hPOD – **h**ypoglycaemia **P**revention in newborns with **O**ral **D**extrose

A randomised controlled trial comparing prophylactic oral dextrose gel with placebo in newborn babies at risk of neonatal hypoglycaemia.

Trial Registration Number:	ACTRN12614001263684
Protocol Date:	version 6, 23 October 2015
Statistical Analyis Plan:	version 3.3, 16 August 2019
SAP Author:	Greg Gamble

Approved by: _____

Dist Prof Jane Harding (Principal Investigator)

Date: 20/8/19

The Liggins Institute, The University of Auckland

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1 ADMINISTRATIVE INFORMATION

1.1 SCOPE

This Statistical Analysis Plan (SAP) describes the analyses and reporting for the hPOD main trial protocol and covers all study outcomes up to and including the 6 week follow up but excludes the economic analysis (secondary outcome 7). This SAP is intended to cover all the analyses that would be required to produce the primary report of the main hPOD study.

It does not include analysis of data to be collected at the two year follow-up, nor analysis of the microbiome biodiversity sub-study.

This document is intended to stand alone from the hPOD protocol but adhere to the main points in the analysis summary specified in the protocol. It is envisaged that the SAP may undergo revision outside of the protocol after blinded review of the data post data lock.

1.2 DOCUMENTS USED IN THE PREPARATION OF THIS REPORT

- hPOD protocol version 6 (23 October 2015), published Harding JE, Hegarty JE, Crowther CA, Edlin R, Gamble G, Alsweiler JM. Randomised trial of neonatal hypoglycaemia prevention with oral dextrose gel (hPOD): study protocol. BMC Pediatr. 2015 Sep 16;15:120. doi: 10.1186/s12887-015-0440-6.
- Australian New Zealand Clinical Trials Registry: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=367361&isReview=true
- hPOD STUDY Trial Management terms of reference (section 2: Data Monitoring Committee) 18 December 2015
- hPOD withdrawl of consent/protocol deviation SOP 28 August 2017
- hPOD case record forms
- Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, Williamson PR, Altman DG, Montgomery A, Lim P, Berlin J, Senn S, Day S, Barbachano Y, Loder E. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017 Dec 19;318(23):2337-2343. doi: 10.1001/jama.2017.18556

2 TRIAL INFORMATION

2.1 AIMS OF THE TRIAL

To determine if prophylactic oral dextrose gel prevents admission to Neonatal Intensive Care Units (NICUs) and secondarily prevents neonatal hypoglycaemia, improves breast feeding rates, reduces healthcare costs to hospital discharge, and improves later neurodevelopmental outcome.

2.2 TRIAL HYPOTHESES

In newborn babies at risk of hypoglycaemia, prophylactic oral dextrose gel (200mg/kg) will be more effective than placebo gel in reducing NICU admission, preventing neonatal hypoglycaemia, improve breast feeding rates and reduce costs as well as potentially reducing the risk of later adverse outcomes.

2.3 RESEARCH PLAN

2.3.1 Study Design

An international, multicentre, two-arm, parallel, randomised double blind placebo controlled trial comparing 40% dextrose gel with placebo to reduce NICU admission in babies at risk of hypoglycaemia within the first 48 hours after birth.

2.3.2 Inclusion Criteria

2.3.2.1 Inclusion Criteria

Babies who are at risk of hypoglycaemia, defined as satisfying **at least ONE** of the following:

1. Infants of diabetic mothers (any type of diabetes)
2. Preterm (< 37 weeks' gestation)
3. Small (< 2.5 kg or < 10^{th} centile on population or customised birthweight chart)
4. Large (> 4.5 kg or > 90^{th} centile on population or customised birthweight chart)

AND satisfy **ALL** of the following:

1. ≥ 35 weeks' gestation
2. Birthweight ≥ 2.2 kg
3. < 1 hour old
4. No apparent indication for NICU admission at time of randomisation

5. Unlikely to require admission to NICU for any other reasons e.g. respiratory distress
6. Mother intending to breast-feed

2.3.2.2 Exclusion Criteria

1. Major congenital abnormality
2. Previous formula feed or intravenous fluids
3. Previous diagnosis of hypoglycaemia
4. Admitted to NICU
5. Imminent admission to NICU

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2.4 STUDY OUTCOMES

2.4.1 Primary outcome:

Admission to NICU. This is defined as admission to NICU for > 4 hours duration, which is the standard definition used by the Australian and New Zealand Neonatal Network. The term NICU is used throughout this document and the study protocol and refers to any unit where the baby is cared for away from the mother. It includes Special Care Baby Units (SCBUs).

