Treatment

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 <u>underlined</u> 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 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 baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **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	**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.

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 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	-	-	-	-	-

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 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

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	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

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).

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** No additional evidence available	**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.
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
○	●	○	○	○

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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 baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **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** (25 fewer to 136 more)

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 dextrose gel group and 72/119 [60%]

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 being 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 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)).

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).

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	• Small increase in neurodevelopmental impairment at ≥2 years (37 more per 1,000). • Two studies reported that there were no adverse events.	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).

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
Neurodevelopmental impairment at ≥2 years [critical]	184 (1 RCT)	⨁◯◯◯ Very low[a]	**RR 1.11** (0.75 to 1.63)	Study population	
				340 per 1,000	**37 more per 1,000** (85 fewer to 214 more)
Adverse events [critical]	528 (2 RCTs)	⨁⨁◯◯ Low[b]	-	Two studies reported that there were no adverse events.	

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
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
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

	JUDGEMENT						
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
○	○	○	●	○

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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 baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **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 ○ Varies ○ Don't know	Formula alone or dextrose gel 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] • 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]	Gregory 2020 (2) reported that babies who received formula at the time of the first dose of oral dextrose gel administration showed the greatest 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.

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)

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 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

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

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). **Considerations for Māori** No additional data available **Considerations or Pacific** No additional data available	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	-	-	-	-	-

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>Correction of hypoglycaemia (< 2.6 mmol/L) (formula versus dextrose gel) [critical]</td><td>CRITICAL</td><td>⨁⨁◯◯ Low[a]</td></tr><tr><td>Correction of hypoglycaemia (formula versus donor human milk) [critical]</td><td>CRITICAL</td><td>⨁◯◯◯ Very low[b]</td></tr><tr><td>Recurrent neonatal hypoglycaemia (dextrose gel plus formula versus dextrose gel plus breastfeeding) [critical]</td><td>CRITICAL</td><td>⨁⨁◯◯ Low[c,d]</td></tr><tr><td>Recurrent neonatal hypoglycaemia (dextrose gel plus formula versus dextrose gel plus donor milk) [critical]</td><td>CRITICAL</td><td>⨁◯◯◯ Very low[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]</td><td>CRITICAL</td><td>⨁◯◯◯ Very low[c,e]</td></tr><tr><td>Adverse effects [critical] - not measured</td><td>CRITICAL</td><td>-</td></tr><tr><td>Fully breastfeeding at hospital discharge [critical] - not measured</td><td>CRITICAL</td><td>-</td></tr></table> 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] • Small reduction in admission to special care or neonatal intensive care nursery [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

	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 donor human milk was significantly more expensive than formula or mother's milk. The cost per litre of donor human mil 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. 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.	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 randomised to receive milk 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			

	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
○	○	○	●	○

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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 baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **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]	**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):**

- 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 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
				Study population	

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) 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

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)	150 per 1,000	**49 fewer per 1,000** (120 fewer to 177 more)	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 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.
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))	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** (226 fewer to 92 more)	
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):

- Little to no effect on hypoglycaemic episodes during treatment (1 more episode)

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):

- 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)
				Study population	

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 (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 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

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)	625 per 1,000	**200 fewer per 1,000** (350 fewer to 31 more)
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)	Study population	
				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

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 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

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

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).

	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 ○ Don't know	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. **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 who 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	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	

● Probably yes ○ Yes ○ Varies ○ Don't know	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
○	○	○	●	○

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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 baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **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

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

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)

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)

ADDITIONAL CONSIDERATIONS

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).
- Little to no difference in hypoglycaemia >48 hours after randomization (OR 0.19 (0.02, 1.76))
- Little to no difference in 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 2.8 mmol/L for at least 24 hours) (mean (SD) 41 (29) hours

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	-	-	-	-	-	
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

vs 74 (58) hours; MD -33 hours [95% CI -66 to -0])

	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	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 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). • neutropenia 9% (95% CI 0 to 19; 2 studies, p = 0.005) • pulmonary hypertension 2% (95% CI 0 to 4; 3 studies, p = 0.005) • thrombocytopenia 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	The NeoGluCO study (1) also reported: • More episodes of hyperglycaemia (blood glucose concentration ≥7.0 mmol/L) (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 diazoxide 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
○	●	○	○	○

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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 baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **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**
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
○	○	○	●	○

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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 baby) 5. Cost (for whānau >=10 NZD per baby, for health system >=100 NZD per baby) **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 for a small number of babies with cardiac conditions or 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 ○ Negligible costs and savings ○ Moderate savings	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 baby is admitted to NICU or remains in hospital after discharge of the mother.	

○ Large savings ○ Varies ○ Don't know	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
○	○	●	○	○

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