ORAL DEXTROSE GEL TO TREAT NEONATAL HYPOGLYCAEMIA:

CLINICAL PRACTICE GUIDELINES

Prepared by:
"The Oral Dextrose Gel to Treat Neonatal Hypoglycaemia Clinical Practice Guidelines" Panel

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Disclaimer

These guidelines are a general guide to appropriate practice to be used subject to the health practitioners' clinical judgement and the preferences of the individual baby's parents or guardians. The document is designed to give information to assist clinical decision making and is based on the best available evidence at the time of release.

Endorsements

Endorsement for these Clinical Practice Guidelines has been received from the Royal Australasian College of Physicians, the New Zealand Hospital Pharmacists' Association and the Neonatal Nurses College of Aotearoa.

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Summary of Clinical Recommendations

Oral dextrose gel to treat neonatal hypoglycaemia

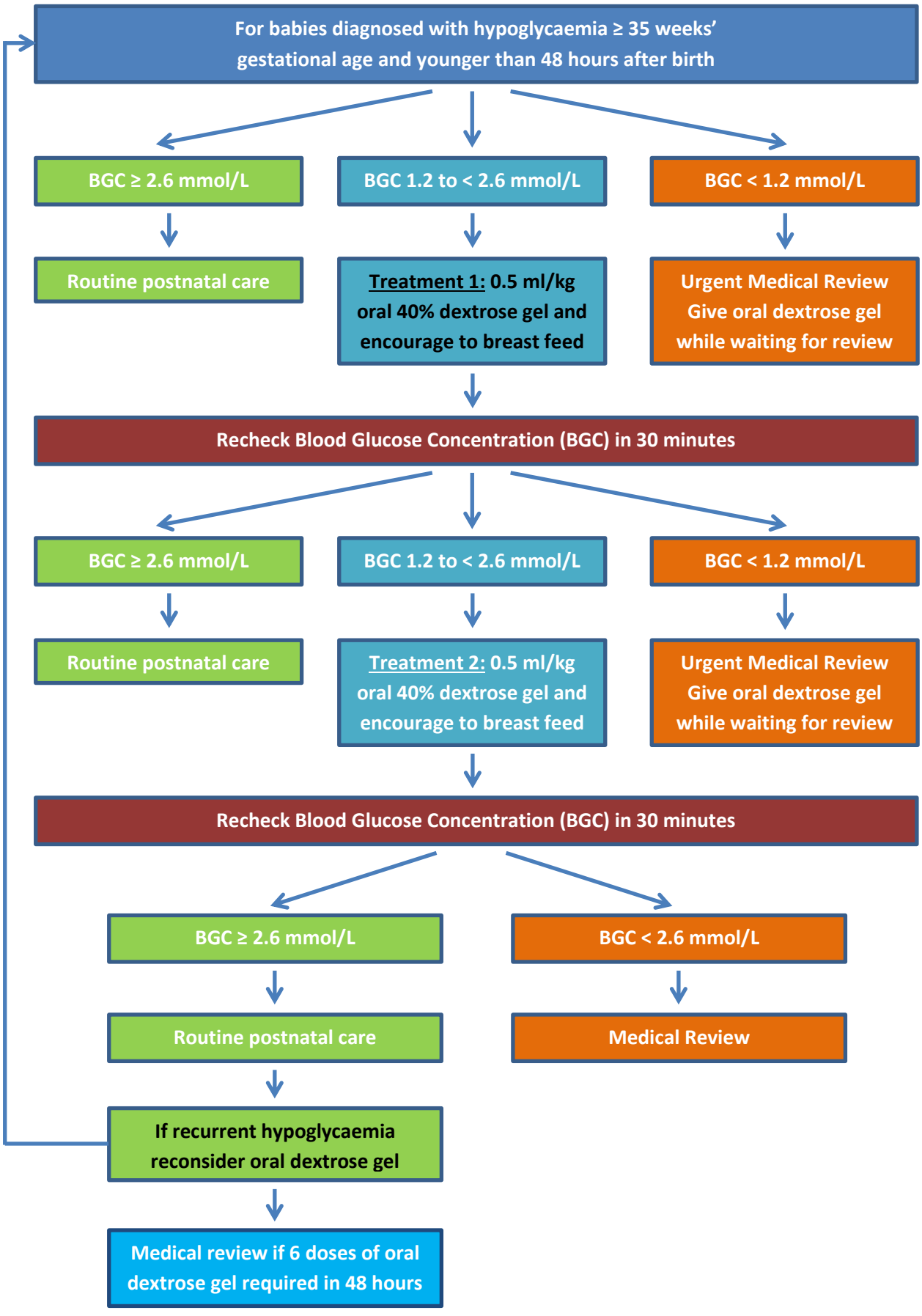
Clinical recommendation	Strength of recommendation		Chapter
	NHMRC	GRADE	
In babies diagnosed with neonatal hypoglycaemia, treat with 40% oral dextrose gel.	**B***	**CONDITIONAL#**	3
• When babies are ≥ 35 weeks' gestational age and younger than 48 hours after birth.	Practice point		5
• Use a dose of 200 mg/kg (0.5 ml/kg), up to two doses given 30 minutes apart per episode of hypoglycaemia and a maximum of six doses of oral dextrose gel in 48 hours.	Practice point		4
• For babies with severe hypoglycaemia (<1.2 mmol/L) use oral dextrose gel as an interim measure while arranging for urgent medical review and treatment.	Practice point		6
• Paediatric medical advice should be sought if a baby has severe hypoglycaemia (<1.2 mmol/L), a blood glucose concentration of <2.6 mmol/L following two doses of oral dextrose gel one hour after first detection of hypoglycaemia, or requires six doses of oral dextrose gel to treat neonatal hypoglycaemia in 48 hours.	Practice point		7
Administration of dextrose gel • Oral dextrose gel can be prescribed by medical practitioners, midwives, pharmacist prescribers working in a neonatal scope of practice, and nurse practitioners with prescribing rights.	Practice point		7
• Using gloves, preferably latex free, massage oral dextrose gel into the buccal mucosa after drying the mouth with gauze.	Practice point		5
• Oral dextrose gel should preferably be administered to the baby in the presence of the mother.	Practice point		5
• Offer the baby a feed, preferably breast milk, immediately after administration of oral dextrose gel.	Practice point		5
• Repeat blood glucose concentration measurement 30 minutes after administering oral dextrose gel and repeat oral dextrose gel if the baby remains hypoglycaemic.	Practice point		6
• Accurate equipment for measuring blood glucose concentration e.g. glucose oxidase method, should be available.	Practice point		6
• The label on the oral dextrose gel bottle should state all preservatives, and that the bottle should only be used for one month after opening.	Practice point		4

*Body of evidence can be trusted to guide practice in most situations.
Benefits probably outweighs harms.

Summary of Research Recommendations

Further research is needed to determine:
• The effects of treatment with oral dextrose gel on the duration and number of episodes of hypoglycaemia.
• The long-term outcomes of hypoglycaemic babies treated with oral dextrose gel.
• The most effective dose of oral dextrose gel to treat neonatal hypoglycaemia.
• The optimal number of doses of oral dextrose gel to treat neonatal hypoglycaemia.
• The optimal timing of repeat doses of oral dextrose gel to treat neonatal hypoglycaemia.
• If oral dextrose gel is safe and effective in hypoglycaemic babies < 35 weeks' gestational age, and in babies older than 48 hours after birth.
• The optimal way of administering oral dextrose gel.
• The role of oral dextrose gel to treat neonatal hypoglycaemia in combination with other treatments.
• The minimum blood glucose concentration that is safe to treat with oral dextrose gel in hypoglycaemic neonates.
• When blood glucose concentrations should be monitored after administration of oral dextrose gel.

Oral Dextrose Gel to Treat Neonatal Hypoglycaemia Flow Chart



Contents

Glossary of Terms

Absolute risk reduction	The risk of an adverse outcome with no treatment less the risk of an adverse outcome with treatment.
Adverse event	An adverse outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it.
Administration	The action of dispensing, giving, or applying a medicine.
Applicability	The degree to which a body of evidence is relevant to a particular health care context.
Blood glucose concentration	Concentration of sugar in the blood.
Cerebral palsy	A group of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.
Clinical impact	Measure of potential benefit from application of the guideline to a population.
Cochrane Review/Cochrane Systematic Review	A systematic review of the evidence usually from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Confidence interval	Gives a range of values for an unknown population outcome estimated from a study. It will depend on the number of study recruits and the variation in the outcome data. A 95% confidence interval (CI) means that if the study was repeated 100 times with a different sample of recruits and a CI calculated each time, the interval would contain the 'true' value of the population outcome 95 times.
Contraindication	A specific situation in which a drug, procedure, or surgery should not be used because it may be harmful to the patient.
Controls	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) – in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Developmental delay	Any significant lag in a child's physical, cognitive, behavioural, emotional or social development, in comparison with the norms.
Dose	A quantity of medicine to be administered at one time.
Evidence based	The best available evidence gained from the scientific method to inform medical decision making. It seeks to assess the quality of evidence of the risk and benefits of treatments (including lack of treatment).
Evidence statement	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Formulation	A mixture of ingredients prepared in a certain way.
Gestational age	The period of time between last menstrual period and birth.
Harms	Adverse effects.
Hypoglycaemia	Blood sugar concentrations below a level necessary to properly support the body's need for energy and stability throughout its cells.
Neonatal	Pertaining to the neonatal period which is the first four weeks after birth.
NICU	Neonatal Intensive Care Unit
Neurological impairment	A group of disorders that relate to the central nervous system (brain and spinal cord). Among the more common diagnostic categories for children are cerebral palsy, epilepsy, blindness, deafness, and developmental delay. A neurological impairment may affect an individual's speech, motor skills, vision, memory, hearing, muscle actions and learning abilities.
Number needed to treat to benefit	The number of patients who need to be treated with the new or intervention treatment (rather than the control treatment) for one patient to benefit from the new treatment.
Observational studies	A study in which the investigators do not seek to intervene, and simply observe the course of events. Changes or differences in one characteristic (e.g. whether

	or not people received the intervention of interest) are studied in relation to changes or differences in other characteristic(s) (e.g. whether or not they died), without action by the investigator. There is a greater risk of selection bias than in experimental studies.
Placebo	An inactive substance or preparation used as a control in an experiment or test to determine the effectiveness of a medicinal drug.
p-value	Used in hypothesis testing where initially it is assumed that there is no difference between two treatments. The p-value is the probability that the difference observed in a study between the two treatments might have occurred by chance. Small p-values indicate evidence against an assumption of no difference. Large p-values indicate insufficient evidence against the assumption of no difference between treatments, NOT that there is actually no difference between treatments. P-values will depend on study size; large studies can detect small differences for example.
Prescribing	To advise and authorise the use of (a medicine or treatment) for someone, especially in writing.
Randomised controlled trial	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
Reduction in risk	The extent to which a treatment reduces a risk of an outcome, in comparison with patients not receiving the treatment of interest.
Regimens	A pattern of treatment, e.g. dose, frequency of a drug.
Risk	The probability of an outcome which is given by the number with the outcome divided by the number with AND without the outcome.
Risk of bias	Bias in the reported outcomes of a study may be caused by an inadequacy in the way the study is designed or conducted. For example if any of the following aspects of the trial were not conducted properly then the trial may be said to have an increased risk of bias: the random allocation of the treatments, allocation concealment, blinding of researchers during intervention and measurement of outcomes, missing outcome data, selective outcome reporting.
Risk ratio	The ratio of risk in two treatment groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of one indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is less than one indicates that the intervention was effective in reducing the risk of that outcome. (Also called relative risk, RR.).
Sample size	The number of units (persons, animals, patients, specified circumstances, etc.) in a population to be studied. The sample size should be big enough to have a high likelihood of detecting a true difference between two groups.
SCBU	Special Care Baby Unit
Systematic review	A review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.

