoglycaemia before discharge home [important]	237 (1 RCT)	⊕⊕⊕⊕ High	**RR 0.54** (0.31 to 0.93)	Study population	
				252 per 1,000	**116 fewer per 1,000** (174 fewer to 18 fewer)
Hypoglycaemic injury on brain imaging - not measured	-	-	-	-	-
Breastmilk feeding exclusively from birth to discharge - not measured	-	-	-	-	-
Duration of initial hospital stay (days) - not measured	-	-	-	-	-
Cost - not measured	-	-	-	-	-

a.Downgraded one level for serious risk bias due to one of the included studies is at high risk of performance and detection bias.
b.Upgraded one level for large effect.
c.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm.
*Absolute effects were calculated based on the control group risk

Considerations for Māori

In the Sugar Babies study of 514 babies in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%) (4). The effects of dextrose gel on the outcomes listed above were also very similar for the 71/237 Māori babies randomised (30%) compared to the findings for the whole cohort, with similar direction of effects and all confidence intervals overlapping (Unpublished data from (2)).

Considerations for Pacific

In the Sugar Babies study of 514 babies in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to

dextrose gel group and 72/119 [60%] babies in the placebo group received formula. However, babies in the dextrose gel group received fewer formula feeds than those in the placebo group, although the volume of formula feeds did not differ significantly between groups. At two weeks of age, fewer babies were formula feeding in the dextrose gel group than in the placebo group (5/118 [4%] vs 15/119 [13%]; RR 0·34. 95% CI 0·13–0·90; p=0·03) (28 fewer per 1000) (2).

<table>
<tr><td></td><td>that in the whole cohort (6/16, 38% vs 260/514, 51%) (4). Only 4 Pacific babies were randomised to dextrose or placebo gel, which is too few for further analysis of the effects of dextrose gel (Unpublished data from (2)).</td><td></td></tr>
<tr><td colspan="3">Undesirable Effects
How substantial are the undesirable anticipated effects?</td></tr>
<tr><td>JUDGEMENT</td><td>RESEARCH EVIDENCE</td><td>ADDITIONAL CONSIDERATIONS</td></tr>
<tr><td>● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know</td><td>

Small increase in neurodevelopmental impairment at ≥2 years (37 more per 1,000).
Two studies reported that there were no adverse events.

<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow-up</th><th rowspan="2">Certainty of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
<tr><th>Risk with placebo gel or no gel</th><th>Risk difference with buccal dextrose gel</th></tr>
<tr><td>Neurodevelopmental impairment at ≥2 years [critical]</td><td>184
(1 RCT)</td><td>⨁◯◯◯
Very low[a]</td><td>RR 1.11
(0.75 to 1.63)</td><td colspan="2">Study population</td></tr>
<tr><td></td><td></td><td></td><td></td><td>340 per 1,000</td><td>37 more per 1,000
(85 fewer to 214 more)</td></tr>
<tr><td>Adverse events [critical]</td><td>528
(2 RCTs)</td><td>⨁⨁◯◯
Low[b]</td><td>-</td><td colspan="2">Two studies reported that there were no adverse events.</td></tr>
</table>
a.Downgraded three levels for extremely serious imprecision due to a very wide confidence interval that appreciably crosses the threshold(s) of interest.
b.Downgraded two levels for very serious imprecision due to no events and the small sample size.
*Absolute effects were calculated based on the control group risk

Considerations for Māori
No additional data available
Considerations or Pacific
</td><td>The Sugar Babies study of 237 babies in Aotearoa New Zealand (71 (30%) Māori) reported that 99% of doses of gel were tolerated (2).
One study of 162 babies from Aotearoa New Zealand (20 (12%) Māori, 8 (5%) Pacific), reported that dextrose gel did not alter the baby's microbiome at 1 or 4 weeks after birth (6).
In the follow-up at 4.5 years of age of 185 babies from the Sugar Babies study (72, 39% Māori), children who received dextrose had lower than average scores in visual processing. However, there were no significant differences observed in the proportion of children with scores below 85 in visual processing or other visual test scores (5). At 9-10 years of age (184 babies, 57 (31%) Māori), those who had been given dextrose gel had lower standard scores in visual perception and a higher proportion of them scored below 85 in visual perception (5).</td></tr>
</table>

	No additional data available	

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		Most of the evidence comes from one trial (Sugar Babies Study) conducted in a single centre in Aotearoa New Zealand (2). In this study, over half of the babies received formula, and if blood glucose concentrations could not be maintained ≥2.6 mmol/L with dextrose gel and feeds, babies were admitted to neonatal care, usually for intravenous dextrose. The balance of effects may differ in other care settings, particularly with less use of formula or greater use of other pharmacologic interventions prior to neonatal care admission.

Outcomes	Importance	Certainty of the evidence (GRADE)
Correction of hypoglycaemia [critical]	CRITICAL	⊕⊕⊕⊕ High[a,b]
Neurodevelopmental impairment at ≥2 years [critical]	CRITICAL	⊕◯◯◯ Very low[c]
Admission to special care nursery or neonatal intensive care nursery [critical]	CRITICAL	⊕⊕⊕◯ Moderate[d]
Adverse events [critical]	CRITICAL	⊕⊕◯◯ Low[e]
Fully breastfeeding at discharge [critical]	CRITICAL	⊕⊕◯◯ Low[a,d]
Separation from mother for treatment of hypoglycaemia before discharge home [important]	IMPORTANT	⊕⊕⊕⊕ High
Hypoglycaemic injury on brain imaging - not measured	IMPORTANT	-
Breastmilk feeding exclusively from birth to discharge - not measured	IMPORTANT	-
Duration of initial hospital stay (days) - not measured	IMPORTANT	-

	Cost - not measured | IMPORTANT | - a.Downgraded one level for serious risk bias due to one of the included studies being at high risk of performance and detection bias. b.Upgraded one level for large effect. c.Downgraded three levels for extremely serious imprecision due to a very wide confidence interval that appreciably crosses the threshold(s) of interest. d.Downgraded one level for serious imprecision due to the confidence interval including the possibility of benefit and harm. e.Downgraded two levels for very serious imprecision due to no events and the small sample size. **Considerations for Māori** Because of small numbers included in the available trials, the findings are less certain for Māori babies **Considerations or Pacific** Because of very small numbers included in the available trials, the findings are very uncertain for Pacific babies	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]*	

	• *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	Buccal dextrose gel compared to other gel or no gel: Moderate certainty evidence showed • Large increase in the correction of hypoglycaemia [critical] • Moderate reduction in the admission to neonatal intensive care nursery [critical] • Large reduction in separation from mother for treatment of hypoglycaemia [important] • Moderate reduction in fully breastfeeding at hospital discharge [critical] • No studies reported adverse events for treatment with dextrose gel [critical]. **Considerations for Māori** Limited evidence suggests that the effects are similar for Māori babies **Considerations or Pacific** No specific evidence about effects for Pacific babies, but baseline risk is likely to be similar to other babies studied	• Moderate increase in the correction of hypoglycaemia for each hypoglycaemic episode • Moderate reduction in major neurological disability at 4.5 years • Small reduction in low educational achievement at 9 to 10 years • Moderate increase in the rate of exclusive breastfeeding after discharge • Little to no effect on time to blood glucose normalisation after intervention and receipt of intravenous treatment for hypoglycaemia before discharge home
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Cost of a of single-dose syringe of dextrose gel, is NZ$15 (Biomed Ltd., Auckland, NZ). Time of applying the gel: 5 minutes. Additional time required for prescription, sourcing gel and documenting treatment. Minimal training required to administer gel.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	We did not do a systematic search for evidence about resource requirements. We are reasonably sure about the costs and resource requirements in the Aotearoa New Zealand setting.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Evidence from a single trial conducted in Aotearoa New Zealand shows that in 2016, treating neonatal hypoglycaemia using dextrose gel had an overall cost of NZ$6,863.81 and standard care (placebo) cost NZ$8,178.25, a saving of NZ$1,314.44 per baby treated. Sensitivity analyses showed that dextrose gel remained cost-saving with wide variations in dextrose gel costs, neonatal intensive care unit costs, caesarean delivery rates and costs of monitoring (7).	This economic analysis was conducted within the context of babies being treated to maintain blood glucose concentration ≥2.6 mmol/L with admission to neonatal care for intravenous dextrose if this could not be achieved with feeding and dextrose gel.
Equity		

What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Dextrose gel does not require refrigeration, has a long shelf-life and is already being distributed around Aotearoa New Zealand. It can be used in any care setting and can be prescribed by a midwife. These factors are likely to favour equitable access to treatment in both rural and urban settings. ***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (9*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (4*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (9*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (4).	

	Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%) (9*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (10*), participants expressed appreciation for the inclusion of prayer or tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (11, 12, 13). *Additionally, a systematic literature review by Graham et al.* (14*),* provides a *of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (14*).* ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (10*).* ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (8*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (8*), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the Sugar Babies trial (71/237 (30%) Māori), 97% of mothers reported that gel treatment was an acceptable and easy treatment for their babies (2). A clinician survey of current practice in 20 maternity hospitals in Aotearoa New Zealand reported that most respondents (190/219, 87%) believed that prescribing or administering oral dextrose gel to treat neonatal hypoglycaemia is beneficial (15). **Considerations for Māori** Evidence from Whānau Experience Study (10) found Whānau Māori had positive experiences with buccal dextrose gel. **Considerations or Pacific** Evidence from Whānau Experience Study found all Pacific mothers interviewed had either a positive or neutral perception of buccal dextrose gel.	In the pre-hPOD trial (n = 413, 8% Māori, 16% Pacific, 22% Asian), which used dextrose gel to prevent hypoglycaemia, most parents found the gel acceptable (364/402, 91%) (Hegarty et al., 2016).
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A survey conducted in Aotearoa New Zealand found that "most practitioners reported that the dextrose gel for treatment was easily available and that guidelines for its use were easy to access and understand" (15). Many studies in different countries have demonstrated the feasibility of implementing dextrose gel, and its implementation has resulted in reduced NICU admissions and increased breastfeeding rates (16, 17, 18, 19, 20, 21, 22, 23, 24). The DESiGN trial (25) showed that it was feasible to give the gel, as most sites in Aotearoa New Zealand were giving it prior to the Aotearoa New Zealand dextrose gel guidelines (26) being published and implemented. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Edwards T, Liu G, Battin M, Harris DL, Hegarty JE, Weston PJ, et al. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. Cochrane Database of Systematic Reviews. 2022;18;3(3):CD011027.
2. Harris DL, Weston PJ, Signal M, Chase JG, Harding JE. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. The Lancet. 2013;382(9910):2077-83.
3. Gupta K, Amboiram P, Balakrishnan U, C A, Abiramalatha T, Devi U. Dextrose gel for neonates at risk with asymptomatic hypoglycemia: a randomized clinical trial. Pediatrics. 2022;149(6):e2021050733.
4. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
5. St Clair SL, Dai DWT, Harris DL, Gamble GD, McKinlay CJD, Nivins S, et al. Mid-childhood outcomes after dextrose gel treatment of neonatal hypoglycaemia: follow-up of the sugar babies randomized trial. Neonatology. 2023;120(1):90-101.
6. St Clair SL, Harding JE, O'Sullivan JM, Gamble GD, Alsweiler JM, Vatanen T. Effect of prophylactic dextrose gel on the neonatal gut microbiome. Archives of Disease in Childhood, Fetal and Neonatal Edition;. 2022;107(5):501-507.
7. Glasgow MJ, Harding JE, Edlin R; for the CHYLD Study Team. Cost analysis of cot-Side screening methods for neonatal hypoglycaemia. Neonatology. 2018;114(2):155-162.
8. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014

9. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
10. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished. 2024.
11. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
12. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
13. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
14. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
15. Liu GX, Grigg CP, Harding JE. New Zealand practitioners views about neonatal hypoglycaemia and its management. Journal of Paediatrics and Child Health. 2021;57(7):1150-1152.
16. Barber RL, Ekin AE, Sivakumar P, Howard K, O'Sullivan TA. Glucose gel as a potential alternative treatment to infant formula for neonatal hypoglycaemia in Australia. International Journal of Environmental Research and Public Health. 2018;15(5):876.
17. Gregory K, Turner D, Benjamin CN, Monthe-Dreze C, Johnson L, Hurwitz S, et al. Incorporating dextrose gel and feeding in the treatment of neonatal hypoglycaemia. Archives of Disease in Childhood, Fetal and Neonatal Edition. 2020;05(1):45-49
18. Makker K, Alissa R, Dudek C, Travers L, Smotherman C, Hudak ML. Glucose gel in infants at risk for transitional neonatal hypoglycemia. American Journal of Perinatology. 2018;35(11):1050-1056.
19. Meneghin F, Manzalini M, Acunzo M, Daniele I, Bastrenta P, Castoldi F, et al. Management of asymptomatic hypoglycemia with 40% oral dextrose gel in near term at-risk infants to reduce intensive care need and promote breastfeeding. Italian Journal of Pediatrics. 2021;47(1):201.
20. Rawat M, Chandrasekharan P, Turkovich S, Barclay N, Perry K, Schroeder E, et al. Oral dextrose gel reduces the need for intravenous dextrose therapy in neonatal hypoglycemia. Biomedicine Hub. 2017;1(3):1–9.
21. Scheans P, Bennett C, Harris D. Using dextrose (glucose) gel to reverse neonatal hypoglycemia. Neonatal Network. 2017;36(4):233-238.
22. Stanzo K, Desai S, Chiruvolu A. Effects of dextrose gel in newborns at risk for neonatal hypoglycemia in a baby-friendly hospital. Journal of Obstetric, Gynecologic and Neonatal Nursing. 2020;49(1):55-64.
23. Stewart CE, Sage EL, Reynolds P. Supporting 'Baby Friendly': a quality improvement initiative for the management of transitional neonatal hypoglycaemia. Archives of Disease in Childhood. Fetal and Noonatal Edition;. 2016;101(4):F344-7.
24. Ter M, Halibullah I, Leung L, Jacobs S. Implementation of dextrose gel in the management of neonatal hypoglycaemia. Journal of Paediatrics and Child Health. 2017;53(4):408-411.
25 Alsweiler JM, Crowther CA, Harding JE. Midwife or doctor leader to implement a national guideline in babies on postnatal wards (DesIGN): a cluster-randomised, controlled, trial. PLoS ONE. 2023;28;18(9):e0291784.
26. Oral Dextrose Gel to Treat Neonatal Hypoglycaemia Clinical Practice Guideline Panel. Oral dextrose gel to treat neonatal hypoglycaemia: New Zealand clinical practice guidelines 2015. Department of Paediatrics: Child and Youth Health, University of Auckland, Auckland, New Zealand. Available from: http://www.fmhs.auckland.ac.nz/clinicalpracticeguidelines

Question 23.

