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Extended Research Article

Glycaemic control in labour with diabetes: GILD, a scoping study

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Abstract

Background: Diabetes in pregnancy is common, affecting 5–10% of pregnant women. Poor glycaemic control in labour is associated with neonatal hypoglycaemia and other adverse outcomes for mother and baby, but tight glucose control is burdensome, intrusive and may not always be necessary. The ideal intrapartum glucose target level is unknown, traditionally 'tight' control (target 4–7 mmol/l) has been recommended; however, this increases the risk of maternal hypoglycaemia.

Objective: To determine the feasibility of a randomised clinical trial to compare clinical and cost-effectiveness of permissive versus intensive intrapartum glycaemic control in labour in pregnancies complicated by diabetes.

Design: A mixed-methods study including audit of clinical guidelines from United Kingdom maternity units, online surveys of women with diabetes and healthcare professionals, service evaluation of intrapartum glycaemic care, Delphi survey and consensus meeting. Data from these work packages led to the design of a clinical trial, and qualitative interviews were held to understand acceptability of the trial.

Setting: National Health Service maternity services and online input from service users.

Participants: Healthcare professionals and women with type 1 or type 2 diabetes mellitus or gestational diabetes (currently pregnant or having birthed after active labour in past 3 years).

Results: There is significant variation in the recommended frequency of testing for gestational diabetes in labour, technologies used to test glucose levels in labour and administer insulin in type 1 diabetes mellitus, and in how neonatal hypoglycaemia is defined. Of surveyed women, 66% would be willing to participate in a future trial, with 23% unsure without further information. The service evaluation showed that once glucose testing had commenced, it was repeated after 1 hour in 18%, 2 hours in 38% and 4 hours in 45% of women. Neonatal hypoglycaemia was considered the most important neonatal outcome for a future trial, with maternal satisfaction the most important maternal outcome. The incidence of neonatal hypoglycaemia (defined as glucose < 2.6 mmol/l) was 47% in type 1 diabetes mellitus, 45% in type 2 diabetes mellitus and 16% in gestational diabetes mellitus. A non-inferiority trial to compare permissive versus intensive glucose control was designed to include all types of diabetes in an umbrella trial (conduct more than one trial simultaneously). Women and healthcare professionals considered the trial design acceptable and feasible, though noted important considerations in the design and conduct.

Limitations: Glucose levels may be poorly recorded in maternity notes and in practice tested more frequently than the study suggests. Sample sizes in some of the work packages were smaller than our pre-specified target, attrition in the Delphi survey was greater than anticipated and the study was conducted during the COVID-19 pandemic impacting results. Willingness to participate in a hypothetical trial might not translate into recruitment to a real trial.

Conclusions: An umbrella trial using a master protocol was designed to compare tight glycaemic control (standard care) with more permissive control in all types of diabetes. Such a trial is feasible and acceptable to women with lived experience of diabetes during pregnancy and by the women and healthcare professionals who took part in qualitative interviews.

Future work: We recommend that a future randomised trial should include an internal pilot phase to test key aspects of trial conduct and clear progression criteria, given the challenges we have identified during this scoping study.

Study registration: This study is registered as researchregistry6832.

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List of abbreviations

ABCD	Association of British Clinical Diabetologists
BAPM	British Association of Perinatal Medicine
BICS	British Intrapartum Care Society
CEAC	cost-effectiveness acceptability curve
CGM	continuous glucose monitor
CRF	case report form
CSII	continuous subcutaneous insulin infusion
CHYLD	Children with HYpoglycaemia and their Later Development
DM	diabetes mellitus
ECG	electrocardiogram
eCRF	electronic clinical research form
EEG	electroencephalogram
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
FCE	Full Consultant Episode
GDM	gestational diabetes mellitus
GDPR	General Data Protection Regulation
GP	general practitioner
GTT	glucose tolerance test
HbA1c	haemoglobin A1c test
HCP	healthcare professional
HDU	high-dependency unit
HES	Hospital Episode Statistics
HRG	Health Resource Group
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
JBDS	Joint British Diabetic Societies
mmol/l	millimoles per litre
MRI	Magnetic Resonance Imaging
MSDS	Maternity Services Data Set
NCTU	Nottingham Clinical Trials Unit
NMB	net monetary benefit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NNRD	National Neonatal Research Database
No	Number
ONS	Office for National Statistics
PARCA-R	Parent Report of Children's Abilities – Revised
PCA	prescription cost analysis
PICO	population, intervention, comparison, outcome
PIS	participant information sheet
PPI	patient and public involvement
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-years
RCM	Royal College of Midwives
RCT	randomised controlled trial
REC	Research Ethics Committee
REDcap	software for building online surveys and databases
SD	standard deviation
SF-12	Short Form questionnaire-12 items
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UKARCOG	UK Audit and Research Collaborative in Obstetrics and Gynaecology
VRIII	variable rate intravenous insulin infusion
WP	work package

Plain language summary

Diabetes in pregnancy currently affects 5–10% of all women. Most have gestational diabetes, which develops during pregnancy and disappears after birth, the rest have diabetes before pregnancy. During labour, blood sugar levels are closely monitored and treated to minimise the effects of exposure of the baby to high sugar levels in the womb, on the baby after birth, which can lead to babies being admitted to the neonatal unit. However, this monitoring can be intrusive for women in labour and is expensive. New evidence questions how important blood sugar levels and frequency of testing is for preventing problems in the baby.

To answer this question, we wanted to design a trial to find the best way to monitor and control blood sugar in labour focusing on its effects on outcomes in babies. To design the trial, we collected information about the methods used in different hospitals to monitor blood sugar and asked women and healthcare professionals for their views on this. We found that most hospitals test blood sugar every hour in labour in women with type 1 and type 2 diabetes but that there was much more variation in frequency of testing for gestational diabetes.

The trial we are proposing would test women needing insulin in labour (type 1 diabetes, type 2 diabetes and some with gestational diabetes) every hour; women with gestational diabetes who do not need insulin would test every 2–4 hours. The women and healthcare professionals we surveyed agreed that we should test whether a new upper target of 10 mmol/l was equally as safe for mother and baby as the current, stricter, upper target of 7 mmol/l and that the most important outcome was the number of babies with low blood sugar. Women would be invited to take part in the study after 28 weeks of pregnancy and allocated (by a computer programme) to tight or relaxed control around a week before birth. Such a study would need several thousand participants.

Scientific summary

Background

Diabetes in pregnancy affects 5–10% of pregnant women. For most women, this is gestational diabetes mellitus (GDM) (87.5%), but 12.5% of women have pre-existing type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). There is evidence that 'tight' glycaemic control in pregnancy reduces the risk of adverse outcomes for the mother and the baby. Maternal hyperglycaemia results in increased fetal insulin production because of excess placental transfer of glucose and can lead to neonatal hypoglycaemia. The ideal intrapartum glucose target level is unknown. Traditionally 'tight' glucose control (target 4–7 mmol/l) is recommended in labour. Treatment with intravenous insulin may be needed during labour to maintain 'tight' control; however, this may be unnecessary, and this increases the risk of maternal hypoglycaemia in labour, which carries a risk to the mother. Hourly intrapartum testing is also intrusive for women and time-consuming for healthcare professionals (HCPs). Conversely, accepting more permissive glucose levels in the mother may be detrimental to the baby.

Objective

To determine the feasibility of a randomised trial to compare the clinical and cost-effectiveness of permissive versus intensive intrapartum glycaemic control in labour in women with pregnancies complicated by diabetes.