2.4.2 Key secondary endpoints:

1. Hypoglycaemia (any blood glucose concentration < 2.6 mmol/L recorded between the time of randomisation and 48 hours after birth);
2. Admission to NICU for hypoglycaemia;
3. Hyperglycaemia (blood glucose concentration > 10 mmol/L recorded between the time of randomisation and 48 hours after birth);
4. Breastfeeding at discharge from hospital (full or exclusive);
5. Received any formula prior to discharge from hospital;
6. Formula feeding at 6 weeks of age;
7. Cost of care until primary discharge home;
8. Maternal satisfaction (via telephone questionnaire at 6 weeks);
9. Neurosensory disability at 2 years' corrected age (any of: legal blindness; sensorineural deafness requiring hearing aids; cerebral palsy; Bayley Scale of Infant Development Version III cognitive, language or motor score lower than one standard deviation below the mean).

Endpoints 7 and 9 are beyond the scope this SAP.

2.5 Adverse and Serious Adverse Event Reporting

The following adverse and serious adverse events will be reported separately for each treatment group (see table in appendix):

1. Hyperglycaemia (blood glucose concentration > 10mmol/l) measured by any method from the time of randomisation to 48 hours after birth.
2. Late hypoglycaemia (blood glucose concentration < 2.6 mmol/l) measured by any method for the first time after 12 hours of age up to and including 48 hours after birth.
3. Delayed feeding – failure to establish breast feeding without supplements by the end of day 3.
4. Systemic sepsis as defined by the Australian and New Zealand Neonatal Network data dictionary (see protocol)
5. Seizures (serious adverse event)
6. Neonatal or infant death (serious adverse event)

2.6 Sample size

Based on data from Auckland City Hospital and Waikato Hospital, 10% of at-risk babies will require admission to NICU. A trial of 2,129 babies (1,014 in each arm, with continuity correction and allowing for 5% drop-out rate), will have 90% power to detect a 40% relative reduction (absolute reduction of 4%) in admission to NICU from 10% to 6% with two-sided alpha of 0.05.

The sample size was further inflated by the steering group (minuted date: 5/2/19) to n=2149 to allow for protocol deviations (including those participants randomised in error).

3 Steering Committee

Professor Jane Harding (Chair), Professor Caroline Crowther,

Dr Jane Alsweiler, Dr Joanne Hegarty, Dr Richard Edlin, Mr Greg Gamble

4 Method of Randomisation and Masking

Eighteen participating hospitals (9 in New Zealand and 9 in Australia) recruited 2149 participants from 09 Jan 2015 until 05 May 2019. Two hospitals, Whakatane and Waitakere closed early (31/5/18 and 30/11/16 respectively).

Recruitment numbers varied widely between sites (5 to 537 babies).

Eligible consented babies were randomised within the first hour after birth using a centralised internet based randomisation facility which was available to all sites.

Within each site babies were first allocated to one randomisation stratum defined by the primary risk for hypoglycaemia (infants of diabetic mothers (any type of diabetes), preterm (< 37 weeks gestation), small (<2.5 kg or < 10th centile on population or customised birthweight chart), large (>4.5kg or > 90th centile on population or customised birthweight chart) or other risk factor) and then each successive baby within the site/primary risk stratum was randomly allocated dextrose gel or matched placebo. Random allocation was balanced within variably sized blocks using the Plan procedure of SAS (v 9.4, SAS Institute Inc, Cary NC, USA).

Participating sites and investigators were blinded to treatment allocation. However a 'taste-test' audit of syringe contents on a subset of unused syringes to ensure that the correct gel has been packaged was performed by the data manager who had no involvement with any other aspect of the study.

5 SEQUENCE OF PLANNED ANALYSIS

5.1 INTERIM ANALYSES

No interim analysis was planned or carried out.

5.2 FINAL ANALYSES AND REPORTING

Data will be analysed by the study statistician independent of the clinical investigators.

Blinded review of data, including form completeness, range checks and some logic checks, were conducted throughout the trial. Further blinded checks of the data will be performed once all the 6 week follow-up data have been collected. Once all outstanding queries have been addressed the data will be locked and final changes made to this SAP after review of blinded data summaries.

Following approval of the final version of this SAP the study statistician will perform the specified analysis and populate the study tables (see appendix) for dissemination of the key statistics and study results to the trial investigators.

Any post-hoc, exploratory analyses which were not identified in this SAP but are completed to support the planned analyses will be clearly identified. Any deviations from the planned analyses detailed in this SAP will be clearly documented with reasons in a post-analysis version of the SAP.

6 GENERAL ISSUES FOR STATISTICAL ANALYSIS

6.1 ANALYSIS SOFTWARE

All analysis will be performed using SAS® software version 9.4 or later (SAS Institute Inc., Cary, NC, USA).