Guideline Panel Membership

Members	Title	Expertise	Affiliation	Role on the panel
Executive Panel Members				
Jane Alsweiler	Dr	Neonatologist	Consultant Neonatologist, NICU, National Women's Health, Auckland City Hospital Senior Lecturer, Department of Paediatrics: Child and Youth Health, University of Auckland and Honorary Senior Lecturer, Liggins Institute, University of Auckland	Executive Group
Jane Harding	Professor	Neonatologist	The Liggins Institute, University of Auckland Deputy Vice Chancellor (Research), University of Auckland	Executive Group
Caroline Crowther	Professor	Maternal fetal medicine subspecialist	The Liggins Institute, University of Auckland	Executive Group
Clinical Practice Guideline Panel				
Mariam Buksh	Dr	Neonatologist	Consultant Neonatologist, NICU, National Women's Health, Auckland City Hospital	Representing Perinatal Society of New Zealand
Karien Mannering	Ms	Neonatal Nurse	NICU, National Women's Health, Auckland City Hospital	Representing Neonatal Nurses College of Aotearoa
Megan Pybus	Dr	General Paediatrician	Paediatrics, MidCentral DHB	Representing Paediatric Society of New Zealand
Simon Rowley	Dr	Paediatrician	NICU, National Women's Health, Auckland City Hospital	Representing Royal Australasian College of Paediatricians
Astrid Budden	Dr	Obstetrician and Gynaecologist	Auckland Obstetric Centre, Parnell, Auckland National Women's Health, Auckland City Hospital	Representing Royal Australian and New Zealand College of Obstetrics and Gynaecology
Mahia Winder	Ms	Māori Midwifery Advisor, Auckland District Health Board	Regional Committee of the New Zealand College of Midwives, Auckland University of Technology Midwifery Advisory Board, Auckland District Health Board's Child and Youth Mortality Review Panel, Ministry of Health's Mother and Baby Workforce Development Committee	Māori (New Zealand)
Barbara Robertshawe	Ms	Paediatric Pharmacist	Pharmacy, Christchurch Women's Hospital, Christchurch	Representing New Zealand Hospital Pharmacists and Pharmaceutical Society of New Zealand
Tim Kenealy	Associate Professor	General Practitioner	Department of Medicine, University of Auckland	Representing New Zealand College of General Practitioners
Deborah Harris	Dr	Neonatal Nurse Practitioner	NICU, Waikato Hospital	Expert
Sandra Mackay	Mrs	Consumer advocate	Consumer	Representing Neonatal Trust
Management Group				
Julie Brown	Dr	Research Synthesis and Clinical Guideline Development	The Liggins Institute, University of Auckland	Research Team
Sonja Woodall	Dr	Clinical Guideline Development	Department of Paediatrics: Child and Youth Health, University of Auckland	Research Team

The New Zealand College of Midwives (NZCoM) declined to the invitation to provide a representative on the guideline development panel

Chapter 1: Need for these Clinical Practice Guidelines and summary of the development process

Neonatal hypoglycaemia is common in the first few days after birth, with 30% of New Zealand babies born at risk (infants of diabetic mothers, preterm or small or large for gestational age) (Nagy 2012). Of these at-risk babies, 50% will develop low blood glucose concentrations (Harris 2012). Standard management of babies in whom low glucose concentrations are detected often involves the use of formula, which can reduce breastfeeding rates (Blomquist 1994), or admission to the Special Care Baby Unit (SCBU)/Neonatal Intensive Care Unit (NICU) for intravenous dextrose (Agrawal 2000), thereby separating the mother and baby and potentially delaying the establishment of breast feeding. Recently, the use of oral dextrose gel for the treatment of neonatal hypoglycaemia has been shown to be effective in reversing hypoglycaemia (Harris 2013) and is increasingly being used in New Zealand maternity hospitals.

There is a need for a national clinical practice guideline to provide evidence based recommendations to guide decision making in clinical practice, and to provide consistency in practice across New Zealand in the use of oral dextrose gel to treat neonatal hypoglycaemia.

Aim of this Clinical Practice Guideline

To provide evidence based recommendations on the use of oral dextrose gel to treat neonatal hypoglycaemia.

Target Audience

- Health professionals who care for pregnant women where the baby is at increased risk of neonatal hypoglycaemia due to factors such as maternal diabetes, growth restriction, macrosomia and preterm birth;
- Health professionals caring for newborns with neonatal hypoglycaemia;
- Pregnant women, their partners and whanau;
- Policy makers in maternity and neonatal care.

Scope of the Clinical Practice Guidelines

To examine the evidence for giving babies with hypoglycaemia oral dextrose gel, for the purpose of improving health outcomes for the baby.

The scope includes the use of oral dextrose gel in babies diagnosed with neonatal hypoglycaemia. This Clinical Practice Guideline will *not* cover the screening criteria or diagnosis of neonatal hypoglycaemia or the use of oral dextrose gel given to *prevent* the development of hypoglycaemia.

Summary of the development process

A multidisciplinary expert advisory Clinical Practice Guidelines Panel (page 7) was established to oversee the development of these Clinical Practice Guidelines to guide the use of oral dextrose gel to treat neonatal hypoglycaemia.

The purpose of the Clinical Practice Guidelines Development Panel was to prepare evidence based guidelines on the best practice for clinical care in the use of oral dextrose gel to treat neonatal hypoglycaemia.

An Executive Group comprising Dr Jane Alsweiler, Professor Caroline Crowther, and Professor Jane Harding guided the overall preparation of the guidelines. The Clinical Practice Guidelines Management Group (the Executive Group, Dr Julie Brown and Dr Sonja Woodall) identified and synthesised the evidence presented in these guidelines.

These Clinical Practice Guidelines were developed using procedures recommended by the National Health and Medical Research Council (NHMRC) (NHMRC 1998) and the former New Zealand Guideline Group (New Zealand Guidelines Group 2012) (**Appendix B and C**).

Key clinical questions for these Clinical Practice Guidelines

The Clinical Practice Guidelines Panel developed a set of clinical questions to be addressed on the use of oral dextrose gel to treat neonatal hypoglycaemia:

- ***What are the short and long term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia?***
- ***Dosage of oral dextrose gel***
    - What is the optimal formulation of oral dextrose gel to treat neonatal hypoglycaemia?
    - What is the most effective dose of oral dextrose gel to treat neonatal hypoglycaemia?
    - What is the optimal number of doses of oral dextrose gel to treat neonatal hypoglycaemia?
    - What is the optimal timing of repeat doses of oral dextrose gel to treat neonatal hypoglycaemia?
- ***Administration of oral dextrose gel***
    - Which babies should receive oral dextrose gel to treat neonatal hypoglycaemia?
    - What is the safest and most effective way to administer oral dextrose gel to treat neonatal hypoglycaemia?
    - At what location should oral dextrose gel be administered to babies to treat neonatal hypoglycaemia?
    - What is the role of oral dextrose gel to treat neonatal hypoglycaemia when used with other treatments?
    - What are the contraindications for using oral dextrose gel to treat neonatal hypoglycaemia?
- ***Effects on blood glucose concentration when using oral dextrose gel***
    - What is the minimum blood glucose concentration that is safe to treat with oral dextrose gel?
    - When should babies with neonatal hypoglycaemia have their blood glucose concentration monitored following treatment with oral dextrose gel?
    - How should blood glucose concentrations be analysed?
- ***Health professionals who prescribe oral dextrose gel***
    - Who should prescribe oral dextrose gel to treat neonatal hypoglycaemia?
    - When should paediatric medical advice be sought for a baby with neonatal hypoglycaemia who is eligible to be treated with oral dextrose gel?
- ***Cost effectiveness of oral dextrose gel***
    - Is it cost effective to treat neonatal hypoglycaemia with oral dextrose gel?

Key clinical outcomes for these Clinical Practice Guidelines

The Clinical Practice Guidelines Panel developed a comprehensive list of relevant neonatal, child, and maternal clinical and health resource utilisation outcomes for these Guidelines. The primary and secondary outcomes are listed below. Most of these outcomes were derived from a key Cochrane systematic review: *Oral dextrose gel for the treatment of hypoglycaemia in newborn infants* (Weston 2014).

Primary outcomes for these Clinical Practice Guidelines

- Treatment of hypoglycaemia (investigator defined)
- Any neurological impairment at two years of age or greater (investigator defined) including any visual impairment; cerebral palsy; motor impairment; hearing impairment or developmental delay

Secondary neonatal outcomes for these Clinical Practice Guidelines

- Improvement of the blood glucose concentration to ≥ 2.6 mmol/L
- Rebound hypoglycaemia (investigator defined)
- Recurrent hypoglycaemia (investigator defined)
- Increment of blood glucose after treatment (change in blood glucose concentration 30 to 90 minutes after treatment)
- Duration of hypoglycaemia (time from detection of hypoglycaemia to achieving a blood glucose concentration above the threshold definition)
- Number of episodes of hypoglycaemia (investigator defined)
- Admission to neonatal intensive care unit (NICU) or special care baby unit (SCBU)
- Separation from the mother for treatment of hypoglycaemia
- Requirement for any additional medications for treatment of hypoglycaemia
- Intravenous dextrose for treatment of hypoglycaemia
- Neonatal seizures
- Abnormal brain imaging
- Length of stay (from birth until discharge)
- Formula given during hospital admission
- Breast feeding (any) after discharge
- Exclusive breast feeding after discharge (World Health Organisation (WHO) definition 2003)

Secondary childhood outcomes for these Clinical Practice Guidelines

- Exclusive breastfeeding at six months of age (WHO definition 2003)
- Developmental delay
- Cerebral palsy
- Visual impairment
- Hearing impairment
- Motor impairment
- Processing difficulty (investigator defined)
- Abnormal brain imaging

Secondary maternal outcomes for these Clinical Practice Guidelines

- Satisfaction with treatment for the newborn
- Impact on quality of life
- Length of postnatal stay in hospital

Format of this guideline
Each chapter within the Guideline follows the same format:

- Description of the evidence for use of oral dextrose gel to treat neonatal hypoglycaemia
- Summary of the judgements of evidence (judgements are used to formulate the clinical practice recommendations and practice points). Research recommendations are made if there is a lack of high quality evidence to answer the clinical question.

Research methods used in these guidelines
The methods used to identify the evidence are summarised below and given in detail in **Appendix A**.

A systematic literature search of multiple electronic databases was undertaken in October 2014. **Appendix A** details the search strategy.