Methods

A mixed-methods scoping study of four work packages:

Work package 1: Assessment of current practice determined by:

a. review of clinical guidelines on intrapartum glycaemic control in pregnant women with diabetes and neonatal hypoglycaemia in UK maternity units
b. survey of practice, training and experience of HCPs involved in caring for women with diabetes in labour in the UK
c. survey of women who have/had diabetes in pregnancy to hear their views on glucose monitoring in labour and the birth outcomes that are important to them
d. a national service evaluation of intrapartum care in pregnant women with diabetes exploring practice and adherence to clinical guidelines on maternal glycaemic control.

Work package 2: Delphi survey followed by a consensus meeting to agree important components of a future trial (types of diabetes, glucose levels in control and intervention arm, frequency of monitoring, maternal and neonatal outcomes).

Work package 3: Design a clinical trial of permissive versus intensive intrapartum glycaemic control in labour for women with diabetes, including consideration of an economic evaluation.

Work package 4: One-to-one virtual interviews with women with diabetes who have experienced labour and HCPs who look after them to understand facilitators or barriers to conducting the trial.

Results

Work package 1a

We collected local unit guidelines of diabetes care in labour from a total of 48 units in England, Wales and Scotland with a further 12 in a joint regional guideline and unit guidelines on neonatal hypoglycaemia covering 55 trusts. There is

significant variation in recommended frequency of testing for GDM in labour, technologies used to test glucose levels in labour and administer insulin in T1DM, and in the operational definition of neonatal hypoglycaemia.

Work packages 1b and 1c

The online surveys were completed by 174 HCPs and 159 women. Confidence of HCPs ranged from 57% reporting feeling fairly or extremely confident in management of T1DM in labour, through to 62% for T2DM and 72% for GDM. Education and training were therefore considered important for successful trial conduct. Of the women surveyed, 66% would be willing to participate in a future trial, with 23% unsure without further information.

Work package 1d

The service evaluation included 594 women from 33 obstetric units. Only 7 women (9%) with T1DM, 7 women (14%) with T2DM and 34 (7%) with GDM had a glucose measurement taken within an hour of admission to Labour Suite (8% overall). Once glucose testing had commenced, it was repeated in 1 hour in 18% overall (34% for T1DM, 14% for T2DM and 16% for GDM). Results for 2 hours was 38% overall (52% for T1DM, 35% for T2DM and 36% for GDM) and for 4 hours 45% overall (58% for T1DM, 50% for T2DM and 42% for GDM) of women re-tested.

The incidence of neonatal hypoglycaemia (defined as glucose < 2.6 mmol/l) was 47% in T1DM, 45% in T2DM and 16% in GDM. The rates of other maternal and neonatal complications were low.

Work package 2

The Delphi survey was conducted in three rounds between February 2022 and March 2022. Round 1 was completed by 133 from 150 registered participants (20 obstetricians, 19 midwives, 5 endocrinologists, 4 neonatologists, 102 parents; 89%), round 2 by 40 participants (12 HCPs and 28 women) and round 3 by 23 (7 HCPs and 16 women). The consensus meeting was attended by 30 participants including obstetricians (7), endocrinologists (4), neonatologists (3), midwives (6), trialists/methodologists (2), health economists (2), health psychologist (1) and women with lived experience of labour with diabetes (5). Consensus was gained on key outcomes for a future trial, with agreement that all types of diabetes should be studied with a permissive glucose target range of 4–10 mmol/l. Neonatal hypoglycaemia should be the primary outcome. Maternal satisfaction was considered an important maternal outcome.

Work package 3

Based on data from previous work packages, a randomised trial using an umbrella design and master protocol has been designed, with an aim to include women with all types of diabetes. The trial will evaluate if a permissive monitoring strategy is non-inferior to a tight control strategy, with a primary outcome of neonatal hypoglycaemia (defined as blood glucose level < 2.6 mmol/l). Key components were identified to conduct a within-trial economic evaluation to estimate the incremental cost per neonatal hypoglycaemia prevented at birth.

Work package 4

Nineteen women and 16 HCPs participated in a 1:1 virtual interview. There was support for the trial, but participants outlined important aspects including the timing of approach and consent and ensuring a multidisciplinary approach to conducting the trial within the hospital.

Patient and public involvement

This study was co-designed from the outset with a patient and public involvement (PPI) co-applicant with a funded PPI advisory group who influenced and guided the development of this project into its final submission.

Conclusions

Data from all work packages have been used to determine the most appropriate design for a future trial. There is eagerness from women with lived experience of diabetes during labour, and HCPs (obstetricians, neonatologists, endocrinologists and midwives) to conduct a randomised clinical trial. An umbrella trial design will enable efficiencies in conduct to minimise burden at participating sites, while allowing women with any type of diabetes to be included. This was considered important by all stakeholders. We also consider it feasible to conduct a within-trial economic evaluation

to estimate the incremental cost per neonatal hypoglycaemia prevented at birth. The trial we have designed was considered necessary, acceptable and feasible by the women and HCPs who took part in interviews.

We therefore recommend that a clinical trial comparing glucose-monitoring strategies in labour, for women with diabetes, is conducted, including an internal pilot phase to test key aspects of trial conduct, given the challenges we have identified during this scoping study.

Study registration

This study is registered as researchregistry6832.

Funding

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Chapter 1 Background and aims

Diabetes in pregnancy affects at least 5–10% of pregnant women or 40,000 women every year and is increasing in the UK.[1] For most women, this is gestational diabetes mellitus (GDM) developing during pregnancy (87.5%), but some women have pre-existing diabetes (12.5%) which can be type 1 diabetes mellitus (T1DM, 7.5%) or type 2 diabetes mellitus (T2DM, 5%).[2] There is evidence that intensive or 'tight' glycaemic control in the periconception period and in pregnancy reduces the risk of adverse outcomes for the mother (pre-eclampsia, diabetes complications, preterm delivery and operative birth) and the baby (congenital anomalies, macrosomia, birth injury, neonatal hypoglycaemia, neonatal unit admission and death).[2] This study, and the clinical trial that has been designed as part of it, focuses on glycaemic control during labour, rather than throughout the pregnancy.

At the start of this project and traditionally, intensive glucose control (target 4–7 mmol/l)[2,3] was recommended in labour. Treatment with intravenous insulin during labour to maintain intensive control, however, increases the risk of maternal hypoglycaemia in labour, which carries a risk to the mother. Hypoglycaemia in labour is reported to happen in up to 50% of mothers[4] and is more likely if the target range is narrow and low. Insulin is much more likely to be required with T1DM and T2DM, with only 15% of women with GDM requiring intravenous insulin to maintain a target of < 7.2 mmol/l in one study.[5] While trained endocrinologists and diabetes specialist nurses supervise antenatal control, midwives, using variable rate intravenous insulin infusion (a 'sliding scale' or VRIII), adjust intrapartum glucose levels. Knowledge and ongoing training are recommended by the Joint British Diabetes Societies (JBDS), although it is unclear if this is happening routinely in practice. The JBDS 2017 guideline[3] also acknowledged that patients undergoing regional analgesia are particularly vulnerable to maternal hypoglycaemia and a more permissive target (4–9 mmol/l) may be more appropriate for them.