6.2 ANALYSIS APPROACH

Analyses will be carried out using the intention-to-treat approach in which randomised participants will be analysed according to the initial treatment allocation. However those babies who were randomised in error (ie did not meet study eligibility criteria at randomisation) will be excluded from all analyses but may be reported separately for safety outcomes. No other protocol deviations will be considered sufficient reason to exclude a participant from the intention-to-treat analysis.

6.3 METHODS FOR WITHDRAWALS, MISSING DATA, OUTLIERS

Babies for whom consent to determine whether the baby has been admitted to NICU or not has been withdrawn and babies who had died in hospital will be included in the analysis and be assumed to have been admitted to NICU. No other imputation of missing primary outcome data will be performed.

For all other analyses all available data for which consent for collection was obtained and not revoked will be used for analysis. No imputation of missing data will be performed.

6.4 COVARIATES AND POTENTIAL CONFOUNDER ADJUSTMENT

Adjusted and unadjusted outcomes will be presented for all endpoints. The main trial results will include adjustment for the randomisation stratification variables; collaborating centre, prioritised primary reason for hypoglycaemia (infant of a diabetic mother (any type of diabetes), late preterm (< 37 weeks gestation), small (<2.5 kg or < 10th centile on population or customised birthweight chart), large (>4.5kg or > 90th centile on population or customised birthweight chart)) and maternal unique identifier as a clustering term.

Since collaborating centres differ widely in the number of participants recruited it is possible that the models which include collaborating centre might not converge or be poorly fitted, especially for those centres with few or no events. If this results in the need for deviation from the planned adjustment, this will be clearly reported.

Secondary analyses will explore between group differences separately in admission to NICU and in hypoglycaemia (any blood glucose concentration < 2.6 mmol/L from randomisation to 48 hours after birth) and include adjustment for reason for risk of hypoglycaemia, gestational age, sex, mode of delivery and receipt of treatment 40% dextrose gel and maternal unique identifier as a clustering term. Since it is expected that these variables will covary the

following adjustments are specified for these analyses; Collaborating centre, maternal unique identifier as a clustering term and either:

1. Infant of a diabetic mother and gestational age and birthweight z score
2. Infant of a diabetic mother and late preterm (< 37 weeks gestation) and birth weight z score.
3. Sex and mode of delivery (vaginal or caesarean section)
4. Treatment 40% dextrose gel.

For these analyses, infant of a diabetic mother and late preterm will be included independent of the primary reason for risk of hypoglycaemia ie not as prioritised groups.

It is not proposed to adjust for baseline differences between treatment arms as potential confounders.

6.5 Exploratory Analyses

Subgroup analyses will be performed with collaborating centres grouped by country (Australian/New Zealand), in those participants randomised from the four largest collaborating centres (Auckland, North Shore, Waikato and Women's and Children's (Adelaide) hospitals), in Level 3 or Level 2 centres separately, separately for each hospital, and separately for each risk factor (see tables).

The following sensitivity analyses will be performed:

- Excluding data from participants for whom there were protocol deviations
- Excluding data from participants who did not receive any of the assigned study gel (modified per protocol analysis)
- Excluding blood glucose data that was not measured using a glucose oxidase method
- Excluding participants for whom the primary outcome is not known

Exploratory analyses will examine possible relationships between effect of dextrose gel prophylaxis on NICU admission (effect size for the primary outcome) and:

- Rate of NICU admission in the control group (Figure 1)
- Incidence of hypoglycaemia in the control group (Figure 2)

6.6 Multiple Comparisons and Multiplicity

The primary outcome will be tested at the 5% significance level. No adjustment to the critical significance level will be made for any secondary, sensitivity or exploratory analyses. However, the number of comparisons will be reported for the reader to interpret in relation to risk of type I error.

6.7 Clustering

Adjustment for multiple births (who were randomised separately) will be completed for all analyses.

6.8 DESCRIPTIVE ANALYSIS

The flow chart of recruitment will be completed (see Appendix 8.1)

Summary statistics will be presented for mothers and their babies included in the intention-to-treat analysis. All demographic continuous variables will be reported as mean, standard deviation, minimum, Q1, median, Q3 and maximum for between group comparison of continuous variables and frequency and percentages for categorical variables (see appendix 8.2.1). Admissions to NICU will be summarised by individual hospital, by level 2 and level 3 units, and by country (see Appendix 8.2.2)

As part of quality assurance the blood glucose concentration (measured by any method) will be plotted for each baby as hours since birth to the end of available data prior to discharge and inspected. Where blood glucose concentrations are recorded on the clinical record and in the electronic download within 15 minutes of each other, they will be considered to be from the same blood sample, and only the electronic record will be included in the analysis.