Where possible the evidence presented in these Clinical Practice Guidelines is based on the gold standard of systematic review and randomised controlled trials. Quality of included studies was assessed using the GRADE methods (http://www.gradeworkinggroup.org/ and adapted NHMRC methods (NHMRC 1998). Evidence tables and summaries of evidence for each question where appropriate were produced (**Appendix B-D**).

The methodological quality of these Clinical Practice Guidelines was assessed using AGREE II (www.agreetrust.org/).

Summary of timeline

14th October 2014	First Panel meeting in Auckland New Zealand.
11th December 2014	Second Panel meeting in Auckland New Zealand.
31st March 2015	Consultation with organisations whose members are involved in the care of babies immediately after birth.
22 June 2015	Release of these Clinical Practice Guidelines.

Updating the guidelines
These guidelines will be reviewed in three years' time and updated as required.

Chapter 2: Background

Neonatal hypoglycaemia

The focus of this evidence based Clinical Practice Guidelines is on the use of oral dextrose gel to treat neonatal hypoglycaemia. Neonatal hypoglycaemia is a common condition affecting 5 to 15% of babies in the first days after birth (Cornblath 2000, Hay 2009). However, the incidence in babies who have additional risk factors is much greater: up to 50% in infants of diabetic mothers (Maayan-Metzger 2009), and 66% in preterm babies (Lucas 1988). Of babies who are at risk for neonatal hypoglycaemia (infant of a diabetic, preterm, small or large for gestation), 50% will develop a blood glucose of < 2.6 mmol/L (Harris 2012). These babies have an increased risk of developmental delay in later life (Woythaler 2011, Silverman 1991, Leitner 2007, Stenninger 1998) and hypoglycaemia can be associated with brain injury (Koh 1988, Lucas 1988, Kerstjens 2012). Indeed, it has been reported that neonatal hypoglycaemia is the only neonatal morbidity that is independently associated with later developmental delay in late preterm babies (Kerstjens 2012). While it is uncertain what degree or duration of hypoglycaemia is necessary before morbidity occurs, it is known that even babies without symptoms can have adverse outcomes, and that prolonged hypoglycaemia can be associated with neurodevelopmental impairment (Lucas 1988, Duvanel 1999). Therefore, prompt treatment of hypoglycaemia is important in reducing these risks.

Use of oral dextrose gel to treat neonatal hypoglycaemia

Two small observational studies in hypoglycaemic babies aged from 28 to 42 weeks' gestation reported an improvement in blood glucose concentrations following treatment with 200mg/kg 40% oral dextrose gel (Ang 1990, Bourchier 1992). These observational studies were followed by two randomised controlled trials; The Northern Ireland Trial (Troughton 2000) and the Sugar Babies Trial (Harris 2013) which have been synthesised in the Cochrane systematic review '*Oral dextrose gel for the treatment of hypoglycaemia in newborn infants*' (Weston 2015, *unpub*). The characteristics of each study are summarised in **Table 1**.

Given the key clinical questions identified by the Clinical Practice Guidelines Panel and the importance of the evidence from the systematic review for these Clinical Practice Guidelines, a summary of this *(unpub)* Cochrane systematic review is provided below. Information includes: inclusion criteria for trials, primary outcomes, geographical location, timing of conduct of the trials, oral dextrose gel regimen used, risk of bias assessment and outcomes reported (primary and secondary).

Eligibility for inclusion in Weston (2015, unpub) Cochrane systematic review

The Cochrane systematic review '*Oral dextrose gel for the treatment of hypoglycaemia in newborn infants'* (Weston 2015, *unpub*) included two randomised controlled trials comparing dextrose gel with placebo, no treatment, or other therapies for treatment of neonatal hypoglycaemia.

Description of the two randomised controlled trials included in the Weston (2015, unpub) Cochrane systematic review

Data were available for 312 neonates (Harris 2013, Troughton 2000).

A randomised, double-blind, placebo-controlled trial; the Sugar Babies Trial (Harris 2013) demonstrated that treatment of neonatal hypoglycaemia in babies ≥ 35 weeks' gestation with

200mg/kg of 40% oral dextrose gel was more effective than feeding alone in reversing hypoglycaemia. It also reduced the rate of NICU admission for hypoglycaemia and increased the likelihood of exclusive breast feeding at two weeks' of age.

A follow-up study to the Sugar Babies Trial (Harris 2013) reported on the outcomes at two years' corrected age of 184 children out of the original 237 (78%) who had been randomised to receive either 40% oral dextrose gel or placebo gel for the treatment of neonatal hypoglycaemia (Harris 2014). Treatment with dextrose gel did not change the incidence of disability or processing problems.

A randomised controlled study; The Northern Ireland Trial (Troughton 2000) randomised 75 hypoglycaemic infants on day 1 who were ≥ 36 weeks' gestation to either 400 mg/kg of 40% oral dextrose gel with feed or feed alone. This trial showed that the use of oral dextrose gel did not significantly increase blood glucose concentrations at 15 and 30 minutes after treatment compared with feed alone. This study has only been presented as an abstract and has not been published in full.

Geographical locations where these trials were conducted
The Sugar Babies Trial (Harris 2013) was conducted in New Zealand and the Northern Ireland Trial (Troughton 2000) was conducted in Northern Ireland.

Era of conduct of these trials
Both trials were conducted between 2000 and 2010.

Oral dextrose gel regimens utilised within these trials
Gestational age of newborns
The Sugar Babies Trial (Harris 2013) treated newborns diagnosed with hypoglycaemia aged ≥ 35 weeks' gestation and younger than 48 hours after birth. The Northern Ireland Trial (Troughton 2000) treated neonates aged ≥ 36 weeks' gestation and younger than 24 hours after birth.

Oral dextrose gel utilised in these trials
Both trials used 40% oral dextrose gel to treat neonatal hypoglycaemia. The Sugar Babies Trial (Harris 2013) treated babies with 200mg/kg and the Northern Ireland Trial (Troughton 2000) treated babies with 400mg/kg.

Blood glucose concentration methods of analysis
The Sugar Babies Trial (Harris 2013) measured blood glucose concentrations by a glucose oxidase analyser (Radiometer, ABL800 FLEX, Copenhagen, Denmark), with a coefficient of variation of 2.1%. The Northern Ireland Trial (Troughton 2000) measured blood glucose concentrations by HemoCue, with a coefficient of variation of 2.3% (Teng 1995). However, Dahlberg (1997) found that falsely low glucose values occurred using the HemoCue method and they did not recommend this method in the diagnosis of hypoglycaemia in newborns.

Table 1. Characteristics of included trials (*Weston 2015, unpub)*

	The Sugar Babies Trial (Harris 2013)	**The Northern Ireland Trial** (Troughton (2000)
Methods	Randomised double-blind placebo-controlled trial.	Randomised controlled trial.
Participants	242 infants ≥ 35 weeks' gestation, < 48 hours old and at risk of hypoglycaemia.	75 hypoglycaemic (≤ 2.5 mmol/L) babies ≥ 36 weeks' gestation, < 24 hours old and admitted to NICU.
Risk factors	Infant of a diabetic mother, small (birthweight < 10^{th} centile, or < 2500g) or large (birthweight > 90^{th} centile or > 4500g), preterm (35 or 36 weeks' gestation), or other reasons such as poor feeding.	Not reported.
Interventions	Infants who became hypoglycaemic (< 2.6 mmol/L) were randomised to receive 40% dextrose gel (0.5ml/kg) or placebo gel massaged into the buccal membrane and encouraged to feed.	Hypostop (40% dextrose, 1ml/kg) massaged into the buccal membrane plus a feed compared with feeding alone.
Blood Glucose Analysis	Measured by the glucose oxidase method (Radiometer, ABL800 FLEX, Denmark).	Measured by HemoCue blood glucose analyser.
Monitoring of blood glucose concentration	Blood glucose concentration was measured 30 minutes following gel treatment. Dextrose gel was repeated if the hypoglycaemia persisted. A maximum of 6 doses of gel could be given with a 48 hour period.	Blood glucose concentration was measured at baseline, 15 and 30 minutes following gel treatment.
Primary Outcomes	Treatment failure defined as a blood glucose concentration of ≤ 2.6mmol/L, 30 minutes after the second of two treatment doses of gel.	Change in blood glucose concentration at 15 and 30 minutes following treatment compared to baseline.
Secondary Outcomes	1. Admission to NICU. 2. Frequency of breast feeding. 3. Total volume and frequency of expressed breast milk and infant formula, intravenous dextrose and dextrose gel in the first 48 hours. 4. Method of feeding two weeks after birth. 5. Incidence of rebound hypoglycaemia (defined as a further episode of hypoglycaemia occurring less than 6 hours after successful treatment). 6. Incidence of recurrent hypoglycaemia (defined as a further episode of hypoglycaemia after successful treatment, within 48 hours after birth). 7. Time taken to achieve interstitial glucose concentrations ≥ 2.6 mmol/L after treatment. 8. Total duration of interstitial glucose concentrations < 2.6 mmol/L in the first 48 hours after birth.	1. Subsequent requirement for intravenous dextrose. 2. Volume taken at the next feed following randomisation in bottle fed babies.

Risk of bias of trials included in Weston (2015, unpub) Cochrane systematic review
The risk of bias of the included trials (selection bias, performance and detection bias, attrition bias, reporting bias, other bias) is shown in **Table 2**.

Selection bias
The Sugar Babies Trial had adequate sequence generation (Harris 2013) using a computer generated blocked randomisation with variable block sizes.

The Northern Ireland Trial did not provide sufficient evidence to determine if adequate sequence generation had been performed (Troughton 2000).

Allocation concealment
The Sugar Babies Trial maintained allocation concealment (Harris 2013) by entering data into a computer which provided a randomisation number corresponding to the numbered treatment pack.

The Northern Ireland Trial provided insufficient information to determine if adequate allocation concealment had been performed (Troughton 2000).

Blinding (performance bias and detection bias)
Both dextrose and placebo gels were identical in appearance in the Sugar Babies Trial (Harris 2013). Clinicians, families and all study investigators were masked to group allocation until data analysis was complete.

There was no evidence to determine the risk of performance bias and detection bias in the Northern Ireland Trial (Troughton 2000).

Incomplete outcome data (attrition bias)
The Sugar Babies Trial reported that five babies were randomised in error and were excluded from the analysis (Harris 2013) and also reported a loss of 22% to follow-up at two years' of age (Harris 2014).

There was insufficient detail to determine attrition bias in the Northern Ireland Trial (Troughton 2000).

Selective reporting (reporting bias)
There was no evidence of selective reporting in the Sugar Babies Trial (Harris 2013). There was insufficient detail to make a judgement for the Northern Ireland Trial (Troughton 2000).

Other bias
In the Sugar Babies Trial, more mothers who intended to breast feed were allocated to the dextrose gel group than to the placebo gel group; and fewer boys were allocated to the dextrose gel group than to the placebo group (Harris 2013).

There was insufficient detail available to determine risk of other bias in the Northern Ireland Trial (Troughton 2000).