However, accepting more permissive glucose levels in the mother may be detrimental to the baby. Maternal hyperglycaemia results in increased fetal insulin production because of excess placental transfer of glucose. Theoretically, avoidance of maternal hyperglycaemia in labour could reduce the risk of neonatal hypoglycaemia by preventing the acute rise in fetal insulin prior to birth. Prevention of neonatal hypoglycaemia is a priority for women with diabetes. It is common within the first 24 hours of birth occurring in up to 50% of babies born to women with T1DM or T2DM[6] and 7–20% of women with GDM.[7,8] It can range from mild and asymptomatic to more prolonged and severe, potentially causing long-term neurodevelopmental problems for the baby. Although rare, litigation from such cases is a financial cost to the NHS. Between 2002 and 2011, 25 such claims had a total cost of £162 M.[9]

Neonatal hypoglycaemia is a leading cause of neonatal unit admission in early-term neonates (37–38 week's gestation).[10] Currently, within the UK, there is a focus on providing safer care to term babies (≥ 37 weeks) while reducing the number of neonatal unit admissions. One of the focuses of the Avoiding Term Admissions Into Neonatal units programme has been neonatal hypoglycaemia, which accounted for 12% of all term admissions (> 13,000 over a 3-year period), represented over 76,000 care days and imposed a financial burden of over £25 M on the NHS.[11] Many mothers of these babies requiring neonatal care for hypoglycaemia had diabetes (25% estimated from similar studies[12]).

In babies of mothers with diabetes, the majority (86%) were admitted to the neonatal unit within 4 hours of birth, a period known to be associated with a physiological transient fall in neonatal blood glucose amenable to feeding interventions.[11] Appropriate management of mothers during labour and babies in the postnatal ward may prevent such admissions by reducing the risk of hypoglycaemia or enabling its management with increased feeding in the postnatal ward.

As stated earlier, traditionally intensive intrapartum glucose control (target 4–7 mmol/l)[2,3] was recommended at the commencement of this project. However, there was no consensus that this target is ideal, how well or how quickly these targets should be achieved, or whether clinicians are better at controlling targets than women self-managing their diabetes. It was unclear if an identical approach was optimal in differing scenarios: type of diabetes (T1DM, T2DM or GDM), antenatal treatment (diet, metformin and/or insulin) and fetal risks (macrosomia, prematurity). In addition, the safety for the mother of intensive control has recently been questioned, with some researchers advocating more permissive targets, for example, 8 mmol/l,[13] citing evidence in other disciplines in medicine that

intensive control is associated with increased morbidity and mortality. In 2022, the JBDS have amended their guideline on 'Managing diabetes and hyperglycaemia during labour and birth', based on a pragmatic rather than evidence-based approach suggesting that a target of 5–8 mmol/l may be safer for women in labour and reduce the risk of maternal hypoglycaemia.[1]

With new technologies, such as continuous glucose monitors (CGMs), it is now possible to assess the percentage time in the target range for glucose during labour.[14] How this will affect the risk of complications in comparison to traditional hourly finger-prick testing is uncertain. Their accuracy in the intrapartum setting is also debated. The traditional view that optimal antenatal control reduces complications such as macrosomia and optimal intrapartum control reduces the risk of neonatal hypoglycaemia is challenged by evidence that antenatal control may be a more significant factor than intrapartum control in reducing the risk of neonatal hypoglycaemia. Hourly intrapartum testing is also intrusive for women and time consuming for healthcare professional (HCPs).

There are no published randomised trials comparing different intrapartum glycaemic targets and the occurrence of neonatal hypoglycaemia. A systematic review included 23 cohort studies (2835 women) and found a positive relationship between intrapartum glucose levels and the risk of neonatal hypoglycaemia in 6 studies, no relationship in 12 studies and a relationship in some analyses in 5 studies.[4] The studies were too heterogeneous to allow meta-analyses with variations in target maternal glucose levels, the definition of neonatal hypoglycaemia and the incidence of confounders including prematurity (5–30%), macrosomia (9–56%), maternal hypoglycaemia (0–56%) and third-trimester control [haemoglobin A1c test (HbA1c)], with many studies failing to report these confounders. Of the 6 studies that found a significant relationship between intrapartum glucose and neonatal hypoglycaemia, none clearly adjusted for known confounders and only 1 of the 23 included studies was reported as low risk of bias in all 6 domains assessed.

The international nature of the studies, with only five UK studies included, may limit the applicability of the findings to the UK NHS. In addition, the studies were conducted over a long period (1978–2016) during which the care of women with diabetes has changed dramatically and the thresholds for diagnosing GDM have been significantly lowered following the Hypoglycaemia and Adverse Pregnancy Outcomes study published in 2008.[15] This systematic review[4] and other recent studies[16–18] suggest that optimising antenatal glycaemic control influences the risk of fetal hyperinsulinaemia more than intensive intrapartum control. Given the recent systematic review (2018) within a year of the conception of this study in 2019 and the lack of intervening new evidence, a systematic review was not repeated.

While neonatal hypoglycaemia is common (one or more readings in the hypoglycaemia range recorded in 94% of infants of mothers with T1DM[14] and 12% of infants of mothers with GDM[5]), there is no universally agreed definition. A 2015 survey of all 161 neonatal units in England[19] found that the majority (88%) used a value of < 2.6 mmol/l, but values ranged from 2.0 to 3.0 mmol/l. Similarly, the method for testing glucose levels and duration of monitoring differed widely; management practices were not assessed. The British Association of Perinatal Medicine (BAPM) addressed this issue with the publication of their guideline 'Identification and Management of Neonatal Hypoglycaemia in the Full-Term Infant' in 2017.[20]

A high-quality randomised controlled trial (RCT) of permissive versus intensive maternal intrapartum glucose control in pregnancies complicated by diabetes is required to answer what is optimal management for both mother and baby. However, due to the uncertainties outlined above (types of diabetes to be included in trial, target glucose levels, frequency of monitoring, technology used for monitoring, selection of maternal and neonatal primary and secondary outcomes), it is not clear if such a trial would be feasible.

Aim

To determine the feasibility of a randomised clinical trial for assessing the clinical and cost-effectiveness of permissive versus intensive intrapartum glycaemic control in women with pregnancies complicated by diabetes.

TABLE 1 Summary of content of research by chapter

Chapter 2	Determining current practice and acceptability of research in this area (work package 1) This chapter is divided further into review of two UK maternity unit guidance (intrapartum glycaemic control and neonatal hypoglycaemia), two national cross-sectional surveys and a national service evaluation of intrapartum care in pregnant women with diabetes exploring current practice and adherence to clinical guidelines on maternal glycaemic control. The service evaluations and two surveys were: a. Review current local clinical guidelines from the UK on intrapartum care in pregnant women with diabetes and neonatal hypoglycaemia in the babies b. Survey of current practice, training and experience of midwifery staff and other HCPs in intrapartum glycaemic control in the UK c. Survey of views of women who have/had diabetes in pregnancy on glucose monitoring in labour and the birth outcomes which are important to them d. Service evaluation of UK maternity units in care of women with diabetes in labour at term
Chapter 3	Delphi process and consensus-building (work package 2) The aim of this work was to reach consensus on the most important clinical components of a future trial of permissive vs. intensive intrapartum glycaemic control in pregnancies with diabetes
Chapter 4	Design of a randomised clinical trial (work package 3) This chapter describes the process of designing a RCT comparing blood glucose-monitoring strategies in labour for women with diabetes, based upon findings from previous work packages
Chapter 5	Determining the acceptability of our proposed randomised trial (work package 4) To understand facilitators or barriers to conducting the trial comparing permissive to intensive glycaemic control that was designed in the earlier work package, we undertook qualitative interview with both women and HCPs, which will be described in detail in this chapter