Serious adverse events will be tabulated and compared between treatment arms (see appendix 8.2.3).

Secondary outcomes will be tabulated and compared between treatment arms (see appendix 8.2.4)

Tolerance of study gel, assessment of blinding, protocol deviation and withdrawal rates will be tabulated and compared between treatment arms (see appendix 8.2.5)

Day 3 and 6 week outcomes will also be tabulated and compared between treatment arms (see appendix 8.2.6).

7 STATISTICAL ANALYSES

The binary primary outcome of admission to NICU or not will be analysed using a mixed-effects logistic regression with adjustment for collaborating centre, primary risk for hypoglycaemia and maternal unique identifier as a clustering term. The results will be presented as relative risk with 95% confidence intervals. This is the primary analysis of this trial and will be tested at the 5% significance level using a two sided test of significance.

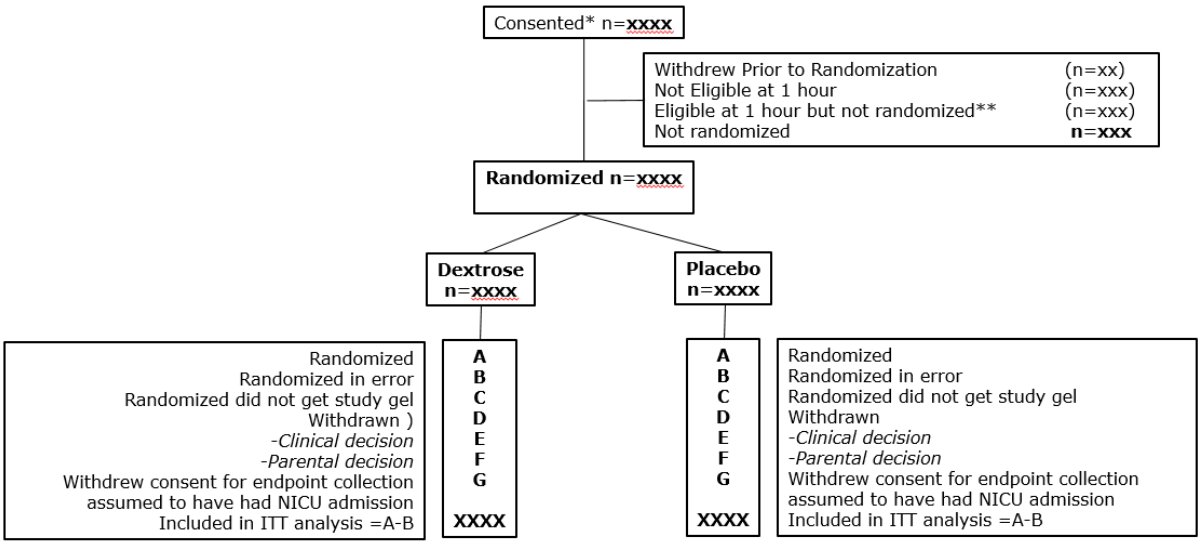
The number needed to treat to prevent one NICU admission, and 95% confidence intervals will be calculated.

All secondary outcomes included in the scope of this SAP will be examined using the same approach with covariates as described in section 6.4.

Blood glucose concentrations will be analysed using a mixed model approach to repeated measures. Blood glucose measurements by any method recorded after the time randomisation will be rounded to the nearest hour of age and treatment main effects and an age by treatment arm interaction effect will be fitted with adjustment for collaborating centre. Significant interaction effects will be explored using the method of Tukey to preserve an overall 5% significance level. Models will be fitted initially assuming an unstructured covariance matrix. However, if the model fails to converge first order autoregressive or compound symmetry covariance structures will be examined. Blood glucose results from the time of randomisation until at most 48 hours of age or discharge may be available. However, the protocol does not require blood glucose recordings to be made for the entire duration of hospitalisation, so in the event that there are sparse data at later ages, time course data may be right censored to permit efficient description of the glucose time profile by treatment group. These data will be plotted as least–square adjusted means with 95% confidence intervals for each treatment group. Post-hoc comparison between groups of mean blood glucose concentrations will at made at each hour of age and a false discovery rate protected p value presented. The completeness of in-hospital blood glucose data over time will be described for the entire first 48 hours after birth and for the analysis time period (should these differ). These analyses will be repeated with age binned into 30 minute intervals, and after excluding any blood glucose data from a non-glucose oxidase method.