Table 2. Risk of bias of included trials (*Weston 2015,unpub*)

Trial (Author, Year)	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias
The Sugar Babies Trial (Harris, 2013)						
Northern Ireland Trial (Troughton, 2000)						

Low risk of bias	Unclear risk of bias

Outcomes for these Clinical Practice Guidelines reported in the included trials

Primary outcomes

The Sugar Babies Trial reported on both of the primary outcomes on the treatment of hypoglycaemia and neurological impairment at two years of age or greater (Harris 2013, Harris 2014).

Neonatal outcomes

The Sugar Babies Trial (Harris 2013) reported on 6 of the 15 neonatal outcomes. The Northern Ireland Trial (Troughton (2000) reported on 2 of the 15 neonatal outcomes.

Childhood outcomes

The Sugar Babies Trial (Harris 2014) reported on 1 of the 8 childhood outcomes.

Maternal outcomes

The Sugar Babies Trial (Harris 2013) reported on 1 of the 3 maternal outcomes, although this was not listed as an outcome of the trial.

Chapter 3: Benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia

3.1 What are the short and long term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia?

Primary Outcomes for these Clinical Practice Guidelines:

Primary Outcomes are outlined in **Table 3**

Treatment of hypoglycaemia (investigator defined) – The Sugar Babies Trial (Harris 2013) reported that 86.4% of babies were successfully treated for neonatal hypoglycaemia with oral dextrose gel, compared to 75.6% of controls (RR 1.14 (95% CI 1.01 to 1.29)).

Any neurological impairment at 2 years of age or greater (investigator defined) including any of: visual impairment; cerebral palsy; motor impairment; hearing impairment or developmental delay. The Sugar Babies Trial follow-up study defined neurosensory disability to be any of cognitive language, or motor score on Bayley III assessment below -1 SD; cerebral palsy; blindness or deafness (Harris 2014). Treatment with oral dextrose gel did not change the incidence of neurosensory disability at two years' corrected age (RR 1.14 (0.78 to 1.67))**.**

Table 3. Primary outcomes

Primary Outcome	Dextrose Gel	Placebo Gel	Risk ratio (RR) (95% confidence interval)	Number of trials	Trials contributing data	Number of children
Treatment of hypoglycaemia (investigator defined)	102 (n=118) (86.4%)	90 (n=119) (75.6%)	1.14 (1.01-1.29) *	1	Sugar Babies Trial (Harris 2013)	237
Neurosensory disability	35 (n=90) (39%)	32 (n=94) (34%)	1.14 (0.78-1.67)	1	Follow-up to the Sugar Babies Trial (Harris 2014)	184

* ($p<0.05$)

Secondary neonatal outcomes for these Clinical Practice Guidelines:

Neonatal outcomes are summarised in **Table 4**

Improvement of the blood glucose concentration to ≥ 2.6 mmol/L: The Sugar Babies Trial (Harris 2013) reported that 86.4% of babies treated with oral dextrose gel had a significantly improved blood glucose concentration to ≥ 2.6 mmol/L, compared to 75.6% of controls (RR 1.14 (95% CI 1.01 to 1.29)).

Rebound hypoglycaemia (investigator defined): The Sugar Babies Trial defined this as an episode of hypoglycaemia within 6 hours after successful treatment with oral dextrose gel (blood or interstitial glucose concentration ≥ 2.6 mmol/L for ≥ 1 hour after treatment) (Harris 2013). The Sugar Babies Trial reported that episodes per baby of rebound hypoglycaemia were uncommon with no difference between oral dextrose gel and placebo groups for blood (RR 1.46 (0.67 to 3.26)) or interstitial (RR 1.20 (0.40 - 3.57)) glucose concentrations (Harris 2013).

Recurrent hypoglycaemia (investigator defined): The Sugar Babies Trial defined this as an episode of hypoglycaemia after successful treatment of oral dextrose gel within 48 hours after birth (Harris 2013). The Sugar Babies Trial reported that three or more episodes per baby of recurrent hypoglycaemia were less common in the oral dextrose gel group (4%) than in the placebo group (17%) when measured by interstitial (RR 0.44 (0.21 to 0.86), p=0.01), but not blood (RR 0.89 (0.55 to 1.44)), glucose concentrations (Harris 2013)

Increment of blood glucose after treatment (change in blood glucose concentration 30 to 90 minutes after treatment): The Northern Ireland Trial (Troughton 2000) reported that oral dextrose gel treatment did not significantly increase blood glucose concentrations 15 to 30 minutes after treatment (mean difference = 0.40 (-0.1 - 0.94) mmol/L).

Admission to NICU or SCBU: The overall incidence of admission to NICU or SCBU for any reason, was not different between babies who received oral dextrose gel (38%) compared to placebo gel (46%) in the Sugar Babies Trial (Harris 2013) (RR 0.83 (0.61 to 1.11)).

Separation from the mother for treatment of hypoglycaemia: Oral dextrose gel (14%) was associated with a significant reduction in the incidence of separation of mother and infant for treatment of hypoglycaemia compared with placebo gel (25%) in the Sugar Babies Trial (Harris 2013) (RR 0.54 (0.31 to 0.93)).

IV treatment: Oral dextrose gel (13%) did not alter the need for IV treatment for hypoglycaemia compared with placebo gel (17%) in both trials (RR 0.81 (0.29 to 2.25)).

Neonatal seizures: There were no serious adverse events (defined as death or seizures) in the Sugar Babies Trial (Harris 2013). Therefore, the odds ratio is not estimable.

Formula given during hospital admission: There was no difference in the number of infants who received formula in hospital between oral dextrose gel (58%) and placebo gel (60%) groups (RR 0.95 (0.77 to 1.18)) in the Sugar Babies Trial (Harris 2013).

Exclusive breast feeding after discharge (WHO 2003): Oral dextrose gel (96%) compared to placebo gel (87%) was associated with a significant increase in the likelihood of exclusive breast feeding at two weeks of age (RR 1.10 (1.01 to 1.18)) in the Sugar Babies Trial (Harris 2013).

Table 4. Secondary neonatal outcomes

Secondary Outcome	Dextrose Gel n_1=118	Placebo Gel n_2=119	Risk ratio (95% CI)	Number of infants	Trial(s) contributing data
Improvement in BGC to ≥ 2.6 mmol/L, n (%)	102 (86)	90 (76)	1.14 (1.01-1.29)§	237	Sugar Babies Trial (Harris 2013)
Rebound Hypoglycaemic episodes per baby, n (%)					
Blood Glucose 0 1 2	 104 (88) 12 (10) 2 (2)	 109 (92) 9 (7) 1 (1)	 1.46 (0.67-3.26)	 237	 Sugar Babies Trial (Harris 2013)
Interstitial Glucose 0 1 2	 20 (80) 3 (11) 2 (2)	 25 (83) 3 (10) 2 (7)	 1.20 (0.40-3.57)	 237	 Sugar Babies Trial (Harris 2013)
Recurrent Hypoglycaemic episodes per baby, n (%)					
Blood Glucose 0 1 2 ≥3	 90 (76) 23 (20) 5 (4) 0	 91 (76) 22 (19) 4 (3) 2 (2)	 0.89 (0.55-1.44)	 237	 Sugar Babies Trial (Harris 2013)
Interstitial Glucose 0 1 2 ≥3	 16 (64) 8 (32) 0 1 (4)	 18 (60) 4 (13) 3 (10) 5 (17)	 0.44 (0.21-0.86)*	 237	 Sugar Babies Trial (Harris 2013)
Change in BGC 30mins after treatment†, mean ± SEM	1.8 ± 0.2	1.4 ± 0.2	0.40 (-0.1-0.94)‡	75	Northern Ireland Trial (Troughton 2000)
Admission to NICU or SCBU, n (%)	45 (38)	55 (46)	0.83 (0.61-1.11)	237	Sugar Babies Trial (Harris 2013)
Separation from mother for treatment of hypoglycaemia, n (%)	16 (14)	30 (25)	0.54 (0.31-0.93)§	237	Sugar Babies Trial (Harris 2013)
Intravenous treatment for hypoglycaemia‖, n (%)	21 (13)	26 (17)	0.81 (0.29-2.25)	312	Sugar Babies Trial (Harris 2013) & Northern Ireland Trial (Troughton 2000)
Formula given in hospital, n (%)	68 (58)	72 (60)	0.95 (0.77-1.18)	237	Sugar Babies Trial (Harris 2013)
Exclusive breast feeding after discharge (WHO 2003), n (%)	113 (96)	104(87)	1.10 (1.01-1.18)§	237	Sugar Babies Trial (Harris 2013)

* *P*=0.01; § *P*<0.05; † n_1=39, n_2=36; ‡ Mean difference ± SEM Weston (2015, unpub); ‖ n_1=157, n_2=155;
BGC = Blood glucose concentration mmol/L; CI=confidence interval

No data were reported for the following secondary neonatal outcomes for these Clinical Practice Guidelines in either trial:

- *Duration of hypoglycaemia (time from detection of hypoglycaemia to achieving a blood glucose concentration above the threshold definition)*
- *Number of episodes of hypoglycaemia (investigator defined)*
- *Requirement for any additional medications for hypoglycaemia*
- *Abnormal brain imaging*
- *Length of stay (from birth until discharge)*
- *Breast feeding (any) after discharge*

Secondary childhood outcomes for these Clinical Practice Guidelines

Processing difficulty: The Sugar Babies Trial follow-up study defined processing difficulty as clinically assessed executive function or global motion coherence perception threshold worse than 1.5 SD from the mean (Harris 2014). Oral dextrose gel compared with placebo gel did not change the incidence of processing difficulty at two years' corrected age (RR 0.52 (0.23 to 1.15)) (**Table 5**).

No data were reported for the following secondary neonatal outcomes in either trial:

- *Exclusive breast feeding at six months of age (WHO 2003*)
- *Abnormal brain imaging*
- *Developmental delay*
- *Cerebral palsy*
- *Visual impairment*
- *Hearing impairment*
- *Motor impairment*

Table 5. Secondary childhood outcome

Secondary Outcome	Dextrose Gel n=90	Placebo Gel n=94	Risk ratio (RR) (95% confidence interval)	Number of trials	Trials contributing data	Number of children
Processing difficulty	8 (10%)	16 (17%)	0.52 (0.23-1.15)	1	Sugar Babies Trial follow-up study (Harris 2014)	184

Weston (*2015, unpub*)

Secondary maternal outcomes for these Clinical Practice Guidelines

Satisfaction with treatment for the newborn: No data were reported on the overall satisfaction with treatment for the newborn. The Sugar Babies Trial, however, reported that mothers of 96% of the oral dextrose gel and 95% of the placebo group infants found the gel treatment to be an "acceptable" and "easy treatment" for their babies (Harris 2013).

Impact on quality of life: No data were reported on the short and long term impact on quality of life.

Length of stay in hospital (postnatal): No data were reported on the postnatal length of stay in hospital for the mother.

Evidence Summary for the use of oral dextrose gel to treat neonatal hypoglycaemia

Randomised controlled trial evidence addressing the key outcomes is limited. Only one trial reported on the primary outcomes of the treatment of hypoglycaemia and the incidence of neurological impairment at two years of age. One trial found that oral dextrose gel is helpful in the treatment of neonatal hypoglycaemia, reducing maternal-infant separation for the treatment of hypoglycaemia and in supporting breast-feeding after discharge.