Objectives

- Assess common themes and variation in current UK clinical guidelines in intrapartum glycaemic care in women with all forms of diabetes (T1DM, T2DM, GDM) and neonatal hypoglycaemia in their babies (work package 1a).
- Determine current practice, training and experience of midwifery staff in intrapartum glycaemic control in the UK (work package 1b).
- Record the views of women with diabetes in a current or recent pregnancy on acceptability of participating in research in intrapartum glucose control (work package 1c).
- Ascertain the views of women on important outcomes for any future trial(s) (work package 1c).
- Assess adherence to local clinical guidelines in intrapartum glycaemic care in diabetes (work package 1d).
- Determine the incidence of important outcomes, for example, number of women with diabetes whose term babies had hypoglycaemia or were admitted to the neonatal unit within 24 hours of birth (work package 1d).
- Compare maternal and fetal outcomes in mothers who had 'tight' glycaemic control in labour and mothers who maintained a more relaxed control (work package 1d).
- Determine the presence of other risk factors (size of the baby/macrosomia/growth restriction, presence of infection/sepsis, hypothermia, third-trimester control) associated with neonatal hypoglycaemia (potential confounders) (work package 1d).
- To reach consensus on the most important clinical components of a future trial of permissive versus intensive intrapartum glycaemic control (types of diabetes to be included, glucose levels, frequency of monitoring, outcomes) in pregnancies complicated by diabetes (work package 2).

- Through assimilation of information collected in earlier work packages, establish if a trial of intensive versus permissive intrapartum glycaemic control is feasible and determine an appropriate trial design (work package 3).
- Understand facilitators or barriers to conducting a trial comparing permissive to intensive glycaemic control for women with diabetes (work package 4).
- Consider the health economic assessment in the definitive trial and whether such an assessment is unnecessary (work package 4).

Study design

This was a mixed-methods study, and each chapter describes study methods in detail. The results chapters are divided into the four original work packages of the project, as described in *Table 1*.

Chapter 2 Determining current practice and acceptability of research in this area

Audit of clinical guidelines

Aims

To assess common themes and variation in current UK clinical guidelines in intrapartum glycaemic care in women with all forms of diabetes and neonatal hypoglycaemia in the babies.

Methods

Local clinical guidelines were sought from all Delivery Suites across the UK from June to December 2021. Guidelines were requested that covered the management of intrapartum glycaemic control and neonatal hypoglycaemia in the immediate post partum period. Where possible, guidelines which were accessible online were collected directly by the study team. Those which are not available online were first requested via the British Intrapartum Care Society (BICS). Reminders were sent if no response was received after an initial request. Where still no response was received, personal contacts of the co-applicants were also contacted by e-mail.

A data-collection sheet was developed by the study team and the relevant information collected from each of the guidelines in turn. Data collection was undertaken by two medical students for each topic (these data were presented in the consensus meeting), and data were checked by the Chief Investigator to minimise any errors (data presented in the final monograph). Results were tabulated and summarised.

No participants were involved in this work package.

Results

Intrapartum care of women with diabetes guidelines

Of the 143 NHS trusts that provided NHS maternity care at the outset of this project, we collected local unit guidelines of diabetes care in labour from a total of 48 units (34%) with a further 12 in a joint regional guideline (total 42%). Guidelines were collected from maternity units in England, Scotland and Wales but there were none received from Northern Ireland. We requested the latest guidelines from each maternity unit, and these ranged from 2017 to 2021 with policies of review planned at between 1 and 3 years. The regional guideline had insufficient information to allow detailed analysis; therefore, the results are derived from the 48 unit guidelines. Guidelines were received from both large and small obstetric units, increasing the likelihood that the results from this analysis are generalisable to UK maternity units.

Testing frequency for T1DM was 1 hourly for the first stage in all cases and also in T2DM 47/48 (98%); one unit recommended 2 hourly testing for T2DM. Most units continued with hourly testing in the second stage, with only two units (4%) recommending testing every 30 minutes. Testing in GDM was much more varied, with only 58% (28/48) of units recommending hourly glucose testing for all types of GDM, in line with the National Institute for Health and Care Excellence (NICE) guidance. Testing frequency in GDM was dependent on antenatal treatment in 38% (14/48) of units; three units (6%) recommended no testing at all or one test on admission for women with GDM on metformin or diet for antenatal control. The remaining 34 units treated women with GDM in labour alike, regardless of their antenatal management (*Table 2*).

All units that specified the technology for testing (38/48; 79%) reported using finger-prick testing, with only four units (8%) specifying that CGM/sensors could also be used.

In all cases, the lower target value for glucose in labour was 4 mmol/l. The upper target value was much more varied, with 7 mmol/l being the commonest value (35/48; 73%) (*Table 3*).

TABLE 2 Frequency of glucose testing in established labour

		Testing based on antenatal management to maintain glycaemic control (*n* = 14)		
Frequency testing	**GDM – all types (*n* = 34)**	**GDM – insulin**	**GDM – metformin**	**GDM – diet**
One hourly	28	12	5	
Two hourly	2	2	5	7
Four hourly			2	3
On admission			1	2
No test			1	2
Unclear/not specified	4			

Note
Regardless of their antenatal management, 34 units treated women with GDM in labour alike. Testing frequency in GDM was dependent on antenatal treatment in 38% (14/48) of units; three units (6%) recommended no testing at all or one test on admission for women with GDM on metformin or diet for antenatal control (*n* = 48).

TABLE 3 Upper target glucose values in labour

	Upper target (mmol/l)				
Glucose level	6	7	8	7.8	9
Number (%) guidelines	2 (4%)	36 (75%)	7 (15%)	2 (4%)	1 (2%)

For those on antenatal insulin administered via a continuous subcutaneous insulin infusion (CSII) pump, there was recommendation that this could be continued in labour in 18 (38%) guidelines; for those on antenatal basal (long-acting) insulin continuation in labour was recommended in 13 (26%) of guidelines. Metformin was discontinued for labour, and insulin via a VRIII (sliding scale) was the recommendation if glucose were above target in all but one guideline (where subcutaneous long-acting insulin was recommended).

Treatment for hyperglycaemia was recommended after two raised values in most guidelines that included this level of detail (27/38; 71%; *Table 4*). Intravenous fluids were recommended at the same time as the insulin infusion in 45 (94%) guidelines.

Information on treatment of low blood glucose was available in fewer clinical guidelines (*n* = 23) with others referring to their trust hypoglycaemia pathway/guidelines which were not available for review. Of those where details were available, treatment was recommended after the first low value in all cases. There was variation in recommendations for how to treat low glucose values, with oral glucose being the commonest recommendation (15/23; 65%; *Table 5*). Multiple options were recommended in some guidelines.

TABLE 4 Number of recommended glucose values above upper target value before treatment recommended

Recommended number of raised glucose values prior to treatment	**One**	**Two**	**Unclear/not specified**
Number of guidelines	11	27	10

TABLE 5 Recommended treatment for hypoglycaemia in labour

Oral glucose/sugary drink	**Food intake**	**i.v. glucose 5%**	**i.v. glucose 10%**	**i.v. glucose 20%**	**Unspecified/not clear**
15	5	6	5	3	25

i.v., intravenous.

TABLE 6 Recommendation on oral intake in labour

Not allowed	Allowed	Unclear/not specified
22	8	18

Information on whether oral intake was permissible in labour was available in 30 guidelines, with only 8 (27%) specifically stating that it was allowed (*Table 6*).