8 APPENDIX

8.1 DRAFT CONSORT DIAGRAM



* *This is total number consented from monthly reports from centres*
***Patient level reasons not collected*

8.2 DRAFT TABLES

8.2.1 Maternal and Baby Baseline Characteristics

	Placebo	Dextrose	P
Mother (n=x)			
N			
Maternal Age (yr)			
Prioritized Ethnicity			
Maori			
Pacific			
Chinese			
Indian			
Other			
NZ European			
Diabetic			
Type 1 Diabetes			
Type 2 Diabetes			
Gestational Diabetes			
Diabetes Management			
Diet			
Metformin			
Insulin			
Antenatal Corticosteroids			
Prelabour prolonged rupture of membranes			
Chorioamnionitis			
Mode of delivery			
Normal Vaginal			
Instrumental Vaginal			
Caesarean			
Elective Caesarean			
Emergency Caesarean			
Dextrose containing IV fluids given < 4 hours before birth			
Baby (n=XX)			
Birth information			
Singleton			
Twin			
Triplet			
Baby discharged with mother			
Female n(%)			

Birthweight (g)			
Length (cm)			
Head Circumference at birth (cm)			
Birthweight (z -score)			
Length (z-score) Head Circumference (z-score)			
Gestational age (wk)			
Apgar Score at 1 minute			
Apgar Score at 5 min			
Apgar score < 7 at 5 minutes			
Apgar Score at 10min (if Apgar was < 7 at 5 minutes)			
Primary Reason for Risk of Hypoglycaemia			
Infant of diabetic mother			
Preterm (< 37 weeks gestation)			
Small (< 2.5kg or < 10th centile)			
Large (> 4.5kg or > 90th centile)			
Babies with Two Risk Factors			
Babies with Three Risk Factors			

Values are number (%), mean (SD) or median (min, Q1,Q3, max) unless otherwise indicated

8.2.2 Primary Outcome Admissions to NICU

	Placebo	Dextrose	Adj[1] RR (95% CI)	Adj[2] RR (95% CI)	Adj[3] RR (95% CI)	Adj[4] RR (95% CI)	Adj[5] RR (95% CI)
	n/N (%)	n/N (%)					
New Zealand							
Auckland City (n=406)							
Hawke's Bay (n=52)							
Southland (n=6)							
North Shore (n=371)							
Tauranga (n=122)							
Waikato (n=368)							
Waitakere (n=26)							
Whakatane (n=5)							
Whangarei (n=13)							
OVERALL New Zealand (n=1369, 64%)							
Australia							
Angliss (n=21)							
Box Hill (n=23)							
Mackay Base (n=11)							
The Mater (Sydney) (n=18)							
Tamworth Rural Hospital (n=44)							
The Townsville (n=48)							
University of Geelong (n=56)							
Women's and Children's Adelaide (n=537)							
Westmead (n=44)							
OVERALL Australia (n=780, 36%)							
OVERALL 'big four hospitals': Auckland, North Shore, Waikato, Women's and Children's (Adelaide) (n=1534, 71%)							
OVERALL Level 3 or 4 Centres							
OVERALL Level 2 Centres							
OVERALL NICU admissions in those with the following reasons for							

Hypoglycaemia							
Infant of diabetic mother							
Preterm (< 37 weeks gestation)							
Small (< 2.5kg or < 10th centile)							
Large (> 4.5kg or > 90th centile)							
Sex							
Male							
Female							
Mode of Delivery							
Vaginal							
Caesarean section							
Exploratory Analyses							
Excluding data from participants for whom there were protocol deviations							
Excluding data from participants who did not receive any of the assigned study gel							
Excluding participants for whom the primary outcome is not known							
OVERALL							

Adjusted for multiple births and:

Adjusted[1] for collaborating centre and primary reason for risk of hypoglycaemia (maternal diabetes, preterm, small or large for gestational age)

Adjusted[2] for collaborating centre, infant of a diabetic mother, gestational age and birthweight z-score

Adjusted[3] for collaborating centre, infant of a diabetic mother, late preterm (<37 weeks gestation) and birth weight z score

Adjusted[4] for collaborating centre, sex and mode of delivery (vaginal or caesarean section)