Should formula vs. control be used for treatment of neonatal hypoglycaemia?	
POPULATION:	Babies with neonatal hypoglycaemia
INTERVENTION:	formula
COMPARISON:	control
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies)

	4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Formula is sometimes used to treat neonatal hypoglycaemia by providing a source of glucose to help increase blood glucose concentrations. This may be particularly important when breastfeeding is not feasible or is insufficient.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are authors of cited paper.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large	Formula alone or dextrose plus formula compared to other interventions results in (1): • Correction of hypoglycaemia (RCT: large effect when comparing formula to oral dextrose gel without feeding (192 more per 1,000); Cohort study: moderate effect when comparing formula to donor human milk (90 more per 1,000) [Critical]	Gregory 2020 (2) reported that babies who received formula at the time of the first dose of oral dextrose gel administration showed the greatest

○ Varies ○ Don't know	• Recurrent neonatal hypoglycaemia (Cohort study: large reduction when comparing oral dextrose gel plus formula to oral dextrose gel plus breastfeeding (453 fewer per 1,000); small reduction when comparing oral dextrose gel plus formula to oral dextrose gel plus donor human milk (30 fewer per 1,000) [critical] • Small reduction in admission to special care or neonatal intensive care nursery when comparing formula to oral dextrose gel plus breastfeeding or donor human milk (24 fewer per 1,000) [critical]	increase in blood glucose concentration, with a median rise of 0.83 mmol/L. In comparison, breastfed babies or those who were not fed had a lower median increase of 0.56 mmol/L. Also, babies who received formula with their first dose of oral dextrose gel were less likely to require a second dose. Harris 2017 (3) reported that the increase in blood glucose concentration after infant formula (+0.21 mmol/L 95% CI 0.04 to 0.29 mmol/L) was similar to that after dextrose gel (+0.17mmol/L, 95% CI 0.04 to 0.29) and greater than after other feedings. Breastfeeding led to a smaller, non-significant increase in blood glucose concentration (+0.11 mmol/L, 95% CI -0.02 to 2.46 mmol/L), while expressed mother's own breastmilk was associated with a slight, non-significant decrease in blood glucose concentrations (−0.08 mmol/L, 95% -0.21 to 0.05 mmol/L). Breastfeeding (but not formula or expressed mother's own milk) was associated with a lower risk of needing a second treatment. Sen 2020 (4) reported that there was no significant difference in the median increase in blood glucose concentrations after babies were given dextrose gel plus donor human milk (+1.05 mmol/L) or formula (+0.94

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with control	Risk difference with formula
Correction of hypoglycaemia (< 2.6 mmol/L) (formula versus dextrose gel) [critical]	222 (1 RCT)	⨁⨁◯◯ Low[a]	**RR 1.27** (1.11 to 1.46)	Study population	
				710 per 1,000	**192 more per 1,000** (78 more to 327 more)
Correction of hypoglycaemia (formula versus donor human milk) [critical]	358 (1 non-randomised study)	⨁◯◯◯ Very low[b]	**OR 1.44** (0.91 to 2.25)	Study population	
				491 per 1,000	**90 more per 1,000** (24 fewer to 194 more)
Recurrent neonatal hypoglycaemia (dextrose gel plus formula versus dextrose gel plus breastfeeding) [critical]	66 (1 non-randomised study)	⨁⨁◯◯ Low[c,d]	**OR 0.14** (0.05 to 0.41)	Study population	
				758 per 1,000	**453 fewer per 1,000** (622 fewer to 196 fewer)
Recurrent neonatal hypoglycaemia (dextrose gel plus formula versus dextrose gel plus donor milk) [critical]	66 (1 non-randomised study)	⨁◯◯◯ Very low[c]	**OR 0.87** (0.31 to 2.45)	Study population	
				333 per 1,000	**30 fewer per 1,000** (199 fewer to 217 more)

Neurodevelopmental impairment [critical] - not measured	-	-	-	-	-
Admission to special care nursery or neonatal intensive care nursery [critical]	418 (2 non-randomised studies)	⨁◯◯◯ Very low[c,e]	**OR 0.76** (0.37 to 1.56)	Study population	
				110 per 1,000	**24 fewer per 1,000** (66 fewer to 51 more)
Fully breastfeeding at hospital discharge [critical] - not measured	-	-	-	-	-
Separation from mother for treatment of hypoglycaemia before discharge home [important] - not measured	-	-	-	-	-
Hypoglycaemic injury on brain imaging [important] - not measured	-	-	-	-	-
Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	-	-	-	-	-
Duration of initial hospital stay [important] - not measured	-	-	-	-	-
Cost [important] - not measured	-	-	-	-	-

a.Downgraded two levels for very serious risk of bias due to unclear risk of selection bias, performance bias, detection bias and reporting bias.
b.Downgraded one level for serious risk of bias due to the low quality of the study.
c.Downgraded one level for serious imprecision due to wide confidence interval and small sample size.
d.Upgraded one level for large effect.
e. Downgraded one level for serious inconsistency due to significant heterogeneity.
*Absolute effects were calculated based on the control group risk

There is no evidence comparing formula to intravenous dextrose.

Considerations for Māori

No additional data available

Considerations or Pacific

No additional data available

mmol/L) but these were both significantly higher than after dextrose gel plus breastfeeding (+0.39 mmol/L).

Zhou et al. (5) conducted a pre- and post-implementation study in Canada to evaluate the effectiveness of dextrose gel in treating neonatal hypoglycaemia following the introduction of a new clinical guideline in October 2018. The study compared outcomes between babies treated with formula only and those treated with oral dextrose gel (unclear about the feeding) for their first episode of hypoglycaemia. The median blood glucose concentration after treatment was higher in the formula group (3.3 mmol/L, p<0.05) compared to the dextrose gel group (number not provided). Although not statistically significant, the dextrose gel group had a higher proportion of neonates experiencing a second hypoglycaemia episode and a higher rate of NICU admissions for intravenous dextrose than the formula group (numbers not provided). There were no significant differences between the groups in the average volume of the formula used per feed at discharge, rates of exclusive breastfeeding at discharge, or breastfeeding quality as measured by the LATCH score (numbers not provided).

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No studies reported any adverse events associated with feeding formula to babies with hypoglycaemia (1).	Burakevych 2019 (6) reported that dextrose gel plus breastmilk treatment (expressed mother's own milk or breastfeeding) was not associated with glucose instability (blood glucose concentrations outside the central range of 3–4 mmol/L). In contrast, treatment with formula plus dextrose gel or intravenous dextrose was associated with instability. There is some concern that administering one or two doses of formula within the first few hours could reduce the likelihood of fully breastfeeding, but no evidence was identified. In an RCT conducted in five centres in Aotearoa New Zealand and Australia (7) 532 moderate to late preterm babies (15.8% Māori) born between 32 and 35 weeks' gestation and receiving IV fluids were randomised to receive milk supplement (almost always formula) or exclusively mother's milk until they reached full feeds of only mother's milk. There was no difference between groups in the rate of fully breastmilk feeding at discharge, or at 4 months' corrected age.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with control	Risk difference with formula
Adverse effects [critical] - not measured	-	-	-	-	-

Considerations for Māori
No additional data available
Considerations or Pacific
No additional data available

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Outcomes	Importance	Certainty of the evidence (GRADE)
Correction of hypoglycaemia (< 2.6 mmol/L) (formula versus dextrose gel) [critical]	CRITICAL	⊕⊕◯◯ Low[a]
Correction of hypoglycaemia (formula versus donor human milk) [critical]	CRITICAL	⊕◯◯◯ Very low[b]
Recurrent neonatal hypoglycaemia (dextrose gel plus formula versus dextrose gel plus breastfeeding) [critical]	CRITICAL	⊕⊕◯◯ Low[c,d]
Recurrent neonatal hypoglycaemia (dextrose gel plus formula versus dextrose gel plus donor milk) [critical]	CRITICAL	⊕◯◯◯ Very low[c]
Neurodevelopmental impairment [critical] - not measured	CRITICAL	-
Admission to special care nursery or neonatal intensive care nursery [critical]	CRITICAL	⊕◯◯◯ Very low[c,e]
Adverse effects [critical] - not measured	CRITICAL	-
Fully breastfeeding at hospital discharge [critical] - not measured	CRITICAL	-

a.Downgraded two levels for very serious risk of bias due to unclear risk of selection bias, performance bias, detection bias and reporting bias.
b.Downgraded one level for serious risk of bias due to the low quality of the study.
c.Downgraded one level for serious imprecision due to wide confidence interval and small sample size.
d.Upgraded one level for large effect.
e.Downgraded one level for serious inconsistency due to significant heterogeneity.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Formula alone or dextrose plus formula compared to other interventions Very low certainty evidence showed • Large effect on correction of neonatal hypoglycaemia when comparing formula alone to oral dextrose gel with feed [critical] • Moderate effect on correction of neonatal hypoglycaemia when comparing formula alone to donor human milk [critical] • Large reduction in recurrent hypoglycaemia when comparing oral dextrose gel plus formula to oral dextrose gel plus breastfeeding [critical] • Small reduction in recurrent hypoglycaemia when comparing oral dextrose gel plus formula to oral dextrose gel plus donor human milk [critical]	Dextrose gel plus formula feeding led to increases in blood glucose concentrations that were similar to those after dextrose gel plus donor human milk and greater than after dextrose gel plus breastfeeding or expressed mother's own milk. Formula feeding also led to increases in blood glucose concentrations similar to those after dextrose gel and greater

	• Small reduction in admission to special care or neonatal intensive care nursery [critical] **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	than after expressed mother's own milk or breastfeeding. Initial formula feeding was associated with fewer subsequent hypoglycaemic episodes in one study, but in another, breastfeeding were associated with fewer subsequent hypoglycaemic episodes. Treatment with dextrose gel plus formula was linked to glucose instability, while dextrose gel plus expressed mother's own milk or breastfeeding was not. In preterm babies, supplementation of mother's own milk with formula did not alter the rate of fully breastfeeding at hospital discharge.
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	The costs can vary depending on the type of formula used and the quantity required. The typical price range for a 900g container of formula in a community setting in New Zealand is approximately NZD $20 to $50. The estimated cost per litre of formula in Aotearoa New Zealand would be approximately NZD $3.19 to $7.96. Additionally, resource requirements may include staff time for preparation and feeding, potential costs for additional feeding equipment, and considerations for storage and handling of the formula.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ● Low ○ Moderate ○ High ○ No included studies	A formal assessment of the certainty of evidence of the cost of formula for the treatment of neonatal hypoglycaemia was not undertaken.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	There are no studies that assess the specific cost-effectiveness of formula, particularly in the context of treating neonatal hypoglycaemia. However, a few studies suggest that formula is generally more cost-effective than pasteurised donor human milk in the short term. In the long term, exclusive breastfeeding might offer longer-term cost savings than formula. A study conducted in Germany (8) comparing the costs of feeding preterm infants donor human milk, mother's own milk, and formula found that DHM was significantly more expensive than formula or mother's milk. The cost per litre of DHM was €306.95, with a total cost of €82.88 per litre for production and use. In contrast, formula costs €10.28 per litre. This suggests that formula has much lower direct costs than donor human milk. Formula typically ranges from NZ$20 to $50 for a 900g container, depending on the type and quantity used. Additional costs of formula include factors such as staff time for preparation and feeding, as well as potential expenses for feeding equipment and storage. For comparison, oral dextrose gel is priced at approximately NZ$15 per single-dose syringe. The administration of dextrose gel costs an additional NZ$15 (9) and requires minimal training. The use of IV dextrose for treating neonatal hypoglycaemia is associated with significantly higher costs. A 500mL preparation of 10% IV glucose solution costs approximately NZ$27 (10), and the initial infusion rate recommended for hypoglycaemic neonates is 60mL/kg/day (11). The administration of IV dextrose also often necessitates admission to a NICU with an average cost of NZ$2,200 per day in Aotearoa New Zealand. There are substantial expenses related to staff training, time for setting up and maintaining the IV infusion, as well as ongoing care in the NICU. Thus, the cost of use of formula as a treatment option is likely to be similar to that of dextrose gel and substantially lower than that of intravenous dextrose.	

Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (14)*. However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (15). *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (14). *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (15). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (14). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori***	

	In the Whānau Experience study (12), *participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (16)(17)(18)*Additionally, a systematic literature review by Graham et al.* (19) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (19). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (12). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (13). *Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (13) *71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	In the Whānau Experiences Study (12) , all Pacific mothers indicated a strong preference for breastfeeding their babies, with most favouring exclusive breastfeeding over formula feeding. Only 2 out of 10 participants in this group accepted formula. Similarly, among Asian mothers, some struggled with transitioning to formula feeding as they had initially planned to breastfeed exclusively. In the Growing Up in New Zealand cohort (20), exclusive breastfeeding was highly valued by many wāhine Māori due to its alignment with Tikanga Māori, indicating that formula use may be less acceptable, particularly when cultural traditions strongly emphasise breastfeeding.	In the RCT including 532 babies (7), (15.8% Māori) born between 32 and 35 weeks' gestation, parents of 16/271 babies randomised to receive exclusively mother's milk nevertheless decided to give their baby formula (a protocol deviation), but 0/261 babies

	A survey in New Zealand (21) showed that health professionals preferred minimising formula use to support breastfeeding while ensuring effective treatment and for that reason viewed dextrose gel for neonatal hypoglycaemia positively.	randomised to receive supplements experienced a protocol deviation.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Formula is widely available and used in most neonatal care settings.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies

	JUDGEMENT						
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Iqbal A, Harding JE, Lin L. Infant formula for the prevention and treatment of neonatal hypoglycaemia – a systematic review and meta-analysis. Unpublished; 2024.
2. Gregory K, Turner D, Benjamin CN, Monthe-Dreze C, Johnson L, Hurwitz S, et al. Incorporating dextrose gel and feeding in the treatment of neonatal hypoglycaemia. Archives of Disease in Childhood, Fetal and Neonatal Edition. 2020 Jan;105(1):45-49.
3. Harris DL, Gamble GD, Weston PJ, Harding JE.. What happens to blood glucose concentrations after oral treatment for neonatal hypoglycemia?. The Journal of Pediatrics. 2017;190:136-141.
4. Sen S, Andrews C, Anderson E, Turner D, Monthé-Drèze C, Wachman EM. Type of feeding provided with dextrose gel impacts hypoglycemia outcomes: comparing donor milk, formula, and breastfeeding. Journal of Perinatology. 2020;40(11):1705-1711
5. Zhou K, Pang A, Huang T. 44 Management of Neonatal Hypoglycemia using Dextrose 40% Oral Gel in Term and Late Preterm Neonates. Paediatrics & Child Health. 2020;25(Suppl 2):e19.
6. Burakevych N, McKinlay CJD, Harris D., Alsweiler JM., Harding JE. Factors influencing glycaemic stability after neonatal hypoglycaemia and relationship to neurodevelopmental outcome. Scientific Reports. 2019;9:8312
7. Alexander T, Asadi S, Meyer M, Harding JE, Jiang Y, Alsweiler JM, Muelbert M, Bloomfield FH for the DIAMOND Trial Group. Nutritional support for moderate-to-late preterm infants – A randomized trial. New England Journal of Medicine. 2024; 390:1493-1504
8. Fengler J, Heckmann M, Lange A, Kramer A, Flessa S. Cost analysis showed that feeding preterm infants with donor human milk was significantly more expensive than mother's milk or formula. Acta Paediatrica. 2020;109(5):959-966.
9. Glasgow MJ, Edlin R, Harding JE. Cost-utility analysis of prophylactic dextrose gel vs standard care for neonatal hypoglycemia in at-risk infants. The Journal of Pediatrics. 2020;226:80-86.e1.
10. CapesMedical. IV fluids. 2023 [cited 2 February 2024]; Available from:https://www.capesmedical.co.nz/shop/Intravenous++Administration/IV+Fluids.html; 2023.
11. Newborn Services Clinical Practice Committee, Starship Child Health. Hypoglycaemia in the neonate. 16 April 2024 [cited 2 September 2024]; Available from: https://starship.org.nz/guidelines/hypoglycaemia-in-the-neonate/
12. Whānau Experiences Study Group, . Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
13. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
14. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
15. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-91.
16. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
17. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
18. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
19. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
20. Bennett D, Gilchrist CA, Menzies RL, Harwood M, Kingi TK, Atatoa Carr P, et al. Determinants of exclusive breastfeeding for wāhine Māori. New Zealand Medical Journal. 2022;20;135(1555):73-87
21. Liu GX, Grigg CP, Harding JE. New Zealand practitioners views about neonatal hypoglycaemia and its management. Journal of Paediatrics and Child Health. 2021; 57(7):1150-1152.

Question 24.

Should intravenous dextrose vs. other treatment or no treatment be used for treatment of neonatal hypoglycaemia?	
POPULATION:	Babies with neonatal hypoglycaemia
INTERVENTION:	intravenous dextrose
COMPARISON:	other treatment or no treatment
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* The usual first-line treatment for asymptomatic hypoglycaemia is increased feeding. Oral dextrose gel is an effective and safe treatment for babies whose blood glucose concentrations are not corrected by increased feeding. However, babies whose low blood glucose concentrations are severe,

	persist after increased feeding and dextrose gel treatment, or who develop symptomatic hypoglycaemia, are often admitted to the neonatal intensive care unit (NICU) for treatment with intravenous (IV) dextrose. However, the evidence to support this clinical practice is limited and variation exists regarding the dose of dextrose administered and the effectiveness of infusion in different groups of babies.
CONFLICT OF INTERESTS:	CC, DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Intravenous (IV) dextrose treatments were compared at different doses or using different infusion protocols (1) Intravenous dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk) (2): • Small reduction in hypoglycaemic episodes (defined as blood glucose concentration <2.2 mmol/L) (49 fewer per 1,000) [critical] • Moderate reduction in neonatal mortality (19 fewer per 1,000) [adverse effect, critical] • Small reduction in necrotising enterocolitis (40 fewer per 1,000) [adverse effect, critical] • Moderate reduction in duration of initial hospital stay (1.48 days lower) [important] • No data for the following outcomes: neurodevelopmental impairment [critical], admission to special care nursery or neonatal intensive care nursey [critical], breastmilk feeding exclusively from birth to hospital discharge [important], separation from the mother for treatment of hypoglycaemia before discharge home [important], hypoglycaemic injury on brain imaging [important], breastmilk feeding exclusively from birth to hospital discharge [important], cost [important] IV 10% dextrose (2mL/kg bolus over 10 minutes followed by infusion at 4-6mg/kg/min) compared to treatment with breastmilk, formula, dextrose gel and breastmilk, or dextrose gel and formula (3): • No data for any critical or important outcomes	IV dextrose (no detail of dose) compared to no IV dextrose (no detail) (7): Little to no effect on psychological test scores at 4 years IV 10% dextrose (2mL/kg bolus of IV 10% dextrose over 10 minutes, followed by infusion at 4-6mg/kg/min) compared to treatment with formula, dextrose gel and breastmilk, or dextrose gel and formula (3): Little to no effect on duration of hypoglycaemia IV dextrose minibolus (200mg/kg followed by continuous infusion at 8 mg/kg/min) compared to continuous infusion only (4): Little to no effect on the proportion of babies who had corrected hypoglycaemia within 10 minutes of infusion IV 20% dextrose continuous infusion (at an initiation rate of 8mg/kg/min)

IV dextrose minibolus (200mg/kg followed by continuous infusion at 8mg/kg/min) compared to continuous infusion only (4):
No data for any critical or important outcomes
IV 20% dextrose continuous infusion (at an initiation rate of 8mg/kg/min) compared to IV 15% dextrose continuous infusion (at the same initiation rate of 8 mg/kg/min) (5):

- Moderate reduction in hypoglycemic episodes (defined as blood glucose concentration <2.6 mmol/L) (92 fewer per 1,000) [critical]
- No data for any other critical or important outcomes

IV 10% dextrose with dose tailored to baseline blood glucose concentration (BCG) (if baseline BCG < 1.1 mmol/L mg/dL: 2mL/kg bolus followed by continuous infusion at 60mL/kg/day; if baseline BGC 1.1-1.7 mmol/L: continuous infusion at 60mL/kg/day; if baseline BGC 1.7-2.4 mmol/L: continuous infusion at 30 mL/kg/day) compared to no tailored approach infusion (2mL/kg bolus followed by continuous infusion at 60mL/kg/day) (6):

- Large reduction on cost of NICU stay (US $ 5,441 per baby or US $ 4,417 when adjusted) [important]
- No data for any other critical or important outcomes

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with other treatment or no treatment	Risk difference with intravenous dextrose
Hypoglycaemia after initial treatment until discharge home [critical] - IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk)	80 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 0.67** (0.20 to 2.18)	Study population	
				150 per 1,000	**49 fewer per 1,000** (120 fewer to 177 more)
Hypoglycaemia after initial treatment [critical] (IV 20% dextrose continuous infusion (at an initiation rate of	121 (1 RCT)	⨁◯◯◯ Very low[b,c]	**RR 0.87** (0.68 to 1.13)	Study population	
				705 per 1,000	**92 fewer per 1,000**

compared to IV 15% dextrose continuous infusion (at the same initiation rate of 8mg/kg/min) (5):
Little to no effect on average plasma glucose concentrations
IV 10% dextrose with dose tailored to baseline blood glucose concentration (BCG) (if baseline BCG < 1.1 mmol/L mg/dL: 2mL/kg bolus followed by continuous infusion at 60mL/kg/day; if baseline BGC 1.1-1.7 mmol/L: continuous infusion at 60mL/kg/day; if baseline BGC 1.7-2.4 mmol/L: continuous infusion at 30 mL/kg/day) compared no tailored approach (2mL/kg bolus followed by continuous infusion at 60mL/kg/day) (6):
Little to no effect on time to correction of hypoglycaemia
Moderate reduction in duration of NICU stay (1.5 days or 1.9 days when adjusted)

Five of six studies were conducted in a high-income country.
Only the study of IV 10% dextrose versus oral sucrose bolus was conducted in a lower-middle-income country.

The 3 studies comparing IV dextrose to other treatments for hypoglycaemia were all of at-risk

	8mg/kg/min) compared to IV 15% dextrose continuous infusion (at the same initiation rate of 8mg/kg/min))					(226 fewer to 92 more)	babies (all risk groups in 1 study, large for gestational age (LGA) in 1 study, and small for gestational age (SGA) in 1 study). Of the 3 studies comparing different IV dextrose preparations, 1 did not describe inclusion criteria and 2 included at-risk and not-at-risk babies.
	Neurodevelopmental impairment [critical] - not measured	-	-	-	-	-	
	Adverse effects - mortality [critical]- IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk)	80 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 0.75** (0.18 to 3.14)	Study population		
					75 per 1,000	**19 fewer per 1,000** (62 fewer to 161 more)	
	Adverse effects - necrotising enterocolitis [critical]- IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk)	80 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 0.20** (0.01 to 4.20)	Study population		
					50 per 1,000	**40 fewer per 1,000** (50 fewer to 160 more)	
	Hypoglycaemic injury on brain imaging [important] - not measured	-	-	-	-	-	
	Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	-	-	-	-	-	
	Duration of initial hospital stay [important]- IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk)	80 (1 RCT)	⨁◯◯◯ Very low[a,b]	-	The mean duration of initial hospital stay [important]- was **11.36** days	MD **1.48 days lower** (4.36 lower to 1.4 higher)	

Cost [important]- IV 10% dextrose with dose tailored to baseline blood glucose concentration compared to no tailored approach infusion	0 (1 non-randomised study)	⊕⊕◯◯ Low	-	Compared to no tailored approach, IV 10% dextrose with dose tailored to baseline blood glucose concentration results in a decrease in NICU total costs from median US $14 030 (IQR: $5847, $30 753) to median US $8470 (IQR: $5650, $19 019) by an adjusted median difference of $4417 (95% CI $571, $8263).	

a.Downgraded one level for serious indirectness due to the sample population only comprising SGA, moderate to late preterm infants.
b.Downgraded two levels for very serious imprecision due to small sample size and wide confidence intervals.
c.Downgraded one level for serious risk of bias due to overall moderate to low quality of the included study.
*Absolute effects were calculated based on the control group risk.

Considerations for Māori
No additional evidence available
Considerations for Pacific
No additional evidence available

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk) (2): • Large reduction in fully breastmilk feeding at hospital discharge (200 fewer per 1,000) [critical] • Little to no effect on feeding intolerance [adverse effect, critical] IV 10% dextrose compared to treatment with breastmilk or formula (3): • Little to no effect on hypoglycaemic episodes during treatment (1 more episode) IV 10% dextrose compared to treatment with dextrose gel and breastmilk, or dextrose gel and formula (3):	IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk) (2): may increase the risk of a hyperglycaemic episode (blood glucose concentration > 4.4mmol/L) six hours after initiating treatment

- Little to no effect on hypoglycaemic episodes during treatment (1 more episode)

<u>IV 20% dextrose continuous infusion (at an initiation rate of 8mg/kg/min) compared to IV 15% dextrose continuous infusion (at the same initiation rate of 8mg/kg/min) (5):</u>

- Little to no effect on phlebitis [adverse effect, critical]

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with other treatment or no treatment	Risk difference with intravenous dextrose
Hypoglycaemia after initial treatment until discharge home [critical]- IV 10% dextrose compared to treatment with breastmilk or formula	128 (1 non-randomised study)	⨁⨁◯◯ Low[a]	-	The median hypoglycaemia after initial treatment until discharge home [critical]- IV 10% dextrose compared to treatment with breastmilk or formula was **1** episodes	median **1 episodes more** (1 more to 1 more)
Adverse effects - feeding intolerance [critical] -IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk)	80 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 1.0** (0.3 to 3.1)	Study population	
				100 per 1,000	**0 fewer per 1,000** (70 fewer to 210 more)
Fully breastfeeding at hospital discharge [important]- IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk)	80 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 0.68** (0.44 to 1.05)	Study population	
				625 per 1,000	**200 fewer per 1,000** (350 fewer to 31 more)
				Study population	

(RR 2.33 (95% CI 0.65, 8.39), p = 0.19; 80 infants)

Of the 3 studies comparing IV dextrose to other treatments for hypoglycaemia, 2 were in high-income countries and 1 was in a lower-middle-income country. All studies were all of at-risk babies (all risk groups in 1 study, LGA in 1 study, and SGA in 1 study).

In a cohort of 404 children from Aotearoa New Zealand 115 (115 (28%) Māori, 14 (3%) Pacific), those with neurosensory impairment at 2 years had a faster increase in glucose concentrations after hypoglycaemia and a higher glucose concentration in the first 12 hours after birth than those who did not have neurosensory impairment (8). This effect was only seen among babies treated with dextrose, but those treated with IV dextrose rather than oral dextrose had higher glucose concentrations in the first 12 hours.

In the same children, administration of IV dextrose resulted in a higher maximum and range of interstitial glucose concentrations, and a lower minimum compared to treatments involving dextrose gel combined with breast milk, exclusive breast milk, or formula alone. The risk of

Adverse effects - phlebitis [critical] (IV 20% dextrose continuous infusion (at an initiation rate of 8mg/kg/min) compared to IV 15% dextrose continuous infusion (at the same initiation rate of 8mg/kg/min))	121 (1 RCT)	⨁⨁◯◯ Low[a]	**RR 0.99** (0.74 to 1.33)	607 per 1,000	**6 fewer per 1,000** (158 fewer to 200 more)	

a.Downgraded two levels for very serious imprecision due to small sample size and wide confidence intervals.
b.Downgraded one level for serious indirectness due to the sample population only comprising SGA, moderate to late preterm infants.
*Absolute effects were calculated based on the control group risk.