Neonatal hypoglycaemia guidelines

Of the 143 NHS trusts that provided NHS maternity care at the outset of this study, we collected unit guidelines on neonatal hypoglycaemia covering 55 trusts (36%). This comprised 39 individual trust-level guidelines and regional guidelines for the West Midlands Neonatal Network (further 8 of the 10 trusts included), West of Scotland (further 6 of the 7 included health boards) and all Wales (further 2 of the 6 health boards) regions. These guidelines were published between 2018 and 2021.

The most common recommendation for the timing of the first glucose test in neonates was 2–4 hours (45/55; 82%) after birth; second was 4 hours after birth (8/55; 15%). In terms of timing of the glucose test to the feeding of the baby, most guidelines recommended testing before the second feed, with only three guidelines having other recommendations (not specified to feed just time).

Blood glucose continued to be monitored until two consecutive readings of > 2.0 mmol/l were obtained in 27 cases (49%) and two consecutive readings of > 2.6 mmol/l were obtained in 16 cases (29%). The commonest other recommendation was requiring three measurements > 2.6 mmol/l (n = 9; 16%). Of the remaining three guidelines, two did not specify the duration of testing and one recommended two readings > 3.0 mmol/l.

Where specified, the commonest test routinely used to measure glucose in the neonate was a blood gas analyser – only one guideline (2%) did not specify this equipment. Other devices were less commonly used including glucometer point-of-care analyser (n = 10/51; 20%) and laboratory-processed test (n = 4; 8%). No method was specified in four guidelines. Only five guidelines (9%) specifically stated that neonatal hypoglycaemia should be confirmed with a laboratory-processed sample.

In terms of preventative measures, 49 guidelines (89%) included information to encourage staff to keep babies warm, promote skin-to-skin contact and offer early feeds, with the majority including some preventative measures (96%). This was supplemented by written information on risks, signs and symptoms, and treatment of hypoglycaemia in the baby being provided by 44 trusts (75%). Some trusts included these information leaflets as an appendix to the guideline.

Symptoms suggestive of hypoglycaemia were included in all guidelines, with the commonest symptom being seizures (89%). The top 12 symptoms (*Figure 1*) were itemised, with the commonest 'other' symptom being cyanosis (10/55; 18%).

Of the 39 individual trust-level guidelines, neonatal hypoglycaemia was defined as glucose < 2.6 mmol/l in 26 guidelines and < 2.5 mmol/l in the other 12 guidelines (the level was unclear in 1 guideline). Detailed analysis of the treatment threshold and management of neonatal hypoglycaemia are summarised in *Table 7*. This analysis found that most guidelines had diagnostic criteria and management plans classified into three different groups: asymptomatic hypoglycaemia, symptomatic hypoglycaemia and severe hypoglycaemia. There was variation in the threshold for diagnosis, with < 2.0 mmol/l being the commonest (most likely or mode) operational threshold that would trigger medical intervention (see *Table 7*). Similarly, severe hypoglycaemia was more commonly defined as a glucose level < 1.0 mmol/l in the neonate. The most common recommendation for the treatment of asymptomatic hypoglycaemia was buccal glucose gel (40%) and repeating the glucose level prior to the next feed and continuing until two consecutive values were above the threshold level. Intravenous glucose was most commonly recommended for symptomatic or severe neonatal hypoglycaemia, with the glucose being rechecked within 30 minutes of treatment and continued for 24 hours. Most maternity units managed babies with asymptomatic hypoglycaemia on the postnatal

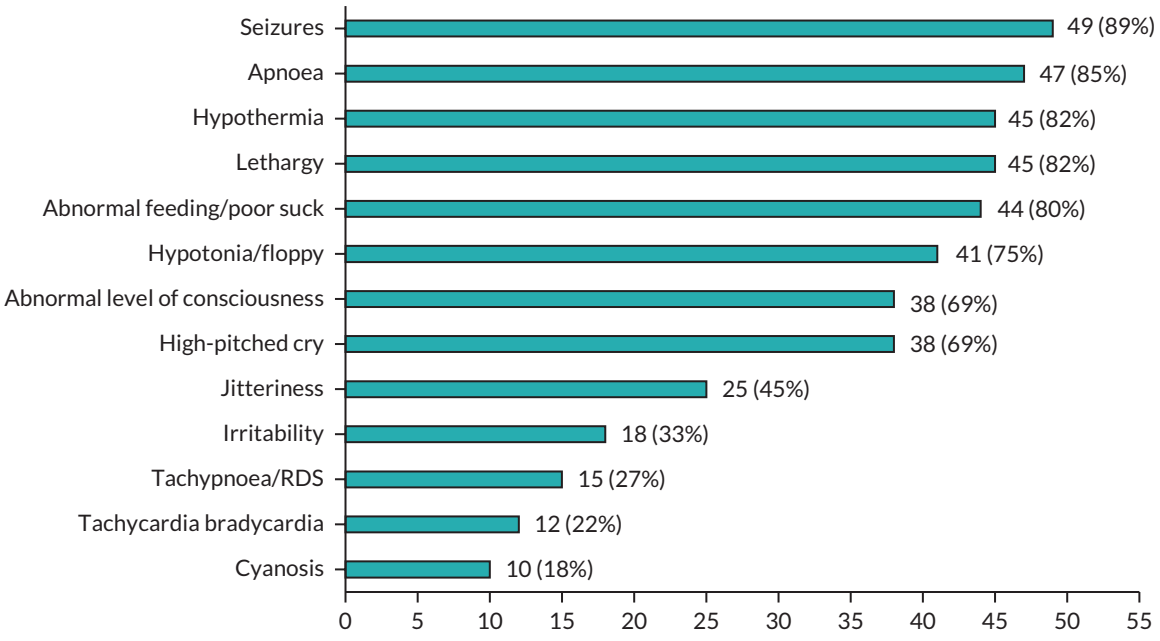

FIGURE 1 Horizontal bar chart of symptoms suggestive of hypoglycaemia included in guidelines (ordered by frequency). RDS, respiratory distress syndrome.

wards initially but would transfer those with symptoms or severe neonatal hypoglycaemia to the neonatal unit for treatment.

Patient and public involvement

The study patient and public involvement (PPI) advisory group were not involved in the conduct of work package 1a (the collection and analysis of national guidelines) due to lack of experience and knowledge in this topic area. The PPI advisory group were aware that the guidelines were collected and analysed by the study team and informed further study work packages.

National surveys

Aims

1. To determine current practice, training and experience of midwifery staff and other HCPs in the UK in intrapartum glycaemic control.
2. To record the views of women with diabetes in a current or recent pregnancy on intrapartum testing and acceptability of participating in research in intrapartum glucose control.
3. To ascertain the views of women on important outcomes for any future trial(s).

Methods

Two online surveys were designed: one for HCPs and the other for women. Draft surveys were designed using Microsoft Word (Microsoft Corporation, Redmond, WA, USA) to enable an audit trail of changes to be maintained. The surveys were designed to be completed within 10 minutes to minimise the burden of participation. Once questions had been agreed upon, surveys were built in JISC Online Surveys© and user-tested by the study team. Surveys required completion in one sitting; there was no option to pause and return to the survey at a later time point. Participation was open and voluntary, with results remaining anonymous. Contact e-mails were submitted only for the purpose of invitation to participate in future work packages or a prize draw. Anonymised data were used for analysis.