See **Appendix B,** NHMRC (page 43), **Appendix C,** Grade (page 46) and **Appendix D**, Grade (page 50) – Evidence Summaries.

Recommendation	Strength of recommendation	
	NHMRC	GRADE
In babies diagnosed with neonatal hypoglycaemia, treat with 40% oral dextrose gel.	**B***	**Conditional#**

*Body of evidence can be trusted to guide practice in most situations.
#Benefits probably outweighs harms.

Research recommendations:

- Further research is required to investigate the effects of treatment with oral dextrose gel on the duration and number of episodes of hypoglycaemia.
- Further follow-up of the infants into later childhood and adulthood from the randomised controlled trials is needed to assess the long-term impact, if any, of the use of oral dextrose gel to treat neonatal hypoglycaemia.
- There is a need to better assess the impact, if any, on maternal outcomes of using oral dextrose gel to treat neonatal hypoglycaemia.

Chapter 4: Dosage of oral dextrose gel

Currently, there is insufficient evidence to identify any effect of the dosage of oral dextrose gel on outcomes.

4.1 What is the optimal formulation of oral dextrose gel to treat neonatal hypoglycaemia?

Two studies treated newborn babies diagnosed with neonatal hypoglycaemia with 40% oral dextrose gel.

The Sugar Babies Trial used Dextrose 40% Gel supplied by Biomed Ltd (Auckland, New Zealand): glucose anhydrous BP 40 g/L, carmellose sodium BP 2g (suspending agent), methyl hydroxybenzoate BP 0.09% and propyl hydroxybenzoate BP 0.01% (preservatives), water to 100ml (Harris 2013).

Oral dextrose gel is hyperosmolar, with an osmolarity of 2020 mOsmol/L (AHFS® 2009). A bottle of dextrose gel is recommended by Biomed Ltd to be used for no more than one month after opening, to minimize the risk of microbial contamination, and can be stored on the shelf or in the fridge. Users are recommended to write the date on the bottle after opening.

The Northern Ireland Trial (Troughton 2000) used Hypostop, currently supplied by BBI Healthcare (Pencoed, Wales, United Kingdom) as GlucoGel® in a formulation that contains water; glucose monohydrate; citric acid; gelling agent (sodium carboxy methyl cellulose) and preservatives E215, E217, E219.

<u>Other formulations available in New Zealand include:</u>

Glucose 15™– Paddock Laboratories Inc. (Minneapolis, MN, USA): purified water, dextrose (d-glucose) USP 40%, glycerin, lemon flavouring, and preservatives (possibly methyl and propyl parabens).

Glucoburst Glucose Gel® – PBM Products (Gordonsville, VA, USA): purified water, dextrose (d-glucose), USP 40%, glycerine, cellulose gum, sodium benzoate (preservative), potassium sorbate (preservative), sodium bisulfate, natural flavouring.

Alcohols are typically avoided in paediatric formulations because of their toxicity (Menon 1984), especially in newborns, or very young children.

Adverse reactions associated with flavourings are uncommon due to the very small amount of chemicals used in flavouring (Kumar 1993).

Practice Points:

- Use 40% oral dextrose gel to treat neonatal hypoglycaemia that does not contain alcohol.
- The label on the bottle should state all preservatives.
- The Clinical Practice Guidelines Panel recommended using the formulation used in the Sugar Babies Trial (Harris 2013).
- The label on the dextrose gel bottle should state all preservatives, and that the bottle should only be used for one month after opening.

4.2 What is the most effective dose of oral dextrose gel to treat neonatal hypoglycaemia?

Two studies reported the dose of oral dextrose gel used to treat neonatal hypoglycaemia. The Northern Ireland Trial administered 400 mg/kg (1ml/Kg) buccally plus feed (not specified) (Troughton 2000). They reported that the volume of the next feed in bottle fed infants was significantly lower in the oral dextrose gel group compared to controls (7.6 ± 1.0 vs 13.1 ± 1.1 ml/Kg, p=0.0001) with no difference in blood glucose concentrations following administration of oral dextrose gel (see Chapter 3). The Sugar Babies Trial administered 200 mg/kg (0.5 ml/Kg) massaged into the buccal mucosa and the baby was encouraged to breastfeed. There was a reduction in the separation of mother and infant for treatment of hypoglycaemia and an increase in breastfeeding at two weeks after hospital discharge (Harris 2013) (see Chapter 3).

The evidence from these two trials shows that the lower dose of 200 mg/kg is effective at treating hypoglycaemia, without adverse effects.

Practice Point:

- Use a dose of 200 mg/kg (0.5 mL/kg) 40% oral dextrose to treat neonatal hypoglycaemia.

Research Recommendation:

- Further research is required to determine the most effective dose of oral dextrose gel to treat neonatal hypoglycaemia.

4.3 What is the optimal number of doses of oral dextrose gel to treat neonatal hypoglycaemia?

The Sugar Babies Trial treated a single episode of hypoglycaemia with up to two doses of oral dextrose gel (Harris 2013). Up to six doses of 40% oral dextrose gel could be given over 48 hours. The Northern Ireland Trial did not specify the number of doses given (Troughton 2000).

The Clinical Guidelines Panel considered that if multiple doses of oral dextrose gel are needed to treat hypoglycaemia, paediatric clinical review and intravenous dextrose treatment should be considered. However, a further dose of oral dextrose gel could be administered while arranging for intravenous dextrose treatment.

Practice Points:

- Use up to two doses of oral dextrose gel, at least 30 minutes apart, per episode of hypoglycaemia and a maximum of six doses of oral dextrose gel in 48 hours.
- Consider a third dose of oral dextrose gel while arranging alternative treatment.

Research Recommendation:

- Further research is required to determine the optimal number of doses of oral dextrose gel to treat neonatal hypoglycaemia.

4.4 What is the optimal timing of repeat doses of oral dextrose gel to treat neonatal hypoglycaemia?

Blood glucose concentrations were measured 30 minutes after oral dextrose gel administration in the Sugar Babies Trial (Harris 2013) and if the baby remained hypoglycaemic, or hypoglycaemia subsequently recurred, treatment was repeated.

Practice Point:

- Recheck the blood glucose concentration 30 minutes after giving oral dextrose gel, and repeat the dose of oral dextrose gel if the baby remains hypoglycaemic.

Research Recommendation:

- Further research is required to determine the optimal timing of repeat doses of oral dextrose gel to treat neonatal hypoglycaemia.

Chapter 5: Administration of oral dextrose gel

5.1 Which babies should receive oral dextrose gel to treat neonatal hypoglycaemia?

The Sugar Babies Trial administered oral dextrose gel to babies with hypoglycaemia who were born at ≥ 35 weeks' gestation and were < 48 hours old (Harris 2013). The Northern Ireland Trial treated babies with hypoglycaemia who were born at ≥ 36 weeks' gestation and were < 24 hours old Troughton (2000).

There are no data available on the use of oral dextrose gel to treat hypoglycaemia in babies < 35 weeks' gestational age.

Practice Point:

- Use 40% oral dextrose gel to treat hypoglycaemia in babies who are ≥ 35 weeks' gestational age and less than 48 hours after birth.

Research Recommendations:

Further research is needed to determine if

- Oral dextrose gel is safe and effective in hypoglycaemic babies < 35 weeks' gestational age, and babies older than 48 hours after birth.

5.2 What is the safest and most effective way to administer oral dextrose gel to treat neonatal hypoglycaemia?

Two trials administered gel into the buccal mucosa (Harris 2013, Troughton 2000). In the Sugar Babies Trial, the baby's mouth was dried with gauze, and then 200 mg/Kg (0.5 ml/Kg) of gel was massaged into the buccal mucosa using standard hospital issue gloves (Harris 2013).

There are reports of latex allergy developing in some groups of patients with multiple exposure to latex gloves e.g. myelomeningocele (Boettcher 2014, Niggemann 1998). Therefore, the Clinical Guidelines Panel discussed and recommended the use of latex free gloves when administering dextrose gel.

Practice Point:

- Using gloves, preferably latex free, massage 40% oral dextrose gel into the buccal mucosa after drying the mouth with gauze.

Research recommendation:

- Further research is required to determine the optimal method of administering oral dextrose gel.

5.3 At what location should babies be administered oral dextrose gel to treat neonatal hypoglycaemia?

The Northern Ireland Trial treated babies for hypoglycaemia with dextrose gel in NICU (Troughton 2000). In the Sugar Babies Trial, babies were treated on the postnatal ward in the presence of the mother (Harris 2013).

Secondary neonatal outcomes for the Clinical Practice Guidelines (See Table 4, Chapter 3)

Admission to NICU or SCBU: The overall incidence of admission to NICU or SCBU for any reason was not different between babies who received oral dextrose gel (38%) compared to placebo gel (46%) in the Sugar Babies Trial (Harris 2013) (RR 0.83 (0.61 to 1.11)).

Separation from the mother for treatment of hypoglycaemia: Oral dextrose gel (14%) was associated with a significant reduction in the incidence of separation of mother and infant for treatment of hypoglycaemia compared with placebo gel (25%) in the Sugar Babies Trial (Harris 2013) (RR 0.54 (0.31 to 0.93)).

Neonatal seizures: There were no serious adverse events (death or seizures) reported in the Sugar Babies Trial (Harris 2013).

Rebound hypoglycaemia: In the Sugar Babies Trial, episodes per baby of rebound hypoglycaemia were uncommon in oral dextrose gel and placebo groups (Harris 2013).

Oral dextrose gel to treat neonatal hypoglycaemia has not been shown to cause adverse events. Therefore, there is not a requirement for dextrose gel to be administered in NICU or SCBU. However, the need for repeat blood glucose measurement suggests that oral dextrose gel should be administered in a location where accurate blood glucose measurement is readily available.

Practice Points:

- Oral dextrose gel should preferably be administered to the baby in the presence of the mother.
- Equipment for accurate blood glucose measurement should be available.

5.4 What is the role of oral dextrose gel to treat neonatal hypoglycaemia when used with other treatments?

Both the Sugar Babies Trial and the Northern Ireland Trial reported that babies were treated with oral dextrose gel and then encouraged to feed (breastmilk or formula) (Harris 2013, Troughton 2000). In both studies, intravenous dextrose was used to treat babies who remained hypoglycaemic following treatment with oral dextrose gel. We found no data on the use of oral dextrose gel to treat hypoglycaemia in combination with other treatments.

Practice Point:

- Offer the baby a feed, preferably breast milk, immediately after administration of oral dextrose gel.

Research Recommendation:

- Further research is needed to determine the role of oral dextrose gel to treat neonatal hypoglycaemia in combination with other treatments e.g. intravenous dextrose.

5.5 What are the contraindications for using oral dextrose gel to treat neonatal hypoglycaemia?

The Sugar Babies Trial excluded babies from their study if there were any serious congenital malformations, terminal disorders or skin abnormalities that would prevent the use of the continuous glucose monitor (Harris 2013).

No data were reported on contraindications for using oral dextrose gel to treat neonatal hypoglycaemia.