Considerations for Māori
No additional evidence available
Considerations for Pacific
No additional evidence available

neurosensory impairment was increased with both shorter and longer durations to achieve the maximum interstitial glucose concentration (P=0.04; lower tertile of time to reach maximum [0.4–2.2 hours] vs middle [2.3–4.2 hours], OR 3.10 [95% CI 1.03 to 9.38]; higher tertile [4.3–6.0 hours] vs middle, OR 3.07 [95% CI 1.01 to 9.24]). The glycaemic response following hypoglycaemia significantly contributed to overall glycaemic instability, and was greater after IV dextrose than after other treatments. The speed of recovery from hypoglycaemia, whether slow or rapid, appeared to be associated with neurosensory impairment (3).

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		Certainty of the relationship between IV dextrose and glycaemic instability, and between glycaemic instability and neurodevelopmental outcome is very low (two observational studies from the same cohort of babies) (3).

Outcomes	Importance	Certainty of the evidence (GRADE)
Hypoglycaemia after initial treatment until discharge home [critical]- IV 10% dextrose compared to treatment with breastmilk or formula	CRITICAL	⨁◯◯◯ Very low[a]
Hypoglycaemia after initial treatment until discharge home [critical] - IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk)	CRITICAL	⨁◯◯◯ Very low[a,b]
Hypoglycaemia after initial treatment [critical] (IV 20% dextrose continuous infusion (at an initiation rate of 8mg/kg/min) compared to IV 15% dextrose continuous infusion (at the same initiation rate of 8mg/kg/min))		⨁◯◯◯ Very low[a,c]

Neurodevelopmental impairment [critical] - not measured	CRITICAL	-
Adverse effects - feeding intolerance [critical] -IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk)	CRITICAL	⊕◯◯◯ Very low[a,b]
Adverse effects - mortality [critical]- IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk)	CRITICAL	⊕◯◯◯ Very low[a,b]
Adverse effects - necrotising enterocolitis [critical]- IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk)	CRITICAL	⊕◯◯◯ Very low[a,b]
Fully breastfeeding at hospital discharge [important]- IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk)	CRITICAL	⊕◯◯◯ Very low[a,b]
Hypoglycaemic injury on brain imaging [important] - not measured	IMPORTANT	-
Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	IMPORTANT	-
Duration of initial hospital stay [important]- IV dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk)	IMPORTANT	⊕◯◯◯ Very low[a,b]
Cost [important]- IV 10% dextrose with dose tailored to baseline blood glucose concentration compared to no tailored approach infusion	IMPORTANT	⊕⊕◯◯ Low
Adverse effects - phlebitis [critical] (IV 20% dextrose continuous infusion (at an initiation rate of 8mg/kg/min) compared to IV 15% dextrose continuous infusion (at the same initiation rate of 8mg/kg/min))	CRITICAL	⊕⊕◯◯ Low[a]

a.Downgraded two levels for very serious imprecision due to small sample size and wide confidence intervals.
b.Downgraded one level for serious indirectness due to the sample population only comprising SGA, moderate to late preterm infants.
c.Downgraded one level for serious risk of bias due to overall moderate to low quality of the included study.

Considerations for Māori

No additional evidence available

Considerations for Pacific

No additional evidence available

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies	Administration of intravenous dextrose results in greater glycaemic instability compared to treatments involving dextrose gel combined with breast milk, exclusive breast milk, or formula alone, and greater glycaemic instability is associated with an increased risk of neurosensory impairment (3). The evidence is consistently rated as low to very low, and the effects remain uncertain.	

○ Don't know	Intravenous (dextrose (10% dextrose 2mL/kg bolus followed by an infusion at 6mg/kg/min) compared to oral sucrose bolus (200mg bolus dissolved in expressed breast milk) • Small reduction in hypoglycaemic episodes (defined as blood glucose concentration <2.2 mmol/L) [critical] • Moderate reduction in neonatal mortality [adverse effect, critical] • Small reduction in necrotising enterocolitis [adverse effect, critical] • Little to no effect on feeding intolerance [adverse effect, critical], duration of initial hospital stay [important] • Large reduction in fully breastmilk feeding at hospital discharge [critical] IV 10% dextrose (2mL/kg bolus of IV 10% dextrose over 10 minutes followed by infusion at a rate of 4-6mg/kg/min) compared to treatment with breastmilk alone: • Little to no effect on the proportion of babies that had corrected hypoglycaemia within 10 minutes of infusion IV 10% dextrose (2mL/kg bolus of IV 10% dextrose over 10 minutes followed by infusion at 4-6mg/kg/min) compared to treatment with breastmilk or formula, dextrose gel and breastmilk, or dextrose gel and formula: • Little to no effect on the hypoglycaemic episodes during treatment IV dextrose minibolus (200mg/kg minibolus followed by continuous infusion at 8mg/kg/min) infusion compared to continuous infusion only: • Little to no effect on the hypoglycaemic episodes during treatment IV 20% dextrose continuous infusion (at an initiation rate of 8mg/kg/min) compared to IV 15% dextrose continuous infusion (at the same initiation rate of 8mg/kg/min) : • Moderate reduction in hypoglycemic episodes [critical] • Little to no effect on phlebitis [adverse effect, critical] • Little to no effect on average plasma glucose levels IV 10% dextrose with dose tailored to baseline blood glucose concentration (BCG) (if baseline BCG < 1.1 mmol/L mg/dL: 2mL/kg bolus followed by continuous infusion at 60mL/kg/day; if baseline BGC 1.1-1.7 mmol/L: continuous infusion at 60mL/kg/day; if baseline BGC 1.7-2.4 mmol/L: continuous infusion at 30 mL/kg/day) compared to the same with no tailored approach to bolus and continuous infusion (2mL/kg bolus followed by continuous infusion at 60mL/kg/day) : • Large reduction in cost of NICU stay [important]	

	• No data for any other critical or important outcomes **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The administration of IV dextrose usually necessitates admission to the neonatal intensive care unit (NICU), incurring substantial costs. Treatment with IV dextrose requires resources including the dextrose preparation itself and care in NICU. In Aotearoa New Zealand, the average cost of NICU has been estimated at NZ$2,200 per day. A 500mL preparation of glucose 10% IV solution costs approximately NZ$26.65 (9) and the initial infusion level for hypoglycaemic neonates recommended by Starship is 60mL/kg/day (10). There is substantial additional cost of staff time to set up and maintain an intravenous infusion.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ● High ○ No included studies	High certainty about the cost of the average cost of NICU, 10% dextrose IV solution.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There is no evidence directly comparing the costs of IV dextrose treatment and different treatment options for neonatal hypoglycaemia. However, NICU admission is usually required for IV dextrose treatment, whereas babies receiving other treatments such as breastmilk or oral dextrose gel are not necessarily admitted to NICU, and care in NICU comes with substantial additional costs. In Aotearoa New Zealand, the average cost of NICU has been estimated at NZ $ 2,200 per day. One study based in the USA found an association with reduced duration of NICU stay (1.5 days) and therefore reduced cost of NICU stay (US $ 5,441 per baby) when babies were treated with an IV dextrose infusion dose tailored according to their initial blood glucose concentration, compared to treating all babies with the same IV 10% dextrose bolus followed by infusion.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (12). *However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (13). *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (12).	

	In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%) (13). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (12). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (14)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (15, 16, 17). *Additionally, a systematic literature review by Graham et al.* (18) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (14). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (14). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (11). *Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (11)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We found no evidence of the acceptability of IV dextrose for the treatment of neonatal hypoglycaemia. In the Whānua experience study (14), one Asian parent expressed fear that their child would be admitted to NICU to be treated with IV dextrose, and were thankful for the option to treat hypoglycaemia with a less invasive dextrose gel instead. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	In a qualitative study conducted in Aotearoa New Zealand (19), six parents were interviewed and reported a range of emotions experienced by families during their initial admission to the NICU, including guilt, fear, and anxiety. The study underscored the importance of comprehensive information and consistent care. Participants who had undergone a pre-admission tour or received continuity of nursing care following NICU admission highlighted the immense value of these experiences, especially during emotionally charged periods.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The existence of guidelines for IV treatment of neonatal hypoglycaemia in Aotearoa New Zealand suggests this intervention is already implemented in New Zealand hospitals. There appears to be some variation in the dose of dextrose in various guidelines, with little evidence to support one dosing regimen over another. However, the administration of IV dextrose requires specialised skills and resources, making it not feasible in many smaller healthcare units. This necessity often mandates the transfer of these babies to higher level facilities equipped and staffed to provide such care. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Roberts LF, Lord L, Crowther CA, Harding JE, Lin L. Intravenous dextrose for the treatment of neonatal hypoglycaemia: a systematic review. Neonatology. In press.
2. Bora R, Deori S.. Transitional Hypoglycaemia Management in Small for Gestational Age Neonates with Sucrose Enriched Expressed Breastmilk in Resource Poor Setting. Journal of Tropical Pediatrics. 2019;1;66(3):267-274
3. Burakevych N, McKinlay CJD, Harris D., Alsweiler JM., Harding JE. Factors influencing glycaemic stability after neonatal hypoglycaemia and relationship to neurodevelopmental outcome. Scientific Reports. 2019;9:8312
4. Lilien LD, Pildes RS, Srinivasan G, Voora S, Yeh TF. Treatment of neonatal hypoglycemia with minibolus and intraveous glucose infusion. Journal of Pediatrics. 1980;97(2):295-8.
5. Vanhatalo T, Tammela O. Glucose infusions into peripheral veins in the management of neonatal hypoglycemia--20% instead of 15%?. Acta Paediatrica. 2010;99(3):350-3.
6. Sen S, Cherkerzian S, Turner D, Monthé-Drèze C, Abdulhayoglu E, Zupancic JAF. A graded approach to intravenous dextrose for neonatal hypoglycemia decreases blood glucose variability, time in the neonatal intensive care unit, and cost of stay. The Journal of Pediatrics. 2021;231:74-80.

7. Brand PL, Molenaar NL, Kaaijk C, Wierenga WS. Neurodevelopmental outcome of hypoglycaemia in healthy, large for gestational age, term newborns. Archives of Disease in Childhood. 2005;90(1):78-81.
8. McKinlay CJ, Alsweiler JM, Ansell JM, Anstice NS, Chase JG, Gamble GD, et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. New England Journal of Medicine. 2015;373(16):1507-18.
9. CapesMedical. IV fluids. 2023 [cited 2 February 2024]; Available from:https://www.capesmedical.co.nz/shop/Intravenous++Administration/IV+Fluids.html; 2023.
10. Newborn Services Clinical Practice Committee, Starship Child Health. Hypoglycaemia in the neonate. 16 April 2024 [cited 2 September 2024]; Available from: https://starship.org.nz/guidelines/hypoglycaemia-in-the-neonate/
11. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
12. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
13. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
14. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
15. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
16. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
17. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
18. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
19. Parai, Colette. Family integrated care in a New Zealand neonatal intensive care unit: a qualitative study. 2020. Master's thesis, University of Otago. Available from: http://hdl.handle.net/10523/10867

Question 25.

Should diazoxide vs. placebo be used for treating neonatal hypoglycaemia?	
POPULATION:	Babies with neonatal hypoglycaemia
INTERVENTION:	diazoxide
COMPARISON:	placebo
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies)

	5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (baby of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Transient hypoglycaemia is the commonest type of neonatal hypoglycaemia. Neurodevelopmental impairment after hypoglycaemia continues to occur in babies who have been treated with buccal dextrose gel and intravenous dextrose. Diazoxide has been proposed as a potential treatment for transitional neonatal hypoglycaemia, owing to its physiological mechanism of directly slowing insulin secretion at the level of pancreatic beta cells. This drug is already used in cases of congenital hyperinsulinism, but may be beneficial in more common types of hypoglycaemia.
CONFLICT OF INTERESTS:	DH, JA, JH, JR, and LL are authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	One recent randomised controlled trial (NeoGluCO) conducted in Aotearoa New Zealand found that a low dose of diazoxide (3 mg/kg/day)) for early management of severe or recurrent neonatal transitional hypoglycaemia (1): • may result in a large increase in the correction of hypoglycaemia after completing the loading of the study drug (469 more per 1,000) • may be associated with a moderate increase in full breastmilk feeding at the hospital discharge (87 more per 1,000)	The NeoGluCO study (1)also found • No difference in time to resolution of hypoglycaemia (adjusted hazard ratio 1.39, 95% CI 0.84-2.23) • Longer time to achieve normoglycaemia (2.6 to 5.4 mmol/L) for ≥24 hours in the diazoxide group (ajdusted ratio of geometric means (aRGM) 1.29, 95% 1.00, 1.67).

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with diazoxide
Correction of hypoglycaemia after completing the loading of the study drug	74 (1 RCT)	⨁⨁⨁◯ Moderate[a]	**RR 1.99** (1.41 to 2.81)	Study population	
				474 per 1,000	**469 more per 1,000** (194 more to 857 more)
Neurodevelopmental impairment - not reported	-	-	-	-	-
Admission to special care nursery or neonatal intensive care nursery - not reported	-	-	-	-	-
Adverse effects - not reported	-	-	-	-	-
Fully breastmilk feeding at hospital discharge	74 (1 RCT)	⨁⨁⨁◯ Moderate[b]	**OR 1.42** (0.55 to 3.68)	Study population	
				474 per 1,000	**87 more per 1,000** (143 fewer to 294 more)
Separation from the mother for treatment of hypoglycaemia before discharge home - not reported	-	-	-	-	-
Hypoglycaemic injury on brain imaging - not reported	-	-	-	-	-
Breastmilk feeding exclusively from birth to discharge - not reported	-	-	-	-	-
Duration of initial hospital stay - not reported	-	-	-	-	-

- Little to no difference in hypoglycaemia >48 hours after randomization (OR 0.19 (0.02, 1.76))
- Exclusive breastfeeding from birth (0/36 in the diazoxide group; 4/38 in the placebo group).