Healthcare professionals survey

The HCP survey was designed by the multidisciplinary co-applicant team. HCPs were asked on their current practice during labour in terms of the numbers of women with diabetes they cared for, frequency of glucose testing and

TABLE 7 Neonatal hypoglycaemia treatment threshold and interventions (*n* = 39)

Glucose value (range)	Symptoms in definition	Treatment	Route	Dose	When is glucose rechecked?	
					Frequency	Duration (consecutive readings above target or time)
Asymptomatic hypoglycaemia						
< 2.6 (1.5–2.5) mmol/l (*n* = 9)[a] < 2.6 (1.0–2.5) (*n* = 2)	No	Dextrose gel 40% Breast milk Formula	Buccal Oral Oral	200 mg/kg 10–15 ml/kg every 3 hours	Hourly *n* = 5 Pre-feed *n* = 3 Pre-feed if 2–2.5; hourly if 1.0–1.9 *n* = 3	Two *n* = 4 Three *n* = 7
< 2.0 (1.0–1.9) mmol/l (*n* = 28)	No	Dextrose gel 40% Breast milk Formula	Buccal Oral Oral	200 mg/kg 10–15 ml/kg every 3 hours	Hourly *n* = 6 Pre-feed *n* = 22	Two *n* = 22 Three *n* = 4 Unclear *n* = 2
Symptomatic hypoglycaemia						
< 2.6 (1.5–2.5 mmol/l) (*n* = 7) < 2.6 (1.0–2.5) (*n* = 14)	Yes	Glucose 10%	i.v.	2.5 ml/kg plus infusion: 60 ml/kg/day *n* = 12 75 ml/kg/day 90 ml/kg/day *n* = 4 5–7 mg/kg/minute *n* = 2 Not specified *n* = 2 Buccal dextrose 40% first (if > 1.5 mmol/l) *n* = 1	15 minutes *n* = 1 30 minutes *n* = 15 60 minutes *n* = 1 Unclear *n* = 4	Two *n* = 3[b] Three *n* = 1 24 hours *n* = 12 Unclear *n* = 5
< 2.0 (1.0–1.9) mmol/l (*n* = 12)	Yes	Glucose 10%	i.v.	2.5 ml/kg plus infusion: 60 ml/kg/day *n* = 8 90 ml/kg/day *n* = 1 Unclear *n* = 3	30 minutes *n* = 9 Unclear *n* = 3	Two *n* = 0 Three *n* = 0 24 hours *n* = 8 Unclear *n* = 4
Severe hypoglycaemia						
< 1.5 mmol/l (*n* = 8)	N/A	Glucose 10%	i.v.	2.5 ml/kg plus infusion: 60 ml/kg/day *n* = 3 90 ml/kg/day *n* = 1 Unclear *n* = 4	15 minutes *n* = 1 30 minutes *n* = 2 Unclear *n* = 5	Two *n* = 0 Three *n* = 2 24 hours *n* = 2 Unclear *n* = 4
< 1.0 mmol/l (*n* = 28)	N/A	Glucose 10%	i.v.	2–2.5 ml/kg plus infusion: 60 ml/kg/day *n* = 16 75 mg/kg/day *n* = 2 90 ml/kg/day *n* = 5 5–7 mg/kg/minute *n* = 2 Unclear *n* = 3	30 minutes *n* = 22 60 minutes *n* = 2 Unclear *n* = 4	Two *n* = 2[b] Three *n* = 1 24 hours *n* = 18 Unclear *n* = 7

i.v., intravenous; N/A, not applicable.
a Two guidelines had a target range of 1.4–2.5 mmol/l and one guideline a target range of 1.6–2.5 mmol/l.
b Glucose target > 3.0 mmol/l in one guideline.

Note
Two guidelines only had information on asymptomatic hypoglycaemia (1.5–2.5 mmol/l).
In four guidelines, there was no different management recommendation if symptomatic or asymptomatic (management based on glucose levels only).
One guideline had no separate management recommendation for severe neonatal hypoglycaemia.
If glucose values were 2.0–2.6 mmol/l, most guidelines recommended to check if the baby was feeding and offer feeding support, keep the baby warm, encourage skin-to-skin contact and repeat glucose before the next feed, with no additional medical intervention.
If there was delay in commencing i.v. treatment, most guidelines supported glucagon, the use of buccal glucose gel and/or IM glucagon.

technology used, what treatment would be started and based on what glucose value. Confidence in caring for women with diabetes (T1DM/T2DM/GDM) was established, and training received on various theoretical and practical aspects of care and the need for training in these aspects for the delivery of any future research trial. Demographic data were collected for the individual and hospital where they worked, with the option of expressing a desire for participation in future work packages. Answers were expressed either as ordinal/nominal variables or as a Likert scale to facilitate the collation of the responses. Informed consent was assumed by the completion of the survey.

The HCP survey was shared by the UK Audit and Research Collaborative in Obstetrics and Gynaecology (UKARCOG) social media channels and by e-mail distribution to local representatives, BICS mailing list, Royal College of Midwives Research Advisors social media account, the GBS3 trial midwives via e-mail and local communications, and local HCP colleagues of study co-applicants. The surveys were highlighted by organisations throughout the time window in which they were active, from August 2021 to October 2021.

Women's survey

For the women's survey, questions were designed to cover four different aspects: (1) screening and consent, (2) demographics, (3) diabetes care in labour (only applicable to those who have previously had a baby) or information given in antenatal period and labour concerns (in those for whom it was their first pregnancy) and (4) views on participating in a research study. Finally, there was optional information on participation in a prize draw and whether they wanted information on the results of the study. Suggested optional responses were offered for each question. This allowed responses for each question to be calculated as a percentage of the total number in the submitted surveys. There was also an option, in each question, for a free text response.

The women's survey was shared by the Gestational Diabetes UK social media channels, National Childbirth Trust, the Nottingham Clinical Trials Unit Bump2Baby social media channels, and the study team Twitter (Twitter, Inc., San Francisco, CA, USA) channels, ensuring that links were given to further groups including Positive Birth Movement and the National Maternity Voices group. The study PPI group also shared the survey with local groups and contacts.

Survey distribution was conducted throughout the time window in which it was active, from August 2021 to October 2021.

Statistical analysis

Sample size estimation was not possible for these surveys as they do not form groups with finite membership. We therefore took a pragmatic approach to aim for responses from 200 women and 300 HCPs, as responses of this order had been achieved in the past.

For the analysis, de-identified data (e-mail addresses removed) were analysed using simple descriptive statistics. Data were presented as graphically as *n* (% total responses).

Results

Healthcare professional survey results

There were 174 completed responses to the online survey (see *Appendix 1*). The greatest number of responses were from clinical midwives (69%) and obstetricians (29.9%). The responses from endocrinologists and diabetes specialist nurses were very limited (1.1%).

Three-quarters of the respondents had more than 5 years of experience in managing women with diabetes in labour. There was a wide geographical distribution of the participants completing the survey. Ninety per cent of respondents were directly involved with intrapartum care of women with diabetes. The median number of women cared for by each person per month was 2 with a range of 0–30 (*Figure 2*).

Of the respondents, 71% reported working in a teaching hospital and 26% in a district general hospital. The remainder worked in a combination of both. Sixty per cent of respondents worked in a maternity unit with 5001–10,000 births annually and 35% in a unit with 2001–5000 births.