Chapter 6: Effect on blood glucose concentration when using oral dextrose gel

6.1 What is the minimum blood glucose concentration that is safe to treat neonatal hypoglycaemia with oral dextrose gel?

The Sugar Babies Trial reported the median blood glucose concentration at the time of randomisation was 2.2 (0.9-2.5) mmol/L (Harris 2013), while the Northern Ireland Trial treated neonates with oral dextrose gel when blood glucose concentrations were ≤ 2.5 mmol/L (Troughton 2000).

The Clinical Guidelines Panel discussed the lower limit of blood glucose concentration that should be treated with oral dextrose gel, and recommended a blood glucose concentration of 1.2 mmol/L as the threshold below which oral dextrose gel should not be the sole treatment. However, the Panel agreed that this cut off may differ amongst local hospitals and institutions, as there isn't a good evidence base for this level.

Practice Point:

- For babies with severe hypoglycaemia (< 1.2 mmol/L) use oral dextrose gel as an interim measure while arranging for urgent additional review and treatment.

Research Recommendation:

- Further research is recommended to determine the minimum blood glucose concentration that is safe to treat with oral dextrose gel in hypoglycaemic neonates.

6.2 When should babies with neonatal hypoglycaemia have their blood glucose concentration monitored following treatment with oral dextrose gel?

Recurrent episodes of hypoglycaemia may increase the risk of neurodevelopmental delay (Duvanel 1999) therefore prompt treatment of hypoglycaemia is important in reducing this risk.

The Sugar Babies Trial measured blood glucose concentrations 30 minutes after oral dextrose gel was administered for treatment of neonatal hypoglycaemia (Harris 2013). The Northern Ireland Trial measured blood glucose concentrations 15 and 30 minutes after oral dextrose gel administration (Troughton 2000). There are no data available on the safety of monitoring blood glucose concentrations over a longer period of time following oral dextrose gel administration.

Practice Point:

- Repeat blood glucose concentration measurement 30 minutes after administering oral dextrose gel and treat with dextrose gel if the baby remains hypoglycaemic.

Research Recommendation:

- Further research is required to determine when blood glucose concentrations should be monitored after administration of oral dextrose gel to treat neonatal hypoglycaemia.

6.3 How should blood glucose concentrations be analysed?

The Sugar Babies Trial measured blood glucose concentrations on a blood gas analyser (ABL 800 FLEX; Radiometer Medical, Copenhagen, Denmark) using the glucose oxidase method (reading range 0.0-60 mmol/L, coefficient of variation 2.1%) (Harris 2013). The Northern Ireland Trial (Troughton 2000) measured blood glucose concentrations by HemoCue, with a coefficient of variation of 2.3% (Teng 1995).

While the bedside non-glucose oxidase measurements such as the HemoCue method provide a shorter analysis time of blood glucose, they are less accurate in the normal neonatal blood glucose range (Dahlberg 1997, Khan 2006, Ho 2004, Roth-Kleiner 2010) as they were developed for use in adults, and particularly diabetics. Glucose oxidase analysers provide the most accurate analysis for hypoglycaemia in newborns.

Practice Point:

- Accurate equipment for measuring blood glucose concentration e.g. glucose oxidase method should be available.

Chapter 7: Health professionals who prescribe oral dextrose gel

Currently, there is insufficient evidence to identify any effect of health professionals who prescribe oral dextrose gel on outcomes.

7.1 Who should prescribe oral dextrose gel to treat neonatal hypoglycaemia?

No data were reported on who should prescribe oral dextrose gel to treat neonatal hypoglycaemia.

Whilst dextrose gel, hypostop and glucogel are not listed in NZ Medsafe, they are already in use to treat hypoglycaemia in diabetic patients and neonatal hypoglycaemia in some New Zealand hospitals.

The New Zealand College of Midwives (INC) (2002) states that there is no defined list of medicines a midwife may prescribe, but the limits as to when a midwife can prescribe are set out in an amendment to Regulation 39 of the Medicines Regulations 1984. It states that; “no registered midwife shall prescribe any prescription of medicine otherwise than for antenatal, intrapartum, and postnatal care”. This is generally accepted as covering a period up to six weeks after the birth of the baby. The 2014 amendment to the Misuse of Drugs Regulations (1977) enables midwives to prescribe the controlled drugs pethidine, morphine and fentanyl.

Definition of Medicine: Any substance or article that (i) is manufactured, imported, sold, or supplied wholly or principally for administering to one or more human beings for a therapeutic purpose; and (ii) achieves, or is likely to achieve, its principal intended action in or on the human body by pharmacological, immunological, or metabolic means (Medicines Act 1981, Ministry of Health).

Practice Point:

- Oral dextrose gel can be prescribed by medical practitioners; midwives; pharmacist prescribers working in a neonatal scope of practice; and nurse practitioners with prescribing rights.

7.2 When should paediatric medical advice be sought for a baby with neonatal hypoglycaemia who is eligible to be treated with oral dextrose gel?

No data were reported on when medical advice should be sought for a baby with neonatal hypoglycaemia who has received oral dextrose gel.

The Clinical Guidelines Panel discussed and recommended that paediatric medical advice should be sought if a baby has severe hypoglycaemia (<1.2 mmol/L), a blood glucose concentration of < 2.6 mmol/L following two doses of oral dextrose gel one hour after first detection of hypoglycaemia, or requires six doses of oral dextrose gel to treat neonatal hypoglycaemia in 48 hours.

Practice Point:

- Paediatric medical advice should be sought if a baby has severe hypoglycaemia (<1.2 mmol/L), a blood glucose concentration of <2.6 mmol/L following two doses of oral dextrose gel one hour after first detection of hypoglycaemia, or requires six doses of oral dextrose gel to treat neonatal hypoglycaemia in 48 hours.

Chapter 8: Cost Effectiveness of oral dextrose gel

8.1 Is it cost effective to treat neonatal hypoglycaemia with oral dextrose gel?

The Sugar Babies Trial reported that oral dextrose gel can be purchased for about US$70 per 100ml or US$2 per baby, can be made up in the hospital pharmacy, and is stable at room temperature (Harris 2013). In New Zealand, Biomed supply Dextrose gel for about $100.00 per 100 mL, approximately NZ$1.80 per dose. The Sugar Babies Trial reported that babies received a median of two doses of gel (Harris 2013), which would approximate to $3.60 per baby. However, this assumes that all of the dextrose gel is used before the bottle expires (one month after opening). If only 5 babies were treated before the bottle of dextrose gel expired, this cost rises to $20 per baby.

In the Sugar Babies Trial, there was no difference in the rate of admission to NICU between the dextrose gel treated (38%) and placebo treated (46%) babies. However, fewer babies treated with oral dextrose gel (14%) compared to the placebo group (25%) were admitted to NICU for hypoglycaemia (Harris 2013). The number needed to treat (NTT) to prevent one such separation based on the Harris (2013) study is 9 babies, (Absolute Risk Reduction (ARR) 11.7%, 95% CI, 5 – 57), (**Table 6**).

Table 6. Number of babies needed to treat

Sugar Babies Trial (Harris 2013)	**Dextrose Gel (118)**	**Placebo Gel (119)**	**NTT**	**ARR (95% CI)**
Admitted to NICU for hypoglycaemia	16 (14%)	30 (25%)	9	11.7 (5 – 57)

It would cost $3.60 x 9 babies = $32.40 in dextrose gel to prevent an admission to NICU or SCBU, excluding associated staff costs, which would be expected to be minimal, as dextrose gel is quick and easy to administer. One night of Level 2 intensive care at Auckland City hospital costs approximately $1475 per night (personal communication) (**Table 7**).

Table 7. Treatment cost comparison

Median number of dextrose gel doses (Harris 2013)	2
Cost per dose	$1.80
Cost to treat 9 babies to prevent admission	$32.40
Cost to treat 9 babies to prevent admission if only 5 babies treated before bottle expires	$180.00
Approx. cost per night of Level 2 care at NICU (ACH)	$1475.00

Practice Point:

- Oral dextrose gel to treat neonatal hypoglycaemia is cost effective if the baby is not admitted to NICU for other medical reasons.

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Appendix A Clinical Practice Guidelines Process and Methods

The following section details the methodology used for the development of these Clinical Practice Guidelines.

Electronic searching
Search strategies were developed by an information specialist in conjunction with the research team (search strings are at the end of this Appendix).
Electronic searches were not date or language limited and the databases searched were:

- Medline
- Embase
- Central
- CINAHL
- Web of Science
- Scopus

Searches took place in October 2014.

Population
The target population were babies who received oral dextrose gel to treat neonatal hypoglycaemia.

Type of studies
We used the highest possible level of evidence to inform clinical practice recommendations. We limited the evidence to eligible randomised clinical trials and systematic reviews. We searched in proceedings of relevant scientific meetings, being American Academy of Pediatrics (2000-2014), European Society for Pediatric Research (2006-2013), Perinatal Society of Australia and New Zealand (2002-2014).

Analyses
These Clinical Practice Guidelines have presented some of the original data from the Cochrane systematic review (Weston 2015, *unpub*). All data are presented as effect estimates with 95% confidence intervals for dichotomous data. Mean differences were calculated between treatment groups where outcomes were measured in the same way for continuous data with standard deviations.

Evidence tables

Evidence was summarised in risk of bias or evidence tables depending on the level of evidence.

Assessment of quality of included studies

A number of internationally recognised tools are available to critically appraise studies. This guideline has been appraised using the AGREE II tool, and evidence was appraised using an adapted NHMRC and GRADE methods.

Search strategies for oral dextrose gel

All databases were searched using the following key words:
Hypoglycaemia OR hypogly*, AND (Glucose AND Gel*) OR dextrose gel*, AND neonat* OR newborn* OR infant*

MEDLINE RCT Search
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1. Hypoglycemia (22147)
2. Hypogly* or low blood sugar or low blood glucose (83268)
3. 1 or 2 (83268)
4. Glucose (132760)
5. Gel* (23963)
6. 4 and 5 (210)
7. Dextrose gel* (8)
8. 6 or 7 (216)
9. 3 and 8 (14)
10. Limit 9 to newborn infant (birth to 1 month) (4)
11. Newborn* or neonat* or infant* (1237161)
12. 9 and 11 (5)
13. 10 or 12 (5)

Embase RCT Search
Database: Embase 1980 to 16 October 2014

1. Hypoglycaemia (51963)
2. Hypogly* (74772)
3. 1 or 2 ((74772)
4. Glucose (271880)
5. Gel* or gel (57931)
6. 4 and 5 (555)
7. Dextrose gel* (11)
8. 6 or 7 (562)
9. 3 and 8 (28)
10. Newborn* or neonat* or infant* (1092983)
11. 9 and 10 (11)

CENTRAL RCT Search

EBM Reviews – Cochrane Central Register of Controlled Trials

1. Hypoglycaemia (1007)
2. Hypogly* (7323)
3. 1 or 2 (7323)
4. Dextrose gel* (4)
5. 3 and 4 (4)
6. Newborn* or neonat* or infant* (37655)
7. 5 and 6 (4)