Babies treated with diazoxide had: (2)

- Shorter duration of intravenous fluid therapy compared to placebo (mean (SD) 114 (51) hours vs 164 (71) hours; mean difference: -50 hours [95% CI -94, to -6])
- Shorter time to achieving full enteral feeds (mean (SD) 117 (51) hours vs 166 (65) hours; MD -49 hours [95% CI -91 to -7])
- Shorter time to reaching euglycaemia (defined as blood glucose measurements consistently exceeding more than 2.8 mmol/L for at least 24 hours) (mean (SD) 41 (29) hours vs 74 (58) hours; MD -33 hours [95% CI -66 to -0])

Cost (cost of intervention, cost of neonatal care and life-long cost) - not reported	-	-	-	-	-	

a.Downgraded one level for serious imprecision due to optimal information size criterion not met.
b.Downgraded one level for serious imprecision due to the confidence interval including both benefits and hard.
*Absolute effects were calculated based on the control group risk .

An earlier systematic review investigating the efficacy of diazoxide in treating transitional neonatal hypoglycaemia found only one RCT conducted in India. This trial involved 30 low-birth weight babies diagnosed with hyperinsulinaemic hypoglycaemia within 5 days after birth. Babies were randomly assigned to receive either oral diazoxide (9 mg/kg/day in 3 divided doses, with an increase to 12 mg/kg/day if hypoglycaemia persisted after 48 hours) or a placebo (2). However, no evidence was found for any of the critical or important outcomes.

Another recent systematic review assessed six cohort studies involving 1,142 children (aged from 1 day to 17 years) with hyperinsulinaemic hypoglycaemia who received diazoxide treatment. Five of these studies provided outcomes relating to the response of neonates to diazoxide, with a pooled proportion of those responsive to diazoxide of 71% (95% CI 50% to 93%, p <0.001) (3). This suggests diazoxide may be associated with the correction of hypoglycaemia.

Considerations for Māori
No additional data available

Considerations for Pacific
No additional data available

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large	The NeoGluCO study (1) had limited power to detect these potential adverse effects. In the systematic review investigating the efficacy of diazoxide in treating transitional neonatal hypoglycaemia, no evidence was found for any of the critical or important	The NeoGluCO study (1) also reported: • More episode of hyperglycaemia episode (blood glucose concentration ≥7.0 mmol/L)

○ Varies ○ Don't know	outcomes (2). In the systematic review of six cohort studies (3), the pooled proportion of participants with each of the reported adverse effects were: • oedema 11% (95% CI 0 to 22; 2 studies, p <0.001) • fluid retention 20% (95% CI -18 to 59; 2 studies, p = 0.008) • gastrointestinal reaction 13% (95% CI -13 to 39; 2 studies, p = 0.045) • hypertrichosis 45% (95% CI -27 to 117; 2 studies, p < 0.001). This is the most common side effect, which is thought to depend on the dose for each patient. However, it can persist for a month after the treatment is stopped (4). • neutropaenia 9% (95% CI 0 to 19; 2 studies, p = 0.005) • pulmonary hypertension 2% (95% CI 0 to 4; 3 studies, p = 0.005) • thrombocytopaenia 2% (95% CI -1 to 5; 2 studies, p = 0.008) In one cohort study of very high-risk babies, 13% developed necrotising enterocolitis (NEC), which has a high mortality rate (5). **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	(diazoxide: median, 0 [IQR, 0-1]; placebo: median, 0 [IQR, 0-0]) ((adjusted count ratio, ACR 3.04 [95% CI, 1.24-7.45]); no newborns had the intervention stopped because of hyperglycaemia . • More episodes of elevated blood glucose concentration (5.5-7.0 mmol/L) (diazoxide: median, 2 [IQR, 1-3]; placebo: median, 0 [IQR, 0-1]) (ACR 2.65 [95% CI, 1.72-4.11])

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		

Outcomes	Importance	Certainty of the evidence (GRADE)
Correction of hypoglycaemia after completing the loading of the study drug	CRITICAL	⨁⨁⨁◯ Moderate[a]
Neurodevelopmental impairment - not reported	CRITICAL	-

Admission to special care nursery or neonatal intensive care nursery - not reported	CRITICAL	-
Adverse effects - not reported	CRITICAL	-
Fully breastmilk feeding at hospital discharge	CRITICAL	⨁⨁⨁◯ Moderate[b]
Separation from the mother for treatment of hypoglycaemia before discharge home - not reported	IMPORTANT	-
Hypoglycaemic injury on brain imaging - not reported	IMPORTANT	-
Breastmilk feeding exclusively from birth to discharge - not reported	IMPORTANT	-
Duration of initial hospital stay - not reported	IMPORTANT	-
Cost (cost of intervention, cost of neonatal care and life-long cost) - not reported	IMPORTANT	-

a.Downgraded one level for serious imprecision due to optimal information size criterion not met.
b.Downgraded one level for serious imprecision due to the confidence interval including both benefits and hard.

The outcome from the NeoGluco Study was assessed as moderate certainty.

The outcomes that were reported from the other RCT provide low certainty evidence as they are derived from only one study with small sample size and include only small-for-gestational-age babies with hyperinsulinaemic hypoglycaemia, narrowing the population that this evidence applies to (2).The systematic review which included six cohort studies, despite reporting them as being of "generally high" quality, found that only 2 of these 6 studies had 7 or more stars on the 9-star Newcastle-Ottawa Scale, indicating higher quality. However, the evidence from observational studies is considered low certainty (3). In addition, this systematic review exclusively focuses on babies with a rare form of hypoglycaemia, known as hyperinsulinemic hypoglycaemia, rather than the more

	prevalent transitional neonatal hypoglycaemia. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects		

Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	Diazoxide compared to placed result in or is associated with • Moderated certainty evidence showed • Large decrease in hypoglycaemia • Moderate increase in full breastmilk feeding at discharge **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	Desirable effects • Large decrease in duration of intravenous fluid therapy • Large decrease in time to achieving full enteral feeds • Large decrease in time to reaching euglycaemia Undesirable effects (may be dose-dependent) • Elevated blood glucose • Hyperglycaemia • oedema • fluid retention • gastrointestinal reaction • hypertrichosis • neutropenia • pulmonary hypertension • thrombocytopaenia • possible risk of NEC
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	100 capsules of 25mg cost NZ $ 110, and a 30ml bottle of 50mg/ml oral liquid costs NZ $ 620 (Pharmac, NZ). There have been reports of manufacturing oral diazoxide within hospital pharmacies, e.g., for the NeoGluCO study conducted in Auckland, Aotearoa New Zealand, diazoxide capsules were combined into a sugar-free paediatric solution (6). This mixture for a 3kg baby costs ~NZ $ 1 for the loading and first maintenance dose. There would be additional pharmacy costs for making up the mixture.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	We are reasonably confident in the costs of the diazoxide. There is no evidence about the additional costs of making up a mixture.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There is no evidence about cost-effectiveness.	
Equity What would be the impact on health equity?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (8)*. However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (9)*.* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (8)*.* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (9)*.* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (8)*.* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (10)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.*	

	Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism (11, 12, 13). *Additionally, a systematic literature review by Graham et al.* (14) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (14). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (10). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (7). *Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (7)*, 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	There is no evidence about the acceptability of diazoxide as a treatment for neonatal hypoglycaemia. The oral administration of diazoxide is likely preferable to parents compared to other treatments such as intravenous dextrose. However, there is currently no information available regarding how acceptable parents find potential adverse effects. **Considerations for Māori** No additional data available	

	Considerations for Pacific No additional data available	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Diazoxide is available in Aotearoa New Zealand under special authority for hyperinsulinism, although the cost remains high for the liquid paediatric formulation (Pharmac, NZ). Use for other indications may be more feasible if the solution is made up in hospital pharmacies (6). The NeoGluco study has finished recruiting, suggesting that the use of diazoxide in babies is feasible in a research setting. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

REFERENCES SUMMARY

1. Laing D, Walsh EPG, Alsweiler JM, Hanning SM, Meyer MP, Ardern J, et al. Diazoxide for Severe or Recurrent Neonatal Hypoglycemia: A Randomized Clinical Trial. JAMA Netword Open. 2024;7(6):e2415764.
2. Laing D, Hanning SM, Harding JE, Mravicich LC, McKinlay CJ. Diazoxide for the treatment of transitional neonatal hypoglycemia: a systematic review. Journal of Neonatology. 2021;35(4):203-208.
3. Chen X, Feng L, Yao H, Yang L, Qin Y. Efficacy and safety of diazoxide for treating hyperinsulinemic hypoglycemia: a systematic review and meta-analysis. PLoS ONE. 2021; 16(2):e0246463.
4. Boskabadi SJ, Ramezaninejad S, Sohrab M, Farhadi R. Diazoxide-induced hypertrichosis in a neonate with transient hyperinsulinism. Clinical Medicine Insights: Case Reports; 2023.
5. Prado, Laura,A., Castro, Marina, Weisz, Dany,E., Jain, Amish, Belik, Jaques. Necrotising enterocolitis in newborns receiving diazoxide.Archives of Disease in Childhood. Fetal and Neonatal Edition. 2021;16:11795476231151330.
6. Laing D, Walsh E, Alsweiler JM, Hanning SM, Meyer MP, Ardern J, et al . Oral diazoxide versus placebo for severe or recurrent neonatal hypoglycaemia: Neonatal Glucose Care Optimisation (NeoGluCO) study – a randomised controlled trial. BMJ Open. 2022;12(8):e059452.
7. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
8. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
9. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
10. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
11. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
12. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
13. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
14. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.

Question 26.

Should glucagon vs. control be used for neonatal hypoglycaemia?	
POPULATION:	Babies with neonatal hypoglycaemia

INTERVENTION:	glucagon
COMPARISON:	control
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Clinical settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn babies over the first few days after birth, particularly in those with recognised risk factors (babies of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* Glucagon is a hormone secreted by the pancreas that opposes the effects of insulin. It is commonly used to treat hypoglycaemia in older children and adults, and can be administered via several routes (intramuscular, intranasal, or intravenous (IV) infusion). However, few studies have addressed its effectiveness in newborn babies.
CONFLICT OF INTERESTS:	JA, JH, JR and LL are authors of a cited paper.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	A systematic review and meta-analysis identified three single-arm non-randomised intervention studies involving 198 newborn babies, suggesting that the rate of correction of hypoglycaemia with glucagon may be as high as 90% (1). Carter 1988 (2) and Nakamura 1995 (3) found that babies had ongoing hypoglycaemia despite receiving intravenous dextrose and were given continuous intravenous (IV) glucagon; babies in Kasirer 2021 (4) received a single 1 mg dose of glucagon by intramuscular injection if the initial blood glucose concentration at 2 hours was <2.8 mmol/L. Kasirer 2021 excluded babies who were born small for gestational age (SGA); Carter 1998 only included babies with a birthweight <5th centile. Rates of correction of hypoglycaemia by 4 hours were 20/23 (80%) (2), 145/158 (92%) (4) and 14/15 (93%) (3). There was no data for any other critical or important outcomes.	Two single-arm non-randomised intervention studies, involving 80 newborn babies, suggest that the rate of recurrence of hypoglycaemia after glucagon may be as high as 49%. In both Carter 1998 (2) and Miralles 2002 (5), babies received continuous IV glucagon and hypoglycaemia recurred in some babies while on the glucagon infusion. The systematic review (1) showed that blood/plasma glucose concentration increased by 2.2 mmol/L at 1 to 2 hours after glucagon administration. The route and dose of administration did not appear to affect the glucose response (1). In non-hypoglycaemic preterm babies (≤32 weeks), the effect of glucagon on hepatic glucose output at 1 hour was similar in SGA and appropriate for gestational age (AGA) babies (n=5 each). Glycogenolysis contributed 75% to 80% of the increase in glucose production (~1.6 mmol/L in both groups) (6). In four babies with severe hypoglycaemia, an IV bolus of glucagon causes a rapid rise in hepatic glucose production, which was sustained for many hours (7).

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with control	Risk difference with glucagon
Correction of hypoglycaemia within 4 hours [critical] assessed with: blood or plasma assay	198 (3 non-randomised studies)	⨁⨁◯◯ Low[a,b]	-	Three single arm non-randomised intervention studies involving 198 newborn babies suggest that the rate of correction of hypoglycaemia with glucagon may be as high as 90%.	
Neurodevelopmental impairment [critical] - not measured	-	-	-	-	-
Admission to special care or neonatal intensive care nursery [critical] - not measured	-	-	-	-	-

Fully breastfeeding at hospital discharge [critical] - not measured	-	-	-	-	-	
Separation from the mother for treatment of hypoglycaemia before discharge home [important] - not measured	-	-	-	-	-	
Hypoglycaemic injury on brain imaging [important] - not measured	-	-	-	-	-	
Breastmilk feeding exclusively from birth to hospital discharge [important] - not measured	-	-	-	-	-	
Duration of initial hospital stay [important] - not measured	-	-	-	-	-	
Cost [important] - not measured	-	-	-	-	-	

a.Downgraded one level for serious indirectness due to single-arm non-randomised intervention studies or case series, no controls
b.Downgraded one level for serious risk of bias due to bias in selection of participants, measurement of outcomes or ascertainment of exposures.

Considerations for Māori
No additional data available
Considerations or Pacific
No additional data available

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No data were available for adverse events (1). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Nausea and vomiting may occur in up to two thirds of adults following treatment with glucagon (1).
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence is very uncertain. **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]*	

	• *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	• Uncertain effect on correcting neonatal hypoglycaemia. • No data for adverse effects. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

Resources required
How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The main costs are the drug and administration time. An injection 1mg syringe kit containing glucagon costs NZ $32 (Pharmac, NZ) The costs of drug administration depends on route of administration, and is likely to be low for intramuscular injection.	

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	We are reasonably certain about the cost of glucagon, but uncertain about the cost of staff time.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There is no evidence of the cost-effectiveness.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism,*	

	income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions. ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (9*). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (10*).* *Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (9*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (10*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (9*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (11*), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (12, 13, 14*).* *Additionally, a systematic literature review by Graham et al.* (15*) provides a summary of 20 years of data from whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (15*).* ***Consideration for Pacific***	

	Some Pacific women interviewed in the Whānau experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work (11). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities (8). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey (8), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	There is no direct evidence about the acceptability of glucagon, or the preferred route of administration. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	One of the hospitals included in the systematic review employed a universal screening policy for babies at 2 hours of age and used glucagon intramuscular injection as first-line treatment (1).