Adjusted[5] for collaborating centre and treatment with dextrose gel

8.2.3 Outcome Hypoglycaemia (any [BG] by any method < 2.6 mmol/l in the first 48 hours)

	Placebo	Dextrose	Adj[1] RR (95% CI)	Adj[2] RR (95% CI)	Adj[3] RR (95% CI)	Adj[4] RR (95% CI)	Adj[5] RR (95% CI)
	n/N (%)	n/N (%)					
New Zealand							
Auckland City (n=406)							
Hawke's Bay (n=52)							
Southland (n=6)							
North Shore (n=371)							
Tauranga (n=122)							
Waikato (n=368)							
Waitakere (n=26)							
Whakatane (n=5)							
Whangarei (n=13)							
OVERALL New Zealand (n=1369, 64%))							
Australia							
Angliss (n=21)							
Box Hill (n=23)							
Mackay Base (n=11)							
The Mater (Sydney) (n=18)							
Tamworth Rural Hospital (n=44)							
The Townsville (n=48)							
University of Geelong (n=56)							
Women's and Children's Adelaide (n=537)							
Westmead (n=44)							
OVERALL Australia (n=780, 36%)							
OVERALL 'big four hospitals': Auckland, North Shore, Waikato, Women's and Children's (Adelaide) (n=1534, 71%)							
OVERALL Level 3 or 4 Centres							
OVERALL Level 2 centres							
OVERALL NICU admissions in those with the following reasons for Hypoglycaemia							
Infant of diabetic mother							
Preterm (< 37 weeks gestation)							

Small (< 2.5kg or < 10th centile)							
Large (> 4.5kg or > 90th centile)							
Sex							
Male							
Female							
Mode of Delivery							
Vaginal							
Caesarean section							
Exploratory Analyses							
Excluding data from participants for whom there were protocol deviations							
Excluding data from participants who did not receive any of the assigned study gel							
OVERALL							

Adjusted for multiple births and:

Adjusted[1] for collaborating centre and primary reason for risk of hypoglycaemia (maternal diabetes, preterm, small or large for gestational age)

Adjusted[2] for collaborating centre, infant of a diabetic mother, gestational age and birthweight z-score

Adjusted[3] for collaborating centre, infant of a diabetic mother, late preterm (<37 weeks gestation) and birth weight z score

Adjusted[4] for collaborating centre, sex and mode of delivery (vaginal or caesarean section)

Adjusted[5] for collaborating centre and treatment with dextrose gel

8.2.4 Outcome Hypoglycaemia (any [BG] by Glucose Oxidase ONLY <2.6 mmol/l in the first 48 hours)

	Placebo	Dextrose	Adj[1] RR (95% CI)	Adj[2] RR (95% CI)	Adj[3] RR (95% CI)	Adj[4] RR (95% CI)	Adj[5] RR (95% CI)
	n/N (%)	n/N (%)					
New Zealand							
Auckland City (n=406)							
Hawke's Bay (n=52)							
Southland (n=6)							
North Shore (n=371)							
Tauranga (n=122)							
Waikato (n=368)							
Waitakere (n=26)							
Whakatane (n=5)							
Whangarei (n=13)							
OVERALL New Zealand (n=1369, 64%))							
Australia							
Angliss (n=21)							
Box Hill (n=23)							
Mackay Base (n=11)							
The Mater (Sydney) (n=18)							
Tamworth Rural Hospital (n=44)							
The Townsville (n=48)							
University of Geelong (n=56)							
Women's and Children's Adelaide (n=537)							
Westmead (n=44)							
OVERALL Australia (n=780, 36%)							
OVERALL 'big four hospitals': Auckland, North Shore, Waikato, Women's and Children's (Adelaide) (n=1534, 71%)							
OVERALL Level 3 or 4 Centres							
OVERALL Level 2 Centres							
OVERALL NICU admissions in those with the following reasons for Hypoglycaemia							
Infant of diabetic mother							
Preterm (< 37 weeks gestation)							

Small (< 2.5kg or < 10th centile)							
Large (> 4.5kg or > 90th centile)							
Sex							
Male							
Female							
Mode of Delivery							
Vaginal							
Caesarean section							
Exploratory Analyses							
Excluding data from participants for whom there were protocol deviations							
Excluding data from participants who did not receive any of the assigned study gel							
OVERALL							

Adjusted for multiple births and:

Adjusted[1] for collaborating centre and primary reason for risk of hypoglycaemia (maternal diabetes, preterm, small or large for gestational age)

Adjusted[2] for collaborating centre, infant of a diabetic mother, gestational age and birthweight z-score

Adjusted[3] for collaborating centre, infant of a diabetic mother, late preterm (<37 weeks gestation) and birth weight z score

Adjusted[4] for collaborating centre, sex and mode of delivery (vaginal or caesarean section)