Appendix B NHMRC Evidence Table Summary

Key question(s): **What are the short and long term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia?**		**Evidence table ref: Weston (2015, unpub)**
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
The evidence is based on The Sugar Babies Trial and the Northern Ireland Trial which are included in the Weston (2015, unpub) Cochrane systematic review.	**A**	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, of SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The Sugar Babies Trial was available to support the finding that oral dextrose gel for treatment of neonatal hypoglycaemia treated episodes of hypoglycaemia, reduced separation from the mother and increased the likelihood of exclusive breast feeding after discharge from hospital. The Northern Ireland Trial reported that dextrose gel treatment did not increase blood glucose concentrations. *Neonatal* No data were reported on the duration and number of episodes of hypoglycaemia, requirement for additional medications, neonatal seizures, abnormal brain imaging, and length of stay in hospital. *Childhood* No data were reported on exclusive breast feeding at 6 months of age and abnormal brain imaging. The use of oral dextrose gel did not change the incidence of neurosensory disability or processing difficulties at two years of age. *Maternal* The Sugar Babies Trial reported on the satisfaction with treatment for the newborn. No data were reported on the impact on quality of life or the length of stay in hospital.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There is evidence of reduced separation of mother and baby and increased likelihood of exclusive breast feeding from one trial. The benefits for the newborn are likely to outweigh any health harms.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight / Restricted

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
The Sugar Babies Trial of oral dextrose gel to treat neonatal hypoglycaemia was conducted in New Zealand. The other study was conducted in Northern Ireland. Both studies were conducted in newborns at risk of neonatal hypoglycaemia.	**A**	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the New Zealand / Australian healthcare context in terms of health services / delivery of care and cultural factors?)*		
The results are directly applicable to the New Zealand / Australian healthcare context and dextrose gel is readily available and already in use in New Zealand.	**A**	Evidence directly applicable to New Zealand / Australian healthcare context
	B	Evidence applicable to New Zealand / Australian healthcare context with few caveats
	C	Evidence probably applicable to New Zealand / Australian healthcare context with some caveats
	D	Evidence not applicable to New Zealand / Australian healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to New Zealand / Australian healthcare context

Evidence statement

The evidence is based on two randomised controlled trials. One of the trials suggests benefits to the newborn by reducing the maternal separation and increasing the likelihood of exclusive breast feeding after discharge from hospital.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*

Oral dextrose gel is recommended as a treatment for neonatal hypoglycaemia.

OVERALL GRADE OF RECOMMENDATION	
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
GPP	**Good Practice Point**

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*	
Will this recommendation result in changes in usual care? We recommend using 40% oral dextrose gel to treat neonatal hypoglycaemia in babies ≥ 35 weeks' gestational age and less than 48 hours after birth.	**YES** NO
Are there any resource implications associated with implementing this recommendation? Availability of dextrose gel and a glucose oxidase method for measuring blood glucose concentrations in maternity hospitals that treat neonatal hypoglycaemia.	**YES** NO
Will the implementation of this recommendation require changes in the way care is currently organised? Changes may be required in some hospitals currently not using the glucose oxidase method to measure blood glucose concentrations in neonates and not treating neonatal hypoglycaemia with oral dextrose gel.	**YES** NO
Are the guideline development group aware of any barriers to implementation of this recommendation? We will conduct a survey to explore any barriers to implementation.	YES **NO**

Appendix C Grade Evidence Table Summaries – Strength of Recommendation

Considered Judgement - Strength of recommendation							
Clinical question: **Short and Long term benefits and harms of oral dextrose gel** What are the short and long term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
Primary Outcomes	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
Treatment of hypoglycaemia		✓			✓		
Any neurological impairment at 2 years of age or greater (investigator defined)		✓			✓		
Secondary Outcomes (Neonatal outcomes)	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
Improvement of blood glucose to ≥ 2.6 mmol/l		✓				✓	
Rebound hypoglycaemia (investigator defined)		✓				✓	
Recurrent hypoglycaemia (investigator defined)		✓				✓	
Increment of blood glucose after treatment		✓				✓	
Duration of hypoglycaemia				Not reported	✓		
Number of episodes of hypoglycaemia (investigator defined)				Not reported		✓	
Admission to NICU or SCBU		✓				✓	
Separation from the mother for treatment of hypoglycaemia		✓				✓	
Requirement for any additional medications for hypoglycaemia				Not reported		✓	
IV treatment		✓				✓	
Neonatal seizures				Not reported	✓		
Abnormal brain imaging				Not reported	✓		
Length of stay from birth until discharge				Not reported		✓	
Formula given during hospital admission		✓				✓	
Breast feeding (any) after discharge				Not reported		✓	
Exclusive breast feeding after discharge (WHO)		✓				✓	
Secondary Outcomes (Childhood outcomes)	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
Exclusive breast feeding at 6 months of age				Not reported		✓	
Abnormal brain imaging				Not reported	✓		
Processing difficulty		✓			✓		
Secondary Outcomes (Maternal outcomes)	**HIGH**	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
Satisfaction with treatment for the newborn				✓		✓	
Impact on quality of life				Not reported		✓	

Length of stay in hospital				Not reported		✓	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement *(For example, low volume or inconsistent evidence, low patient numbers.)*

Primary

The evidence is based on one trial included in the Weston (2015, *unpub*) Cochrane systematic review. The Sugar Babies Trial showed that oral dextrose gel effectively treated episodes of hypoglycaemia (Harris 2013). In the Sugar Babies Trial follow-up study, Harris (2014) showed that oral dextrose gel did not change the incidence of neurosensory disability at two years' corrected age.

Secondary (Neonatal)

The evidence is based on two trials included in the Weston (2015, *unpub*) Cochrane systematic review. No data were reported on the duration of hypoglycaemia. Rebound hypoglycaemia was reported in one study as being uncommon and similar in frequency in babies treated with oral dextrose gel and placebo, whilst recurrent hypoglycaemia was less common in the oral dextrose gel group when measured by interstitial, but not blood glucose concentrations. The Northern Ireland Trial in the Weston (2015, *unpub*) Cochrane systematic review looked at the increment of blood glucose after treatment and reported no difference between the oral dextrose gel and control groups.

The Sugar Babies Trial reported on the admission to the neonatal intensive care unit or the special care baby unit, intravenous treatment, separation from the mother for treatment of hypoglycaemia, formula given during hospital admission and exclusive breast feeding after discharge. No data were reported on the number of episodes of hypoglycaemia, requirement for any additional medications for hypoglycaemia, neonatal seizures, any breast feeding after discharge, abnormal brain imaging, and length of stay from birth until discharge.

Secondary (Childhood)

The evidence is based on the Sugar Babies Trial which is included in the Weston (2015, *unpub*) Cochrane systematic review. No data were reported on the exclusive breast feeding at 6 months of age and abnormal brain imaging. The Sugar Babies Trial follow-up study reported that the use of oral dextrose gel did not change the incidence of processing difficulties.

Secondary (Maternal)

The evidence is based on the Sugar Babies Trial which is included in the Weston (2015, *unpub*) Cochrane systematic review. The Sugar Babies Trial reported on the maternal satisfaction with treatment for the newborn. No data were reported on the impact on quality of life or the length of stay in hospital postnatally.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
The Weston (2015, *unpub*) Cochrane systematic review found that only the Sugar Babies Trial was available to support the finding that oral dextrose gel for treatment of neonatal hypoglycaemia is helpful in treating episodes of hypoglycaemia, reducing maternal-infant separation for hypoglycaemia and in supporting breast-feeding after discharge.	**MODERATE**

Judging the benefits in context

Take account of: prevalence/incidence, severity, population(s) affected, effect size, transferability/generalisability of evidence (between/among geographical areas, populations/groups), sustainedness of the effectiveness of the action/intervention, patient preference.

The evidence suggests reduced maternal-infant separation and increased breast feeding.

4. What harm might the proposed intervention/action do?	
Evidence statement The evidence is based on data from a single trial and appropriate caution is required in extrapolation of findings. No adverse effects were reported for the infant.	**Quality of evidence** **MODERATE**

Judging the harms in context
Take account of: indirect evidence (e.g. extrapolated from comparable intervention/action), incidence/prevalence and severity of possible harms, population(s) most at risk, possible mitigating modifications/additional actions, patient concerns.

No evidence of adverse effects for the infant.

5. What is the likely balance between good and harm?	
Evidence statement There are benefits to the newborn in terms of reduced separation from the mother and increased likelihood of exclusive breast feeding after discharge from hospital.	**Overall quality of evidence** **MODERATE**

Judging the balance of benefits and harms in context
Take account of the likelihood of doing good or harm (likely or unlikely), the impact of good or harm (high or low).

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	**CONDITIONAL**
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against/make no recommendation	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand context?	
Summary statement *Consider evidence of cost effectiveness, financial (cost and value for money), human and other resource implications.*	
<u>Yes</u>	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Draw on boxes 3-6 to make the final recommendation The use of oral dextrose gel to treat neonatal hypoglycaemia is recommended.	**Strength of recommendation** *Please select level* STRONG **CONDITIONAL** WEAK

8. Recommendations for research
Further research is required to investigate the long-term effects of oral dextrose gel to treat neonatal hypoglycaemia.

There is a need to determine the most effective dose, the number of doses, and the timing of repeat doses of oral dextrose gel to treat neonatal hypoglycaemia.

There is a need to determine the timing of blood glucose concentration measurements after babies have been treated with oral dextrose gel to treat neonatal hypoglycaemia.

Appendix D Grade Evidence Table Summaries – Quality of Evidence

Primary Considered Judgement - Quality of Evidence			
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Primary Outcome: Treatment of hypoglycaemia**			
Describe volume of evidence			
The Sugar Babies Trial reported that babies were more likely to be successfully treated for neonatal hypoglycaemia with oral dextrose gel, compared to those treated with placebo.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:		
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:		
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:		
Risk of publication bias			
Likely **Unlikely**	Reasons for conclusion:		
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	**MODERATE**	LOW	VERY LOW (insufficient)
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Primary	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Primary Outcome: Any neurological impairment at two years' of age or greater**			
Describe volume of evidence			
The Sugar Babies Trial follow-up study found that treatment with oral dextrose gel did not change the incidence of neurosensory disability at two years' corrected age.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:		
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:		
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:		
Risk of publication bias			
Likely **Unlikely**	Reasons for conclusion:		
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	**MODERATE**	LOW	VERY LOW (insufficient)
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Improvement of blood glucose concentration to greater than or equal to 2.6 mmol/L**			
Describe volume of evidence			
The Sugar Babies Trial reported that oral dextrose gel compared to placebo gel significantly improved blood glucose concentration to ≥ 2.6 mmol/L.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High

Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.		
Consistency (heterogeneity) of effects		
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:	
Directness of evidence		
Direct No direct evidence Unclear	Reasons for conclusion:	
How confident are you about the precision of the estimate of effect size?		
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:	
Risk of publication bias		
Likely **Unlikely**	Reasons for conclusion:	
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**		
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*		
N/A as no observational studies included		
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*		
N/A as no observational studies included		

Overall strength of evidence:			
HIGH	**MODERATE**	LOW	VERY LOW (insufficient)

Revisions *Explain the nature of post-consultation revisions*	
Post national meeting revisions	**Date:**
Post peer review revisions	**Date:**