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Glucagon is widely available in Aotearoa New Zealand and is commonly used in older children and adults. It is likely to be feasible to administer by the intramuscular route in most settings. **Considerations for Māori** No additional evidence available	

	Considerations for Pacific No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**

	JUDGEMENT						
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

REFERENCES SUMMARY

1. Walsh EPG, Alsweiler JM, Ardern J, Hanning SM, Harding JE, McKinlay CJD. Glucagon for neonatal hypoglycaemia: systematic review and meta-analysis. Neonatology. 2022;119(3):285-294.
2. Carter PE, Lloyd DJ, Duffty P. Glucagon for hypoglycaemia in infants small for gestational age.Archives of Disease in Childhood. 1988;63(10):1264-6.
3. Nakamura, T, Mori , S, Ozawa , H, Nakamoto, M, Nishida, A. Continuous glucagon infusion for severe hypoglycemia in infants. Acta Neonatologica. 1995; (31)1:105-10
4. Kasirer Y, Dotan O, Mimouni FB, Wasserteil N, Hammerman C, Bin-Nun A. The use of intramuscular glucagon to prevent IV glucose infusion in early neonatal hypoglycemia. Journal of Perinatology. 2021;41(5):1158-1165.
5. Miralles RE, Lodha A, Perlman M, Moore AM. Experience with intravenous glucagon infusions as a treatment for resistant neonatal hypoglycemia. Archives of Pediatrics and Adolescent Medicine. 2002;156(10):999-1004.
6. van Kempen AA, Ackermans MT, Endert E, Kok JH, Sauerwein HP. Glucose production in response to glucagon is comparable in preterm AGA and SGA infants. Clinical Nutrition. 2005;24(5):727-36.
7. Mehta A, Wootton R, Cheng KN, Penfold P, Halliday D, Stacey TE. Effect of diazoxide or glucagon on hepatic glucose production rate during extreme neonatal hypoglycaemia. Archives of Disease in Childhood; 1987;62(9):924-30.
8. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
9. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
10. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
11. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
12. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
13. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
14. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
15. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.

Question 27.

Should secondary or tertiary level care settings vs. primary care setting be used for monitoring babies with neonatal hypoglycaemia?	
POPULATION:	Babies with neonatal hypoglycaemia
INTERVENTION:	secondary or tertiary level care settings

COMPARISON:	primary care setting
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies) 3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any hospital setting where neonates are cared for
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn infants over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* However, it is unclear which settings should be used for monitoring babies with neonatal hypoglycaemia. In New Zealand, levels of maternity care are broadly defined as (1): Primary: The Primary Maternity Facility provides a physical setting for assessment, labour and birth, and postnatal care. It may be a stand - alone facility or unit within a Level 1 or 2 general hospital as defined in the New Zealand Role Delineation Model. The Primary Maternity Facility, in conjunction with the Lead Maternity Carer (LMC) or DHB-funded Primary Maternity Services Provider, provides primary maternity inpatient services during labour and birth and the postnatal period until discharge or transfer (the Service). Primary Maternity Facilities have no inpatient Secondary or Tertiary Maternity Services. Location: Greymouth, Blenheim, Masterton, Wanganui, Timaru: babies with minimal complications and gestational age ≥ 35 weeks.

	Secondary: Secondary Maternity Services are those provided where women and / or their babies experience complications that need additional maternity care involving Obstetricians, Paediatricians, other Specialists and secondary care teams. Location: New Plymouth, Hawkes Bay, Palmerston North: For babies with moderate to severe complications and gestational age ≥ 28 weeks; Whangarei, North Shore, Waitemata, Tauranga, Rotorua/Taupo, Gisborne, Hutt, Nelson, Invercargill: babies with moderate complications and gestational age ≥ 32 weeks. Tertiary: Tertiary Maternity Services are additional maternity care provided to women and their babies who have highly complex clinical needs and require consultation with and / or transfer of care to a multidisciplinary specialist team. Location: Auckland (National Women's Hospital) Middlemore, Waikato, Wellington, Christchurch, Dunedin (except surgery). Starship Childrens' Hospital also provides care from a small number of babies with cardiac conditions of complex surgical conditions requiring specialist care.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are authors of the cited paper.

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	We found no evidence for any of the critical or important outcomes. Compared with care in a primary setting, higher levels of care are likely to provide easier and faster access to accurate glucose measuring devices and results of glucose testing, assessment by a paediatrician, and intravenous glucose administration if required. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	In a review of litigation claims related to neonatal hypoglycaemia in the UK (2), 15/28 babies presented on the postnatal wards, 11 developed clinical signs at home, one was in a midwifery-led unit and one was treated in NICU but had recurrence of hypoglycaemia after discharge home. Ten babies (36%) had no clear risk factors that would have been detectable at birth. Likely deficits in care were identified including: Initial glucose measurement on a cotside device were likely to be insufficiently accurate in 27 babies (96%) but in one, a policy of laboratory measurement led to excessive delay because the sample was analysed in a distant laboratory.

		Discharge to the community with risk factors or abnormal signs, without assurance that feeding was sufficient (9 babies, 32%). Delay in referral to a paediatrician or attendance by a paediatrician after concerns were identified (4 babies, 14%). Delayed admission to NICU (3 babies, 11%), or delayed administration of IV dextrose after NICU admission (2 babies, 7%).
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	We found no evidence for any of the critical or important outcomes. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	Compared with care in a primary setting, higher levels of care have been shown to be associated with increased interventions, lower rates of breastfeeding and reduced satisfaction with care (3). In the New Zealand National Infant Feeding Data at Discharge 2022 report, primary Maternity Services achieve a consistently high rate of exclusive breastfeeding, and only 3 of 6 tertiary services are meeting the Baby Friendly Hospital Initiative standard of at least 75% of babies receiving only breastmilk throughout their stay in the maternity service (4). In the New Zealand Midwifery and Maternity Provider Organisation (MMPO) 2016 report of 30,526 babies born in Aotearoa New Zealand, the exclusive breastfeeding rates at 6 weeks were 79.7% for homebirth, 69.2% for birth in a primary facility, 59.7% for birth in a secondary

		facility, and 56.1% for birth in a tertiary facility (5). There is some evidence that prolonged and severe hypoglycaemia is associated with adverse neurodevelopmental outcomes (6). This maybe more likely if access to definitive treatment, particularly intravenous glucose administration, is delayed.
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We found no evidence for any of the critical or important outcomes. Considerations for Māori No additional evidence available Considerations for Pacific No additional evidence available	The cohort reported in the UK litigation study (2) was not typical of babies presenting with hypoglycaemia. They were likely to be babies with severe and prolonged hypoglycaemia causing harm, and whose parents identified deficits in care.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]*	

variability	• *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Secondary or tertiary levels of care are likely to provide easier and faster access to diagnosis and treatment of neonatal hypoglycaemia, which may reduce the risk of adverse neurodevelopmental outcomes. However, this may result in a reduction in exclusive breastfeeding and reduced satisfaction with care. **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs	Secondary and tertiary care settings are likely to be more expensive than primary care, but payments to the LMC and to the care facility are the same for all levels of care unless the	

○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	baby is admitted to NICU or remains in hospital after discharge of the mother. There are substantially greater costs to whānau/family if they need to travel to access secondary or tertiary care settings compared to primary care settings closer to home. If a baby requires transfer from a primary to a secondary or tertiary care setting for additional investigation or treatment there is a substantial additional cost for the healthcare system and also for the whānau/family. Costs of transfer: Flight: Costs range from NZ$2,800 – $13,500 per flight hour. Vehicle: Minimum costs are approximately NZ $200, but total cost depends on distance ($5.29-$6.14 per km). There are additional costs related to the organisation and staffing of transfers.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	We are confident that secondary and tertiary care settings are considerably more expensive than primary care but have not obtained detailed costings.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	The cost of monitoring all babies with neonatal hypoglycaemia in secondary, or tertiary-level care settings is unlikely to favour the intervention. However, it is unclear whether resources may be saved from a potential earlier treatment of neonatal hypoglycaemia to prevent neurodevelopmental impairment.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%) (8). However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%) (9).*	

	Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%) (8*).* *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (9*).* *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (8*).* ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (10*), participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (11, 12, 13*).* *Additionally, a systematic literature review by Graham et al.* (14*) provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst Whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (14). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (10*).* ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (7*). Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (7*), 71% of women reported that they had paid for at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.*	
Acceptability		

Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Studies conducted in Canada (15, 16) examining parental perceptions of neonatal transfers from Level 3 to Level 2 care units, found that early notification, close collaboration, and ongoing, open communication between parents and healthcare teams can increase parental satisfaction rates, reduce distress, and alleviate anxiety. **Considerations for Māori** No additional evidence available **Considerations for Pacific** In the Whānau experience study, some Pacific women reported anxiety around admissions to NICU and separation from their newborn during the vulnerable period post-birth (10). **Considerations for Asian** In the Whānau experience study, a few Asian participants expressed finding the hospital environment challenging, and struggled with long, complicated hospital stays (10).	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	It is unlikely to be feasible for all babies at risk to receive secondary and tertiary levels of care, as there are limited numbers of these units and they may be considerable distances away from where whānau/families are living. Not all infants born at risk of neonatal hypoglycaemia can be identified before birth, and not all babies who develop neonatal hypoglycaemia have identified risk factors (17). **Considerations for Māori** No additional evidence available **Considerations for Pacific** No additional evidence available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

REFERENCES SUMMARY

1. Te Whatu Ora, Health New Zealand . Maternity service specifications. 01 May 2014 [cited 2 February 2024]; Available from: https://www.tewhatuora.govt.nz/our-health-system/nationwide-service-framework-library/about-nationwide-service-specifications/maternity-service-specifications/; 2023.
2. Hawdon JM, Beer J, Sharp D, Upton M; NHS Improvement Patient Safety Programme 'Reducing Term Admissions to Neonatal Units'. Neonatal hypoglycaemia: learning from claims. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2017;102(2):F110-F115.
3. Singh D, Newburn M. (eds). Women's experiences of postnatal care. National Childbirth Trust. London. June 2000
4. New Zealand Breastfeeding Alliance. National Infant Feeding Data at Discharge. 2022. [cited 2 February 2024]]; Available from: https://www.babyfriendly.org.nz/fileadmin/Documents/NZBA_NationalInfantFeedingDataAtDischarge_Report_2022.pdf; 2022.
5. New Zealand College of Midwives. MMPO Report on New Zealands MMPO midwives 2016. January 2019. [cited 2 February 2024]]; Available from:https://www.midwife.org.nz/wp-content/uploads/2019/01/MMPO-report-2016.pdf; 2016.
6. Shah R, Harding J, Brown J, McKinlay C. Neonatal glycaemia and neurodevelopmental outcomes: a systematic review and meta-analysis. Neonatology. 2019;115(2):116-126.

7. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
8. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
9. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
10. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
11. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
12. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
13. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
14. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.
15. Dosani A, Murthy P, Kassam S, Rai B, Lodha AK. Parental perception of neonatal transfers from level 3 to level 2 neonatal intensive care units in Calgary, Alberta: qualitative findings. BMC Health Services Research. 2021;21(1):981.
16. Murthy P, Dosani A, Sikdar KC, Koleade A, Rai B, Scotland J, et al. Parental perception of neonatal retro-transfers from level 3 to level 2 neonatal intensive care units. The Journal of Maternal - Fetal and Neonatal Medicine. 2022;35(25):5546-5554.
17. Hawdon JM, Beer J, Sharp D, Upton M; NHS Improvement Patient Safety Programme 'Reducing Term Admissions to Neonatal Units'. Findings and resources for improvement; 2016. [cited 2 February 2024]]; Available from: https://www.england.nhs.uk/wp-content/uploads/2021/03/reducing-harm-leading-to-avoidable-admission-of-full-term-babies-into-neonatal-units.pdf

Question 28.

Should risk factors for adverse long-term outcomes vs. no risk factors for adverse long-term outcomes be used for guiding the management of babies at risk of neonatal hypoglycaemia?	
POPULATION:	Babies at risk of neonatal hypoglycaemia
INTERVENTION:	risk factors for adverse long-term outcomes
COMPARISON:	no risk factors for adverse long-term outcomes
MAIN OUTCOMES:	- Consideration will be given to the evidence (or lack thereof) for both Māori and non-Māori babies and their whānau. **Critical for making a decision:** 1. Hypoglycaemia (minimum effect size >=20 per 1000 babies) 2. Neurodevelopmental impairment (minimum effect size >=10 per 1000 babies) 3. Admission to special care nursery or neonatal intensive care nursery (minimum effect size >=20 per 1000 babies) 4. Adverse effects (for neonatal mortality minimum effect size >=1 per 1000 babies) 5. Fully breastfeeding at hospital discharge (minimum effect size >=20 per 1000 babies) **Important but not critical:** 1. Separation from the mother for treatment of hypoglycaemia before discharge home (minimum effect size >=20 per 1000 babies) 2. Hypoglycaemic injury on brain imaging (minimum effect size >=10 per 1000 babies)

	3. Breastmilk feeding exclusively from birth to hospital discharge (minimum effect size >=20 per 1000 babies) 4. Duration of initial hospital stay (minimum effect size >=0.5 days per 1000 babies) 5. Cost (for whānau >=10 NZD per 1000 babies, for health system >=100 NZD per 1000 babies) **Less important for decision making:** 1. Time to blood glucose normalisation after intervention 2. Receipt of treatment for hypoglycaemia during initial hospital stay 3. Number of episodes of hypoglycaemia 4. Severity of hypoglycaemia 5. Duration of treatment
SETTING:	Any birth settings
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	*Low blood glucose concentrations (hypoglycaemia) are common in newborn infants over the first few days after birth, particularly in those with recognised risk factors (infants of mothers with diabetes, or born preterm, low or high birthweight). Severe or prolonged hypoglycaemia can lead to brain injury, so early detection and treatment is recommended to reduce the risk of later developmental problems.* It would be useful to know which risk factors are associated with long-term adverse events in babies who develop hypoglycaemia.
CONFLICT OF INTERESTS:	DH, JA, JH, JR and LL are authors of cited papers.

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No evidence for any critical or important outcomes. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	Retrospective observational studies have found no associations between neonatal hypoglycaemia and a range of risk factors used for screening for neonatal hypoglycaemia (e.g., infant of diabetic mother (IDM), preterm, small (SGA) or large for gestational age (LGA)) used for screening (1). However, a negative association between insulin treatment for maternal gestational diabetes and neonatal hypoglycaemia has been identified (2).