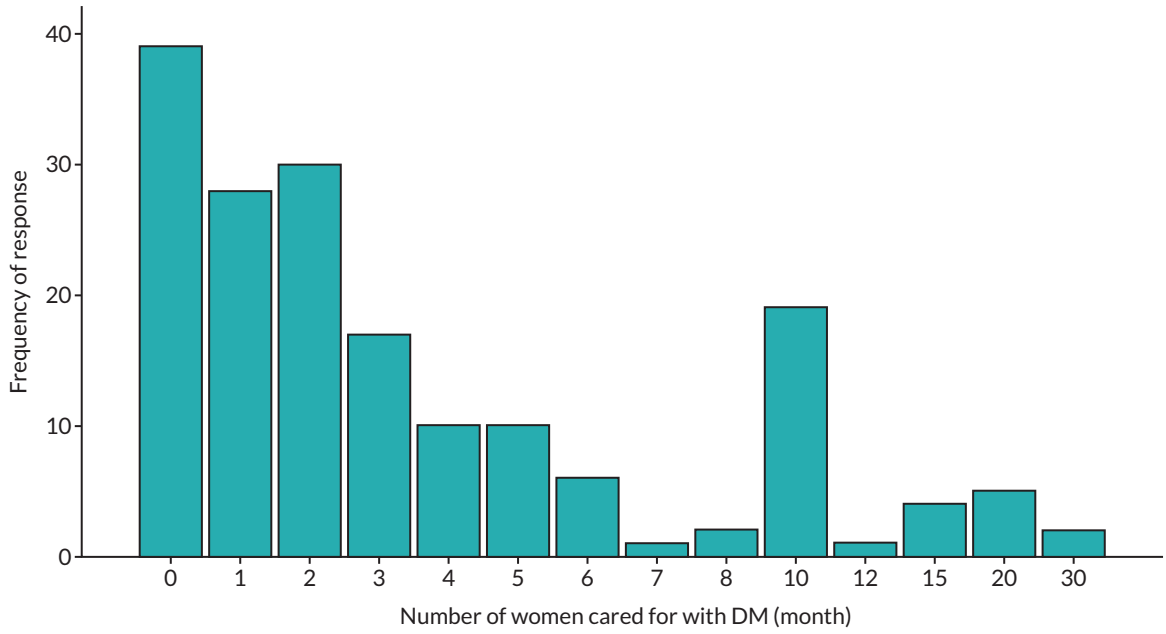

FIGURE 2 Bar chart of estimated number of women with diabetes cared for in labour over 1 month by each respondent (the median number cared for by HCP was 2 per month).

Only 27% of respondents acknowledged that they had a special interest in diabetes. Most respondents worked in a unit that had a diabetes specialist midwife to support the care of women in the antenatal period (78%), with only 15% having support for intrapartum care and 21% having no diabetes specialist midwife at all. Similarly, 80.5% of respondents had access to a diabetes specialist nurse in the antenatal period and 11.5% in the intrapartum period, with the remainder having no access to a diabetes specialist nurse.

There was variation in the frequency of testing depending on the type of diabetes women had, with over 90% of respondents testing glucose hourly in T1DM and T2DM and 69% in GDM (*Figure 3*).

Of the respondents, 99% reported that glucose levels were tested using capillary glucose (finger prick) and 45% used a flash or CGM (e.g. Libre or Dexcom). Most respondents would start insulin when the blood glucose levels were above 7 or 8 mmol/l. The results were similar regardless of the type of diabetes (*Figures 4* and *5*).

This was based upon one (32%) or two (62%) readings in T1DM/T2DM and more likely to be two readings (72%) in GDM. Overwhelmingly, if insulin was required an infusion (VRIII or sliding scale) was used (95%), with only 1% of respondents offering insulin through the patient's own CSII (pump) and one respondent suggesting giving insulin by a subcutaneous injection.

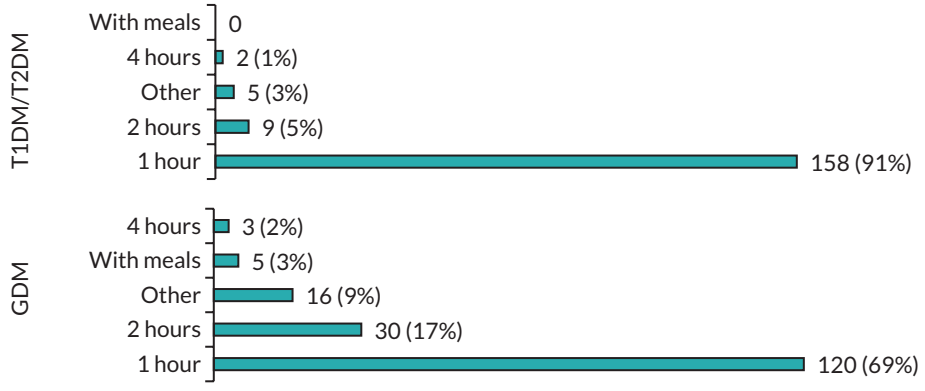

FIGURE 3 Horizontal bar chart of frequency of testing in labour by diabetes type [absolute number of responses (and percentages) reported].

FIGURE 4 Horizontal bar chart of level of blood glucose where commencement of insulin would be recommended in T1DM/T2DM (absolute number of responses reported).

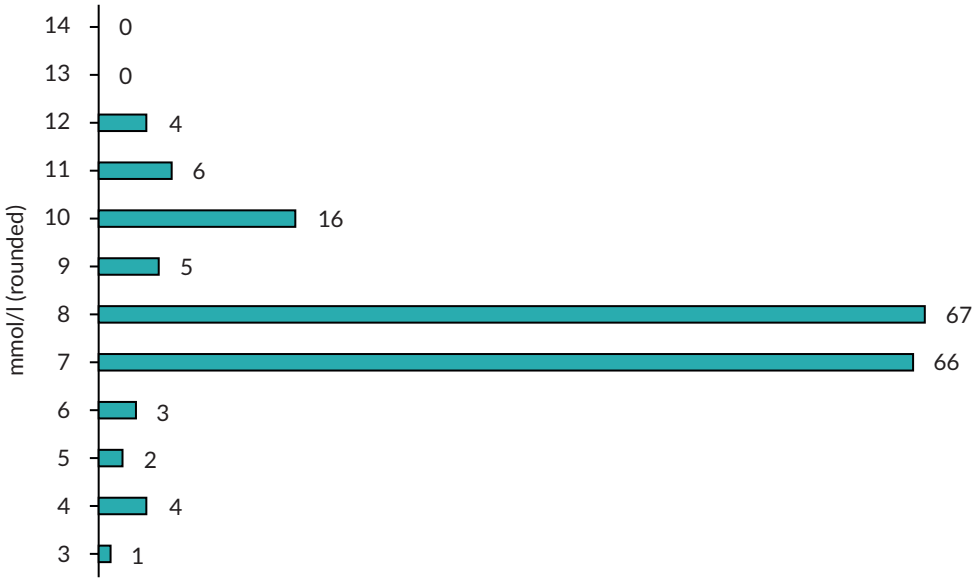

FIGURE 5 Horizontal bar chart of level of blood glucose where commencement of insulin would be recommended in GDM (absolute number of responses reported).

Exploring the confidence of the respondents in caring for women with diabetes in labour, 57% reported feeling fairly or extremely confident in managing women with T1DM. This increased to 62% and 72% for T2DM and GDM, respectively (*Figure 6* for data reported by absolute numbers).

Hospital guidelines were thought to be fairly or extremely useful by 57% of HCPs managing women with diabetes in labour, with 40% finding them slightly helpful and 3% finding them not helpful at all. When asked what other information the respondent would find helpful, there were three main themes. The first centred around making the guidelines clearer, simpler and easier to use; the second theme was around maintaining education and training of the staff; and the third specifically about education on the use of CGM/sensors and CSII.

Only 44% of respondents acknowledged that they had received training on the diabetes control of women in labour. Exploring the various aspects of care, more respondents noted that they had theoretical training in comparison to practical training, with only 42 respondents (24%) having practical training on VRIII and even less at 21 (12%) having any training on CGM/sensors and CSII (pump) (*Figure 7*).