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Rebound hypoglycaemia (investigator defined, within six hours)**			
Describe volume of evidence			
The Sugar Babies Trial reported that episodes of rebound hypoglycaemia were uncommon and similar in frequency in oral dextrose gel and placebo gel groups.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:		
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:		
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:		
Risk of publication bias			
Likely **Unlikely**	Reasons for conclusion:		
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	**MODERATE**	LOW	VERY LOW (insufficient)
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Recurrent hypoglycaemia (investigator defined, within 48 hours)**			
Describe volume of evidence			
The Sugar Babies Trial found that episodes of recurrent hypoglycaemia were less common in the oral dextrose gel group compared to the placebo gel group when measured by interstitial but not blood glucose concentrations.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:		
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:		
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:		
Risk of publication bias			
Likely **Unlikely**	Reasons for conclusion:		
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	**MODERATE**	LOW	VERY LOW (insufficient)
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Increment of blood glucose after treatment**			
Describe volume of evidence			
The Northern Ireland Trial reported that oral dextrose gel treatment did not increase blood glucose concentrations at 15 and 30 minutes after treatment.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	Low	Moderate	High
Insufficient evidence to determine the risk of bias.			
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:		
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:		
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:		
Risk of publication bias			
Likely Unlikely	Reasons for conclusion:		
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	MODERATE	LOW	VERY LOW (**insufficient**)
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Duration of hypoglycaemia**			
Describe volume of evidence			
We found no data on the duration of hypoglycaemia.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	Low	Moderate	High
Not applicable.			
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:	Not applicable.	
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:	Not applicable.	
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:	Not applicable.	
Risk of publication bias			
Likely Unlikely	Reasons for conclusion:	Not applicable.	
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	MODERATE	LOW	VERY LOW **(insufficient)**
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Number of episodes of hypoglycaemia (investigator defined)**			
Describe volume of evidence			
We found no data on the number of episodes of hypoglycaemia.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	Low	Moderate	High
Not applicable.			
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:	Not applicable.	
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:	Not applicable.	
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:	Not applicable.	
Risk of publication bias			
Likely Unlikely	Reasons for conclusion:	Not applicable.	
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	MODERATE	LOW	VERY LOW **(insufficient)**
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Admission to NICU or SCBU**			
Describe volume of evidence			
The Sugar Babies Trial showed that admission rates to NICU or SCBU were similar in babies who received dextrose gel and placebo gel.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:		
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:		
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:		
Risk of publication bias			
Likely **Unlikely**	Reasons for conclusion:		
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	**MODERATE**	LOW	VERY LOW (insufficient)
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Separation from the mother for treatment of hypoglycaemia.**			
Describe volume of evidence			
The Sugar Babies Trial found that oral dextrose gel compared to placebo gel reduced the incidence of separation of mother and infant for the treatment of hypoglycaemia.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:		
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:		
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:		
Risk of publication bias			
Likely **Unlikely**	Reasons for conclusion:		
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	**MODERATE**	LOW	VERY LOW (insufficient)
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Requirement for any additional medications for hypoglycaemia**			
Describe volume of evidence			
We found no data on the requirement for any additional medications for hypoglycaemia.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	Low	Moderate	High
Not applicable.			
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:	Not applicable.	
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:	Not applicable.	
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:	Not applicable.	
Risk of publication bias			
Likely Unlikely	Reasons for conclusion:	Not applicable.	
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	MODERATE	LOW	VERY LOW **(insufficient)**
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **IV treatment**			
Describe volume of evidence			
Both the Sugar Babies Trial and Northern Ireland Trial showed that oral dextrose gel did not alter the need for IV treatment for neonatal hypoglycaemia.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:		
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:		
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:		
Risk of publication bias			
Likely **Unlikely**	Reasons for conclusion:		
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	**MODERATE**	LOW	VERY LOW (insufficient)
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	**Considered Judgement - Quality of Evidence**		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Neonatal seizures**			
Describe volume of evidence			
The Sugar Babies Trial reported that there were no neonatal seizures.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:		
Directness of evidence			
Direct **No direct evidence** Unclear	Reasons for conclusion:	No neonatal seizures were reported.	
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:		
Risk of publication bias			
Likely **Unlikely**	Reasons for conclusion:		
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	**MODERATE**	LOW	VERY LOW **(insufficient)**
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Abnormal brain imaging**			
Describe volume of evidence			
We found no data on abnormal brain imaging.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	Low	Moderate	High
Not applicable.			
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:	Not applicable.	
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:	Not applicable.	
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:	Not applicable.	
Risk of publication bias			
Likely Unlikely	Reasons for conclusion:	Not applicable.	
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	MODERATE	LOW	VERY LOW **(insufficient)**
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence

Clinical question:
What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia?
Secondary Outcome: Neonatal
Length of stay from birth until discharge

Describe volume of evidence

We found no data on the length of stay in hospital from birth until discharge.

Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	Low	Moderate	High

Not applicable.

Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.

Consistency (heterogeneity) of effects		
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:	Not applicable.
Directness of evidence		
Direct No direct evidence Unclear	Reasons for conclusion:	Not applicable.
How confident are you about the precision of the estimate of effect size?		
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:	Not applicable.
Risk of publication bias		
Likely Unlikely	Reasons for conclusion:	Not applicable.

Evidence from high quality observational studies may be upgraded to a higher level of evidence.
Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.

Magnitude of effect
Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.

N/A as no observational studies included

Strength of association
Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so

N/A as no observational studies included

Overall strength of evidence:

HIGH	MODERATE	LOW	VERY LOW **(insufficient)**

Revisions
Explain the nature of post-consultation revisions

Post national meeting revisions	**Date:**
Post peer review revisions	**Date:**

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Formula given during hospital admission**			
Describe volume of evidence			
The Sugar Babies Trial reported that the number of infants given formula in hospital was the same in the oral dextrose gel and placebo gel groups.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:		
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:		
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:		
Risk of publication bias			
Likely **Unlikely**	Reasons for conclusion:		
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	**MODERATE**	LOW	VERY LOW (insufficient)
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Breast feeding (any) after discharge**			
Describe volume of evidence			
We found no data on any breast feeding after discharge.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	Low	Moderate	High
Not applicable.			
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:	Not applicable.	
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:	Not applicable.	
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:	Not applicable.	
Risk of publication bias			
Likely Unlikely	Reasons for conclusion:	Not applicable.	
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	MODERATE	LOW	VERY LOW **(insufficient)**
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Neonatal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Neonatal** **Exclusive breast feeding after discharge (WHO)**			
Describe volume of evidence			
The Sugar Babies Trial reported that oral dextrose gel compared to placebo gel increased the likelihood of exclusive breast feeding at two weeks of age.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:		
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:		
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:		
Risk of publication bias			
Likely **Unlikely**	Reasons for conclusion:		
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	**MODERATE**	LOW	VERY LOW (insufficient)
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Childhood	Considered Judgement - Quality of Evidence		
Clinical question: What are the long term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Childhood** **Exclusive breast feeding at six months of age (WHO)**			
Describe volume of evidence			
We found no data that reported on exclusive breast feeding at six months of age.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	Low	Moderate	High
Not applicable.			
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:	Not applicable.	
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:	Not applicable.	
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:	Not applicable.	
Risk of publication bias			
Likely Unlikely	Reasons for conclusion:	Not applicable.	
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	MODERATE	LOW	VERY LOW **(insufficient)**
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Childhood	Considered Judgement - Quality of Evidence		
Clinical question: What are the long term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Childhood** **Abnormal brain imaging**			
Describe volume of evidence			
We found no data on abnormal brain imaging.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	Low	Moderate	High
Not applicable.			
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:	Not applicable.	
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:	Not applicable.	
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:	Not applicable.	
Risk of publication bias			
Likely Unlikely	Reasons for conclusion:	Not applicable.	
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	MODERATE	LOW	VERY LOW **(insufficient)**
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Childhood	Considered Judgement - Quality of Evidence		
Clinical question: What are the long term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Childhood** **Processing difficulty**			
Describe volume of evidence			
The Sugar Babies Trial follow-up study reported that oral dextrose gel compared with placebo gel did not change the incidence of processing difficulties at two years' corrected age.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:		
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:		
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:		
Risk of publication bias			
Likely **Unlikely**	Reasons for conclusion:		
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	**MODERATE**	LOW	VERY LOW (insufficient)
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Maternal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Maternal** **Satisfaction with treatment for the newborn**			
Describe volume of evidence			
The Sugar Babies Trial reported that mothers from both oral dextrose gel and placebo gel groups were satisfied with the treatment.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	**Low**	Moderate	High
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:	Not applicable.	
Directness of evidence			
Direct **No direct evidence** Unclear	Reasons for conclusion:		
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:	Not applicable.	
Risk of publication bias			
Likely Unlikely	Reasons for conclusion:	Not applicable.	
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	MODERATE	**LOW**	VERY LOW (insufficient)
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Maternal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short and long term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Maternal** **Impact on quality of life**			
Describe volume of evidence			
We found no data on the impact on quality of life.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	Low	Moderate	High
Not applicable.			
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:	Not applicable.	
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:	Not applicable.	
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:	Not applicable.	
Risk of publication bias			
Likely Unlikely	Reasons for conclusion:	Not applicable.	
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	MODERATE	LOW	VERY LOW **(insufficient)**
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	

Maternal	Considered Judgement - Quality of Evidence		
Clinical question: What are the short term benefits and harms of oral dextrose gel to treat neonatal hypoglycaemia? **Secondary Outcome: Maternal** **Length of stay in hospital (postnatal)**			
Describe volume of evidence			
We found no data on the length of stay in hospital postnatally.			
Risk of bias for body of evidence *(Domains are sequence generation, allocation concealment, blinding, losses to follow up, reporting)*	Low	Moderate	High
Not applicable.			
Quality of evidence may be downgraded if evidence is assessed to be inconsistent, indirect, imprecise, or at risk of publication bias.			
Consistency (heterogeneity) of effects			
No inconsistency Serious inconsistency Very serious inconsistency	Reasons for conclusion:	Not applicable.	
Directness of evidence			
Direct No direct evidence Unclear	Reasons for conclusion:	Not applicable.	
How confident are you about the precision of the estimate of effect size?			
No imprecision Some imprecision Serious imprecision	Reasons for conclusion:	Not applicable.	
Risk of publication bias			
Likely Unlikely	Reasons for conclusion:	Not applicable.	
Evidence from high quality observational studies may be upgraded to a higher level of evidence. **Note that this only applies in cases where there is consistent evidence from at least two studies with no plausible confounders, providing direct evidence of effect and with no major threats to validity.**			
Magnitude of effect *Comment here on the magnitude of a treatment or exposure effect. If upgrading, provide a rationale for doing so.*			
N/A as no observational studies included			
Strength of association *Comment here on whether there is evidence of a very strong association between exposure and effect. Pay particular attention to the presence of a dose-response gradient. If upgrading, provide a rationale for doing so*			
N/A as no observational studies included			
Overall strength of evidence:			
HIGH	MODERATE	LOW	VERY LOW **(insufficient)**
Revisions *Explain the nature of post-consultation revisions*			
Post national meeting revisions		**Date:**	
Post peer review revisions		**Date:**	