		In a subgroup analysis of the hPOD trial cohort, there was no difference in long-term outcomes between IDM and babies with other risk factors. However, the higher rate of neurodevelopmental impairment found in the overall cohort of children with hypoglycaemia, was seen in IDM but not in children with other risk factors (3). Whether LGA babies whose mothers did not have diabetes are at increased risk for neonatal hypoglycaemia is contentious, with only half of international/state guidelines considering them at increased risk sufficient to recommend testing (4). In litigation for adverse events due to hypoglycaemia, all the babies were either IDM or SGA, and none were LGA babies (5). There is no evidence that otherwise healthy LGA babies are at increased risk of neurodevelopmental impairment due to neonatal hypoglycaemia (6).
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No direct research evidence. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No direct research evidence. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	*Excerpts from Values summary document* ***Uncertain value, possible variability*** • *Hypoglycaemia [critical]* • *Adverse effect [critical]* ***High value, no important variability*** • *Neurodevelopmental impairment [critical]* • *Fully breastfeeding at hospital discharge [critical]* • *Breastfeeding exclusively from birth to hospital discharge [important]* ***High value, probably no important variability*** • *Admission to special care nursery or neonatal intensive care nursery [critical]* • *Separation from the mother for treatment of hypoglycaemia before discharge home [important]* • *Duration of initial hospital stay [important]* ***Uncertain value and variability*** • *Hypoglycaemic injury on brain imaging [important]* • *Cost [important]*	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Not applicable as no direct research evidence. **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Not applicable **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	Not applicable **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Not applicable **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	***Are there groups or settings that might be disadvantaged in relation to the problem or intervention of interest?*** *There is little published literature and therefore it is unclear if there are any groups or settings that might be disadvantaged in relation to the problem or intervention of interest.* ***Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged groups or settings?*** *There is little published literature. It is unlikely that the effectiveness of interventions would differ for disadvantaged groups or settings. However, within Aotearoa New Zealand, social determinants of health (e.g., colonisation, racism, income, education, employment and housing) are likely to have an impact on the implementation, and therefore the effectiveness, of interventions.* ***Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention for the importance of the problem for disadvantaged groups or settings?*** *Māori babies (190/530, 35.8%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (8)*. However, in the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the proportion of babies who developed hypoglycaemia was similar in Māori babies (79/150, 53%) to that in the whole cohort (260/514, 51%)* (9).	

	Pacific babies (282/693, 40.7%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%) (8). *In the Sugar Babies study of 514 babies at risk of neonatal hypoglycaemia in Aotearoa New Zealand, the number of Pacific babies was very small, but the proportion who developed hypoglycaemia was similar to that in the whole cohort (6/16, 38% vs 260/514, 51%)* (9). *Asian babies (660/2068, 31.9%) are more likely to be at risk of hypoglycaemia than New Zealand Europeans (660/2529, 26.1%)* (8). ***Are there important considerations that people implementing the intervention should consider in order to ensure that inequities are reduced, if possible, and that they are not increased?*** ***Consideration for Māori*** *In the Whānau Experience study* (10)*, participants expressed appreciation for the inclusion of karakia and tikanga before certain interventions.* *Māori are more likely to experience interpersonal, institutional, and structural racism, which requires intentional action on addressing racism within these three levels of racism* (11, 12, 13). *Additionally, a systematic literature review by Graham et al.* (14) *provides a summary of 20 years of data from Whānau Māori experiences in the public health and/or hospital system. A key barrier included perception of racism or discrimination amongst whānau Māori. For instance, perceiving healthcare professionals to be uninterested in their health and wellbeing. Whānau Māori had good experiences when engaging with Māori healthcare providers when they provided whanaungatanga and were "just so welcoming"* (14). ***Consideration for Pacific*** *Some Pacific women interviewed in the Whānau Experience study reported difficulties with accessing the hospital due to cost, transportation and limited availability with work* (10). ***Other considerations*** *The Ministry of Health identify four priority groups for maternity care. These are Māori, Pacific, younger women (<25 years) and women with disabilities* (7). *Most pregnancy, hospital and well child care is free for Aotearoa New Zealand citizens and other eligible women, but accessing these services may incur costs that are challenging for families with limited resources. In addition, there may be a charge if families use some private or specialist services. In the 2014 Maternity Consumer Survey* (7)*, 71% of women reported that they had paid for*	

	at least one pregnancy-related service. Māori, Pacific and younger women were less likely to have paid for services.	

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Not applicable **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Not applicable **Considerations for Māori** No additional data available **Considerations for Pacific** No additional data available	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			

	JUDGEMENT						
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○

REFERENCES SUMMARY

1. Cummings CT, Ritter V, LeBlanc S, Sutton AG. Evaluation of risk factors and approach to screening for asymptomatic neonatal hypoglycemia. Neonatology. 2022;119(1):77-83.
2. Chen X, Feng L, Yao H, Yang L, Qin Y. Efficacy and safety of diazoxide for treating hyperinsulinemic hypoglycemia: a systematic review and meta-analysis. PLoS ONE. 2021;16(2):e0246463.
3. Edwards T, Liu G, Battin M, Harris DL, Hegarty JE, Weston PJ, et al. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. Cochrane Database of Systematic Reviews. 2022;18;3(3):CD011027.
4. O'Brien M, Gilchrist C, Sadler L, Hegarty JE, Alsweiler JM. Infants eligible for neonatal hypoglycemia screening. JAMA Pediatrics. 2023;177(11):1187-1196.
5. Hawdon JM, Beer J, Sharp D, Upton M; NHS Improvement Patient Safety Programme 'Reducing Term Admissions to Neonatal Units'. Neonatal hypoglycaemia: learning from claims. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2017;102(2):F110-F115.
6. Brand PL, Molenaar NL, Kaaijk C, Wierenga WS. Neurodevelopmental outcome of hypoglycaemia in healthy, large for gestational age, term newborns. Archives of Disease in Childhood. 2005;90(1):78-81
7. Ministry of Health New Zealand. Maternity Consumer Survey 2014. Wellington; 1 September 2015 [cited 2 February 2024]; Available from: https://www.health.govt.nz/publication/maternity-consumer-survey-2014
8. Alsweiler JM, Gomes L, Nagy T, Gilchrist CA, Hegarty JE. Adherence to neonatal hypoglycaemia guidelines: A retrospective cohort study. Journal of Paediatrics and Child Health. 2020;56(1):148-154.
9. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. The Journal of Pediatrics. 2012;161(5):787-912012.
10. Whānau Experiences Study Group. Whānau Experiences study: experiences of whānau with pēpi (infants) at risk of neonatal hypoglycaemia. Unpublished; 2024.
11. Came H, McCreanor T, Manson L. Upholding Te Tiriti, ending institutional racism and Crown inaction on health equity. The New Zealand Medical Journal. 2019;132(1492):61-6.
12. Came H, O'Sullivan D, Kidd J, McCreanor T. The Waitangi Tribunal's WAI 2575 Report Implications for decolonizing health systems. Health and Human Rights. 2020;22(1):209-20.
13. Talamaivao N, Harris R, Cormack D, Paine SJ, King P. Racism and health in Aotearoa New Zealand: a systematic review of quantitative studies. The New Zealand Medical Journal. 2020;133(1521):55-68.
14. Graham R, Masters-Awatere B. Experiences of Māori of Aotearoa New Zealand's public health system: a systematic review of two decades of published qualitative research. Australian and New Zealand Journal of Public Health. 2020;44(3):193-200.

Appendix H. Māori Words Used in the Guideline

Disclaimer: many of the descriptions used in this glossary are specific interpretations for the Evidence to Decision tables, and do not denote the fullness of meaning normally associated with the word or term. All efforts have been made to uphold the taonga of each kupu within the writing of these Evidence to Decision Tables and associated Guideline documents.

Karakia	To recite, say or pray a prayer or chant
Māori	Indigenous person of Aotearoa/New Zealand
Pēpi	A baby / infant
Tikanga	The correct procedure or way of doing things
Whānau	Extended family, family group
Whānau Māori	Extended family, family group including people who identify as Māori
Whānaungatanga	Having a sense of connection, kinship, welcoming

Appendix I. Glossary of Clinical and Technical Terms Used in the Guideline

Adrenaline	Another name for Epinephrine. A hormone and neurotransmitter produced by the adrenal glands and certain neurons. It plays a crucial role in the body's response to stress or danger, and can increase blood glucose concentrations.
Amino acids	Organic compounds that serve as the building blocks of proteins.
Apgar score	The Apgar score is a quick assessment of a newborn's health, usually measured at one minute and five minutes after birth. It is based on five criteria: Appearance (skin color), Pulse (heart rate), Grimace (reflex irritability), Activity (muscle tone), and Respiration (breathing rate and effort). Each criterion is scored from 0 to 2, and the scores are then added up to give a total score out of 10.
Apnoea	A temporary cessation of breathing. This is common in preterm babies but also occurs in babies who are unwell for any reason.
Appropriate for gestational age (AGA)	A baby whose size falls within a range considered to be normal for their gestational age.
Congenital hyperinsulinism	A rare condition of abnormally high insulin secretion, usually genetic. The high insulin secretion leads to hypoglycaemia (low blood glucose) which is often severe and difficult to treat and associated with a high risk of brain injury
Desaturation	When the amount of oxygen in the blood drops below the normal level. This is common following apnoea.
Douleur Aiguë Nouveau-né (DAN)	A validated tool used to assess pain in newborn babies on a scale from 0 to 10. It assesses facial expressions, limb movements, and vocal expression (Carbajal et al., 1997).
Electrochemistry	Measurement of the electrical current produced by the reaction between glucose and specific enzymes in glucose testing.
Electroencephalogram (EEG)	A test that measures electrical activity in the brain using small discs (electrodes) attached to the scalp.
Endogenous	Originating from within the organism, including hormones, enzymes, or other substances that are produced internally by the body.

Epinephrine	Another name for adrenaline. A hormone and neurotransmitter produced by the adrenal glands and certain neurons. It plays a crucial role in the body's response to stress or danger, and can increase blood glucose concentrations.
Euglycaemia	The presence of a normal concentrations of glucose in the blood.
Evoked potentials	Evoked potentials record the electrical currents produced after specific stimulation, e.g., sensory evoked potentials after stimulation by touch, auditory evoked potential after stimulation by sound, and visual evoked potentials after stimulation by light.
Fatty acids	The building blocks of the fat in our bodies and in the food we eat.
Gestational diabetes (GDM)	A type of diabetes that develops during pregnancy and resolves after pregnancy.
Glucose dehydrogenase (GDH)	An enzyme used for measuring glucose concentrations. This enzyme only reacts with glucose so is considered a very specific enzyme for this purpose.
Glucose oxidase (GO)	An enzyme used for measuring glucose concentrations. This enzyme only reacts with glucose so is considered a very specific enzyme for this purpose.
Glycogenolysis	The process of breakdown of glycogen in liver and muscles to release glucose.
Haematocrit	The proportion of the blood that is made up by red blood cells, usually expressed as a percentage.
Hepatic	Related to the liver.
Hexokinase	An enzyme used for measuring glucose concentrations. This enzyme reacts with many hexoses (sugars) so is considered less specific for this purpose.
Hyperinsulinaemic hypoglycaemia	Low blood glucose concentrations caused by high levels of insulin.
Hypertrichosis	Excessive hair growth on areas of the body where hair does not normally grow.
Hypoglycaemia	Low blood glucose concentrations
Intravenous (IV)	Into a vein. Usually refers to administering fluids, medications, or nutrients into the body via a vein.

Intraventricular haemorrhage (IVH)	Bleeding into the fluid-filled spaces, or ventricles, inside the brain.
Ketogenesis	A metabolic pathway that produces ketones, usually activated when glucose supply is inadequate e.g., during fasting.
Ketones (includes beta-hydroxybutyrate and acetoacetate)	Molecules produced by the liver during ketogenesis, usually during periods of low food intake (fasting). They serve as an alternative fuel source for the body, particularly for the brain and muscles, when glucose availability is limited.
Lactate	A molecule produced by almost all tissues. High lactate concentrations in the blood are usually considered a marker of inadequate oxygen supply to tissues.
Lead Maternity Carer (LMC)	A registered midwife or a doctor who provides primary maternity care to pregnant women and their newborn baby throughout pregnancy, childbirth, and the postnatal period.
Necrotising enterocolitis	A severe inflammation of the intestine, occurring most commonly in preterm babies. It can cause severe infection and death.
Negative Predictive Value (NPV)	The likelihood that individuals who test negative actually do not have the condition.
Neonatal Facial Coding System (NFCS)	A validated tool used to assess pain in newborn babies through facial expressions, on a scale of 0 (no pain) to 10 (most pain) (Grunau et al., 1987).
Neonatal Infant Pain Scale (NIPS)	A validated tool used to assess pain in newborn babies through facial expression, crying, breathing, and limb movements. Scores range from 0 to 7, with higher scores indicating more pain (Lawrence et al., 1993).
Neonatal intensive care unit (NICU)	A specialised medical unit within a hospital that provides care for newborn babies who are preterm or have serious medical conditions requiring intensive medical and nursing attention.
Neurodevelopment impairment	Impairment in a range of abilities or functions e.g., cognition, communication, behavior or motor skills.
Neurophysiological	The branch of physiology dealing with the functions of the nervous system.
Neutropaenia	An abnormally low level of neutrophils, which are a type of white blood cell important for fighting off infections.
Non-nutritive sucking	The sucking that babies do when there is no milk to swallow, e.g., sucking on a dummy or pacifier.

Oedema	Swelling caused by fluid retention in body tissues.
Pain reactivity	Babies' response or sensitivity to pain stimuli within the first 30 seconds after the painful stimulus.
Pain regulation	Babies' response or sensitivity to pain stimuli after the first 30 seconds following the painful stimulus.
Photometry	Measuring the intensity of light, usually of a specific colour, that is absorbed or emitted by a reaction involving glucose in glucose testing.
Polycythaemia	High concentration of red blood cells in blood.
Positive Predictive Value (PPV)	The likelihood that individuals who test positive actually have the condition.
Premature Infant Pain Profile (PIPP)	A validated tool used to assess pain in newborn babies through physiological and behavioral indicators, using a scale ranging from 0 to 21. Higher scores indicate more pain (Gibbins et al., 2014, Stevens et al., 2014).
Quality Adjusted Life Years (QALYs)	One QALY equals one year lived in perfect health. QALYs take into account the quantity and quality of life lived, adjusted for disease burden.
Sensitivity (True Positive Rate)	The probability of a positive test result if the individual truly has the condition being tested.
Small for gestational age SGA	A baby is smaller than usual for their gestational age, commonly defined as below the 10^{th} centile.
Specificity (True Negative Rate)	The probability of a negative test result if the individual truly does not have the condition being tested.
Thrombocytopaenia	A lower-than-normal number of platelets in the blood, often leading to an increased risk of bleeding.
Very low birthweight	Weight below 1.5 kg at birth.