Adjusted[5] for collaborating centre and treatment with dextrose gel

8.2.5 Adverse Events and Medical Problems

	Placebo	Dextrose	Adj[1] RR (95% CI)	Adj[2] RR (95% CI)	Adj[3] RR (95% CI)	Adj[4] RR (95% CI)	Adj[5] RR (95% CI)
Baby Outcomes	n/N (%)	n/N (%)					
Death before discharge home							
Seizure							
Suspected							
Confirmed							
Confirmed CFN/aEEF/Brainz mon./formal ECG							
Underlying Seizure Cause							
Blood Glucose concentration							
Haemorrhage							
Meningitis (suspected)							
Meningitis (confirmed)							
Hypoxic-ischaemic encephalopathy (HIE)							
Respiratory distress requiring admission to NICU/SCBU							
Hypoxic ischaemic encephalopathy (HIE)							
Sarnat Score =1							
Sarnat Score =2							
Sarnat Score =3							
Inborn error of metabolism							
Pituitary disorder							
Sepsis							
Confirmed							
Early onset (before 3 days)							
Late onset (after 3 days)							
Apnoea							
Hypothermia							
Major congenital abnormality							
Minor congenital abnormality							
Any other major problems							

Adjusted for multiple births and:

Adjusted[1] for collaborating centre and primary reason for risk of hypoglycaemia (maternal diabetes, preterm, small or large for gestational age)

Adjusted[2] for collaborating centre, infant of a diabetic mother, gestational age and birthweight z-score

Adjusted[3] for collaborating centre, infant of a diabetic mother, late preterm (<37 weeks gestation) and birth weight z score

Adjusted[4] for collaborating centre, sex and mode of delivery (vaginal or caesarean section)

Adjusted[5] for collaborating centre and treatment with dextrose gel

8.2.6 Secondary Outcomes

	Placebo	Dextrose	Adj[1] RR (95% CI)	Adj[2] RR (95% CI)	Adj[3] RR (95% CI)	Adj[4] RR (95% CI)	Adj[5] RR (95% CI)
	n/N (%)	n/N (%)					
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Babies treated for hypoglycaemia (any treatment)							
Babies with repeated ǂepisodes of hypoglycaemia							
Number of repeat episodes per baby (for those with > 1 episode)							
Admission to NICU for hypoglycaemia							
First blood glucose concentration (1-4 hours after birth, mmol/L)							
First blood glucose concentration (1-4hours after birth, mmol/L) by GO method only							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
New Zealand Collaborating Centres							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							

Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
Australian Collaborating Centres							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
"Big four Hospitals"							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							

Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							

‡An episode of hypoglycaemia begins with the first occurrence of blood glucose by any method < 2.6mmol/l and continues until the first blood glucose ≥ 2.6mmol/l. Further episodes are defined as repeated hypoglycaemia.

Adjusted for multiple births and:

Adjusted[1] for collaborating centre and primary reason for risk of hypoglycaemia (maternal diabetes, preterm, small or large for gestational age)

Adjusted[2] for collaborating centre, infant of a diabetic mother, gestational age and birthweight z-score

Adjusted[3] for collaborating centre, infant of a diabetic mother, late preterm (<37 weeks gestation) and birth weight z score

Adjusted[4] for collaborating centre, sex and mode of delivery (vaginal or caesarean section)

Adjusted[5] for collaborating centre and treatment with dextrose gel

8.2.7 Secondary Outcomes by hospital

	Placebo	Dextrose	Adj[1] RR (95 % CI)	Adj[2] RR (95 % CI)	Adj[3] RR (95 % CI)	Adj[4] RR (95 % CI)	Adj[5] RR (95 % CI)
Auckland City	n/N (%)	n/N (%)					
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
Hawke's Bay (n=52)							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							

Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Southland							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
North Shore							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to							

discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
Tauranga							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
Waikato							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							

Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
Waitakere							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
Whakatane							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for							

hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
Whangarei							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
Angliss							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							

Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
Box Hill							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							

Mackay Base							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
The Mater (Sydney)							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							

Recommend hPOD study to friends?							
Tamworth Rural Hospital							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
The Townsville							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							

Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
University of Geelong							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
Women's and Children's Adelaide							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							

Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							
Westmead							
Hypoglycaemia: any [BG] by any method < 2.6 mmol/l in the first 48 hours							
Hypoglycaemia: any [BG] by any method < 2.0 mmol/l in the first 48 hours							
Admission to NICU for hypoglycaemia							
Hyperglycaemia: any [BG] by any method > 10 mmol/l in the first 48 hours							
Breastfeeding at discharge from hospital (full or exclusive)							
Received formula prior to discharge from Hospital							
Formula feeding at 6 weeks of age							
Maternal satisfaction at 6 weeks of age							
Involved with the study again?							
Recommend hPOD study to friends?							

Please note it is possible that some models will become unstable with adjustment because of small participant and outcome numbers within some hospitals.