Appendix J. Abbreviations Used in the Guideline

AGA	Appropriate for gestational age
BGC	Blood glucose concentrations
CGM	Continuous glucose monitoring
CI	Confidence interval
DHB	District Health Board
EEG	Electroencephalogram
EtD	Evidence to Decision framework document
GDM	Gestational diabetes mellitus
IDM	Infants of diabetic mothers
IV	Intravenous
LGA	large for gestational age
LMC	lead maternity carer
MD	mean difference
MMPO	Midwifery and Maternity Provider Organisation
MRI	magnetic resonance imaging
NEC	Necrotising enterocolitis
NICU	Neonatal intensive care unit
NPV	Negative predictive value
NZD	NZ dollars
OR	Odds ratio
PPV	Positive predictive value
QALYs	Quality adjusted years
RCT	Randomised controlled trials
RR	Risk ratio
SD	Standard deviation
SGA	Small for gestational age
SMD	Standard mean difference
USD	US dollars
NNS	Non-nutritive sucking
VLBW	Very low birthweight

Appendix K. Conflicts of Interest

Assessment provided by: Sue Brennan

Date: 8 August 2024

Wording used to summarise the declarations of interests and in the assessment is adapted from that used in the executive summary reports published by the WHO Expert Committee on the Selection and Use of Essential Medicines.

Name	Role	Summary of declarations	Assessment
Jane Alsweiler	Governance group, Perinatal Society of Australia and New Zealand nominee	Disclosed employment as Deputy Head of School of Medicine, University of Auckland and as Neonatal Paediatrician, Te Whatu Ora Te Toka Tuma. Disclosed membership of Board for the Perinatal Society of Australia and New Zealand. Disclosed having conducted research and published on perinatal glucose regulation, including some of the primary evidence considered by the Guideline panel. Recipient of multiple grants for research in neonatal hypoglycaemia, most from the Health Research Council of New Zealand, and the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health (NIH). Received funding for the Prime Minister's Science Prize 2002 from the New Zealand Ministry for Business, Innovation and Employment, used to fund the development of the Guideline.	The research declared was considered to be directly related to the recommendations addressed in the Guideline Panel meetings, however the studies were considered to be a relevant academic interest that did not represent a conflict and did not require further management. Other disclosures were *considered not to represent a conflict*.
Astrid Budden	Panel member, Royal Australian and New Zealand College of Obstetricians and Gynaecologists nominee	Disclosed employment as Senior Medical officer in Obstetrics and antenatal diabetes service at Te Whatu Ora Te Toka Tumai.	This disclosure was considered not to represent a conflict and did not require further management
David Barker	Panel member, New Zealand Neonatal Network nominee	Disclosed employment as Senior Medical Officer (Paediatrics) at Te Whatu Ora Health New Zealand. Disclosed research interest on neonatal analgesia and painful procedures (1997 thesis).	These disclosures were *considered not to represent a conflict* and did not require further management.
Kasey Brown	Panel member, Pacific Pharmacists	Disclosed employment as Long Term Conditions Pharmacist Prescriber, Ngāti Porou Oranga	This disclosure was considered not to represent a conflict and did not

Name	Role	Summary of declarations	Assessment
	Association nominee		require further management.
Caroline Crowther	Governance group member	Disclosed employment as Professor of Maternal and Perinatal Health, Liggins Institute, University of Auckland. Disclosed membership of Perinatal Society of New Zealand, Perinatal Society of Australia and New Zealand. Disclosed having conducted research and published on treatment for gestational diabetes and preterm birth including some primary evidence and evidence synthesis considered by the Guideline panel. Recipient of multiple grants for research relating to gestational diabetes and preterm birth from the Health Research Council of New Zealand, the Australian National Health and Medical Research Council.	The research declared was considered to be directly related to the recommendations addressed in the Guideline Panel meetings, however the studies were considered to be a relevant academic interest that did not represent a conflict and did not require further management. Other disclosures were *considered not to represent a conflict*.
Violet Clapham	Governance group, New Zealand College of Midwives nominee	Disclosed employment as Midwifery Advisor at New Zealand College of Midwives|Te Kāreti o ngā Kaiwhakawhānau ki Aotearoa. Disclosed membership of New Zealand College of Midwives. Disclosed role as Lead Maternity Carer midwife. Disclosed research interest in homebirth breastfeeding and neonatal outcomes (2024 thesis)	These disclosures were *considered not to represent a conflict* and did not require further management.
Liza Edmonds	Panel member, Paediatric Society of New Zealand nominee	Disclosed employment as a Senior Medical Officer at Te Whatu Ora Wairarapa and Te Whatu Ora Southern, Associate Professor at Te Tātai Hauora o Hine Victoria University, Honorary Senior clinical lecturer at University of Otago and Department of Child Health University of Otago. Disclosed roles with Te Tāhu Hauora as Chair of the National Mortality Review Committee and member of the SME (previous known as Perinatal and Maternal Mortality Review Committee). Disclosed having conducted research and published on whānau Māori hauora, Recipient of grants from Health Research Council for whānau Māori Hauora.	These disclosures were considered not to represent a conflict and did not require further management. The research concerned was not considered to be directly related to *the recommendations* addressed in the Guideline Panel meetings.
Gwen Glazzard	Panel member, New Zealand College of Midwives nominee	Disclosed membership of New Zealand College of Midwives	This disclosure was considered not to represent a conflict and did not require further management

Name	Role	Summary of declarations	Assessment
Roslyn Gasparini	Panel member, Neonatal Nurses College of Aotearoa nominee- part of the professional arm of the New Zealand Nurses Organisation.	Disclosed employment as a neonatal nurse at the Starship hospital Neonatal Intensive Care Unit, Auckland, and membership of the Neonatal Nurses College of Aotearoa New Zealand.	These disclosures were considered not to represent a conflict and did not require further management.
Deborah Harris	Panel member, Nurse Practitioners New Zealand nominee	Disclosed employment as Deputy Director School of Nursing, Midwifery and Health Practice, Victoria University of Wellington Te Herenga Waka. Disclosed membership of Perinatal Society of New Zealand, Perinatal Society of Australia and New Zealand, Nurse Practitioners New Zealand, College of Nurses, Aotearoa. Disclosed having conducted research and published on neonatal hypoglycaemia, including much of the primary evidence considered by the Guideline panel. Recipient of grants for research in neonatal hypoglycaemia from the Rebecca Roberts Scholarship, Waikato Medical Research Foundation, the Auckland Medical Research Foundation, the Maurice and Phyllis Paykel Trust, and the Health Research Council of New Zealand.	The trials and research concerned were considered to be directly related to the recommendations addressed in the Guideline Panel meetings, however were considered to be a relevant academic interest that did not represent a conflict and did not require further management. Other disclosures were *considered not to represent a conflict*.
Heranush Hopkins	Panel member, ON TRACK consumer network representative	Disclosed receiving payment for role as consumer member of the Guideline Panel.	This disclosure was considered not to represent a conflict and did not require further management.
Jane Harding	Governance group, co-chair	Disclosed employment as Professor of Neonatology at Liggins Institute, University of Auckland. Disclosed membership of Perinatal Society of New Zealand, Perinatal Society of Australia and New Zealand, Paediatric Society of New Zealand, American Pediatric Society. Disclosed having conducted research and published on perinatal glucose regulation, including much of the primary evidence and evidence synthesis considered by the Guideline panel. Recipient of multiple grants for research in neonatal hypoglycaemia, most from the Health Research Council of New Zealand, the Eunice Kennedy Shriver National Institute of Child Health & Human Development	The trials and research concerned were considered to be directly related to the recommendations addressed in the Guideline Panel meetings, however were considered to be a relevant academic interest that did not represent a conflict and did not require further management. Other disclosures were *considered not to represent a conflict*.

Name	Role	Summary of declarations	Assessment
		of the National Institutes of Health (NIH), and the Aotearoa Foundation. Received funding for the Prime Minister's Science Prize 2002 from the New Zealand Ministry for Business, Innovation and Employment, used to fund the development of the Guideline.	
Katarina Komene	Panel member, Nga Maia Māori Midwives Aotearoa nominee	Disclosed employment as a Māori Liaison/Clinical Educator at AUT University. Disclosed membership of the New Zealand College of Midwives and Deputy Chair of Nga Maia Trust Board.	These disclosures were considered not to represent a conflict and did not require further management.
Lisa Kremer	Governance group, co-chair	Disclosed employment as Lecturer and Associate Dean Māori, He Rau Kawakawa ki Ōtākou Whakaihu Waka (School of Pharmacy, University of Otago). Disclosed voluntary role as Vice President of Executive Member on Ngā Kaitiaki o Te Puna Rongoā o Aotearoa (Māori Pharmacists Association).	This disclosure was considered not to represent a conflict and did not require further management.
Luling Lin	Panel member, leader of evidence synthesis team	Disclosed employment as Research Fellow, Liggins Institute, University of Auckland. Disclosed having conducted research and published on neonatal nutrition and neonatal hypoglycaemia including much of the evidence synthesis considered by the Guideline panel. Recipient of funding for evidence synthesis from the Aotearoa Foundation.	The research declared was considered to be directly related to the recommendations addressed in the Guideline Panel meetings, however the studies were considered to be a relevant academic interest that did not represent a conflict and did not require further management. Other disclosures were *considered not to represent a conflict*.
Jessie McQuinn	Panel member, consumer representative	Disclosed receiving payment for role as consumer member of the Guideline Panel. Disclosed participation in a trial of oral dextrose gel for prevention of neonatal hypoglycemia (hPOD).	These disclosures were considered not to represent a conflict and did not require further management.
Lisa Nathan	Panel member, Pasifika Midwives Aotearoa nominee	Disclosed employment as a midwife specialist at Te Toka Tumai – Auckland. Disclosed membership of New Zealand College of Midwives, Midwifery Employee Representation and Advisory Services, Pasifika Midwives Aotearoa, Pasifika Midwife Tāmaki Makaurau (Chair), Te Wakahuia o Hine	These disclosures were considered not to represent a conflict and did not require further management.

Name	Role	Summary of declarations	Assessment
Haunui Royal	Governance group, Cultural advisor	Disclosed employment as Kaiarahi at the Liggins Institute, University of Auckland	This disclosure was considered not to represent a conflict and did not require further management.
Jenny Rogers	Panel member	Disclosed employment as Follow-up Lead and Associate Director Equity, Liggins Institute, University of Auckland. Disclosed having conducted research and published on participant experience related to neonatal hypoglycaemia, including some of the primary evidence considered by the Guideline panel. Disclosed membership of Perinatal Society of New Zealand and Perinatal Society of Australia and New Zealand.	The research declared was considered to be directly related to the recommendations addressed in the Guideline Panel meetings, however the studies were considered to be a relevant academic interest that did not represent a conflict and did not require further management. Other disclosures were *considered not to represent a conflict*.
Raffaella Slight	Panel member, Midwifery Leaders Group nominee	Disclosed employment as a practising midwife at Te Toka Tumai Auckland, and membership of the New Zealand College of Midwives and of Midwifery Employee Representation and Advisory Services.	These disclosures were considered not to represent a conflict and did not require further management.
Esko Wiltshire	Panel member, New Zealand Paediatric Endocrinology Society nominee	Disclosed employment as Professor in paediatrics at the University of Otago Wellington and as a Paediatric Endocrinology at Health New Zealand Capital, Coast and Hutt Valley. Disclosed having received past industry funding (2015-2024) for trials of growth hormone preparations and treatment of diabetes in children and adolescents, including nine trials involving agents that are relevant to glucose metabolism, but none of which are relevant to the recommendations. Disclosed membership of the NZ Pediatric Endocrinology Society, past chair of the International Consortium for Pediatric Endocrinology (including advocacy to WHO for essential medicines used in treatment of hypoglycaemia) and membership and previous committee member/president of Australia and New Zealand Society for Paediatric Diabetes and Endocrinology. Disclosed having conducted indirectly related research and published on hypoglycaemia and its treatment,	The trials concerned were not considered to be directly related to the recommendations addressed in the Guideline Panel meetings. Other disclosures were *considered not to represent a conflict* and did not require further management.

Name	Role	Summary of declarations	Assessment
		particularly in type 1 diabetes not related to neonatal hypoglycaemia.	

Assessment options. [1]

No conflict or minor interest

- This disclosure was *considered not to represent a conflict* and did not require further management.
- These disclosures were *considered not to represent a conflict* and did not require further management.
- These disclosures were *considered to be unrelated, or not directly related*, to the recommendations addressed in the of the Guideline Panel meetings and did not require further management.
- The trials concerned were *not considered to be directly related* to the recommendations addressed in the of the Guideline Panel meetings.
- These disclosures were *considered minor, unrelated to the recommendations* addressed in the of the Guideline Panel meetings.
- The trials concerned were not considered to be directly related to *the recommendations* addressed in the Guideline Panel meetings.
- The research declared was considered to be directly related to the recommendations addressed in the Guideline Panel meetings, however the studies were considered to be a relevant academic interest that did not represent a conflict and did not require further management.

Potential conflict

- This disclosure was considered to represent a moderate conflict of interest. A determination was made that the panel member could contribute to the deliberations for the recommendations but should be excluded from voting on the Evidence to decision judgements and the recommendations [topic].
- This disclosure was considered to represent an ostensible conflict of interest. A determination was made that the panel member should be excluded from the deliberation and recommendation for [topic]. [The panel member] recused themselves from the meeting while the [topic] was being discussed.

[1] As used in (or adapted from) the executive summary reports published by the WHO Expert Committee on the Selection and Use of Essential Medicines