Adjusted for multiple births and:

Adjusted[1] for collaborating centre and primary reason for risk of hypoglycaemia (maternal diabetes, preterm, small or large for gestational age)

Adjusted[2] for collaborating centre, infant of a diabetic mother, gestational age and birthweight z-score

Adjusted[3] for collaborating centre, infant of a diabetic mother, late preterm (<37 weeks gestation) and birth weight z score

Adjusted[4] for collaborating centre, sex and mode of delivery (vaginal or caesarean section)

Adjusted[5] for collaborating centre and treatment with dextrose gel

8.2.8 Hypoglycaemia Treatment

	Placebo	Dextrose	Adj[1] RR (95% CI)	Adj[2] RR (95 % CI)	Adj[3] RR (95 % CI)	Adj[4] RR (95 % CI)	Adj[5] RR (95 % CI)
Number of babies treated with at least one dose of non-study dextrose gel	n/N (%)	n/N (%)					
New Zealand							
Australia							
Big four hospitals							
Level 2 hospitals							
Level 3 hospitals							
OVERALL							
Total number of doses of non-study dextrose gel							
New Zealand							
Australia							
Big four hospitals							
Level 2 hospitals							
Level 3 hospitals							
OVERALL							
Doses of non-study dextrose gel/per hour of followup time per baby	Rate (95% CI)	Rate (95% CI)	P, Rate Diff. (95% CI)				
New Zealand							
Australia							
Big four hospitals							
Level 2 hospitals							
Level 3 hospitals							
OVERALL							
Number of Babies Treated with IV Dextrose	n/N (%)	n/N (%)	P				
New Zealand							
Australia							
Big four hospitals							
Level 2 hospitals							
Level 3 Hospitals							
OVERALL							

Total duration of treatment with IV Dextrose	Median (IQR)	Median (IQR)	P, Median Diff. (95% CI)				
New Zealand							
Australia							
Big four hospitals							
Level 2 hospitals							
Level 3 Hospitals							
OVERALL							

Adjusted for multiple births and:

Adjusted[1] for collaborating centre and primary reason for risk of hypoglycaemia (maternal diabetes, preterm, small or large for gestational age)

Adjusted[2] for collaborating centre, infant of a diabetic mother, gestational age and birthweight z-score

Adjusted[3] for collaborating centre, infant of a diabetic mother, late preterm (<37 weeks gestation) and birth weight z score

Adjusted[4] for collaborating centre, sex and mode of delivery (vaginal or caesarean section)

Adjusted[5] for collaborating centre and treatment with dextrose gel

8.2.9 Trial Administration/Protocol deviations/Withdrawals

	Placebo	Dextrose	Relative Risk (95% CI)
	n/N (%)	n/N (%)	
Tolerance of study gel			
Tolerated (no spill)			
Small spill of gel (few drops)			
Moderate spill of gel (half of volume administered)			
Large spill of gel (all of volume administered)			
Unknown			
Assessment of Study Blinding			
- at 6 weeks mother correctly guessed study group			
Protocol Non-Compliance (number of instances, number of babies with at least one instance)			
Glucose oxidase method			
Other			
N (%) of blood glucose concentrations measured by glucose oxidase method			
N (%) of first blood glucose concentrations (1-4h after birth) measured by glucose oxidase method			
Protocol deviation (number of instances (where appropriate), number of babies with at least one instance)			
Consent			
Randomisation			
Treatment (gel)			
Other			
Withdrawal			
Parental decision			
Clinicians decision			

8.2.10 Day 3 and 6 Week Follow-up Outcome

	Placebo	**Dextrose**	Adj[1] RR (95 % CI)	Adj[2] RR (95 % CI)	Adj[3] RR (95 % CI)	Adj[4] RR (95 % CI)	Adj[5] RR (95 % CI)
	n/N (%)	n/N (%)					
Breast fed on day of discharge?							
Has the baby had any formula milk to day of discharge?							
Has the baby had any formula milk on the day of discharge?							
Breast feeding at 6 weeks?							
Did the baby ever have any formula milk?							
Any formula at 6 weeks?							
Babies General Health							
Healthy							
Some concerns							
Significant problems							

Adjusted for multiple births and:

Adjusted[1] for collaborating centre and primary reason for risk of hypoglycaemia (maternal diabetes, preterm, small or large for gestational age)

Adjusted[2] for collaborating centre, infant of a diabetic mother, gestational age and birthweight z-score

Adjusted[3] for collaborating centre, infant of a diabetic mother, late preterm (<37 weeks gestation) and birth weight z score

Adjusted[4] for collaborating centre, sex and mode of delivery (vaginal or caesarean section)

Adjusted[5] for collaborating centre and treatment with dextrose gel

8.3 LIST OF FIGURES