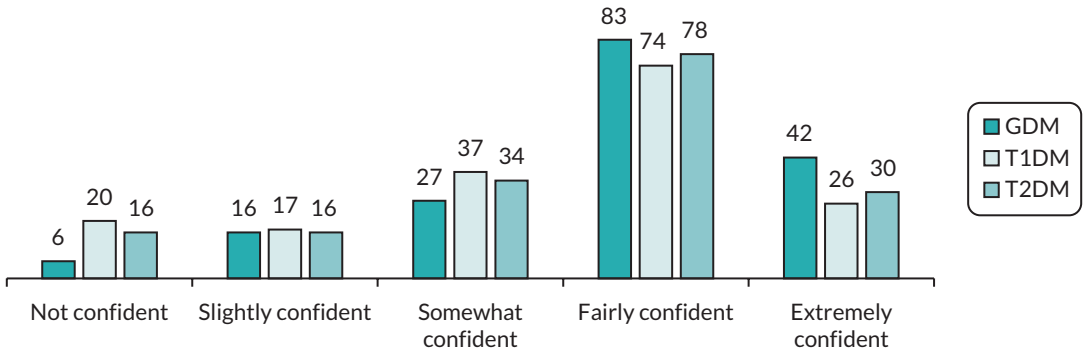

FIGURE 6 Bar chart of confidence of HCP in looking after women with T1DM, T2DM and GDM in labour.

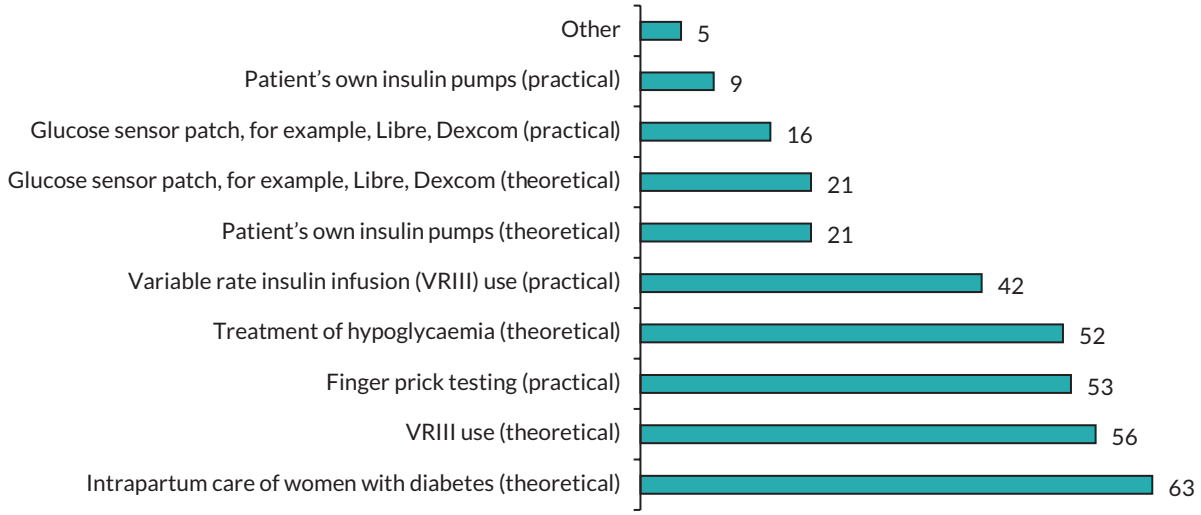

FIGURE 7 Horizontal bar chart of frequency of training received by responding HCP in intrapartum diabetes care (denominator absolute values of those who received training, total number reporting receiving any training = 77; 44%).

When specifically asked if there was to be a research study undertaken in the management of glucose control in labour for women with diabetes, 61.5% of respondents felt that training would be necessary, 36% helpful but not mandatory and 2% unnecessary.

Of the nine various aspects of training listed above, theoretical training was prioritised to practical training by most respondents (*Table 8*).

On the topic of maternal hypoglycaemia, only 108 respondents (62%) felt extremely or fairly confident in dealing with this problem, with 49 (28%) feeling slightly or somewhat confident and 17 (10%) feeling not confident.

Focusing on results for diagnosis of neonatal hypoglycaemia in a term newborn baby whose mother has diabetes, 105 (60%) were extremely or fairly confident, 37 (22%) were slightly or somewhat confident and 32 (18%) were not confident. This compared with confidence responses for the treatment of neonatal hypoglycaemia of 90 (52%) extremely or fairly confident, 39 (22%) slightly or somewhat confident or 45 (26%) not confident, respectively. This was also highlighted by the response to the importance of neonatal training in hypoglycaemia for a research study which was deemed fairly or extremely important by 126 (72%).

TABLE 8 Importance of training in various aspects of intrapartum diabetes care for a future clinical trial

	Importance		
Training	**Extremely/fairly**	**Somewhat/slightly**	**Not important**
Theory: intrapartum care	145 (83%)	24	5
Theory: VRIII	144 (78%)	23	7
Theory: CSII (pump)	136 (78%)	36	2
Theory: CGM/sensor	136 (81%)	34	4
Theory: treatment of maternal hypoglycaemia	141 (72%)	27	6
Practical: finger-prick testing	92 (53%)	59	23
Practical: CGM/sensor	122 (70%)	45	7
Practical: VRIII	135 (78%)	29	9
Practical: CSII (pump)	132 (76%)	36	6

Women's survey results

A response was obtained from 159 women in this survey (see *Appendix 2*). The commonest age range of women who responded was 30–34 years (45%) with an age range of 20–45 years.

Eighty-one per cent of respondents (*n* = 128) had given birth in the previous 3 years and had diabetes during the pregnancy, but were not pregnant at the time of responding; 7% (*n* = 11) were in their first pregnancy with diabetes and 11% (*n* = 18) were currently pregnant and had diabetes in this and a previous pregnancy. Two women had GDM in a previous pregnancy and had not yet had screening for GDM in their current pregnancy.

Of the 28 women who responded to their gestation, the majority (*n* = 15; 54%) were in the third trimester of pregnancy, with the remainder quite evenly split to under 12 weeks (*n* = 6; 21%) and over 12 weeks (*n* = 7; 25%).

Most of the respondents had GDM (*n* = 151; 95%) with five women (3%) having T1DM and two women (1%) T2DM and one woman having latent autoimmune diabetes in adults.

Most women were White British (*n* = 123; 77%), with 15% of women from ethnic minority groups, the commonest of which was Indian ethnicity (*n* = 10; 6%).

We divided the country geographically by country and further subdivided England along the regions represented by the 15 Clinical Research Network regions. The geographical location of the women was diverse, with the commonest regions being the West Midlands (13%) and East Midlands (12%). All regions except for North Thames were represented.

For those who had delivered their baby, their recall of the frequency of testing of blood glucose during labour was varied. The commonest response was every hour in 31% (*n* = 46), although a significant number reported not being tested at all (*n* = 39; 26%) or when they ate a meal (*n* = 11; 7%). The commonest 'other' response was once, on admission only (*n* = 6).

When asked how they found the frequency of blood glucose monitoring during labour, the majority felt that it was about right (*n* = 60; 55%). Three women reported the use of a CGM/sensor, with the remainder who were tested having this done by finger prick.

Comparison of the view of women on frequency based on their recollection of how often they were tested shows that repeatedly women who were tested every hour felt this was 'too often' and women who were tested every 4 hours had the largest group who felt that this was 'not often enough' (*Figure 8*).

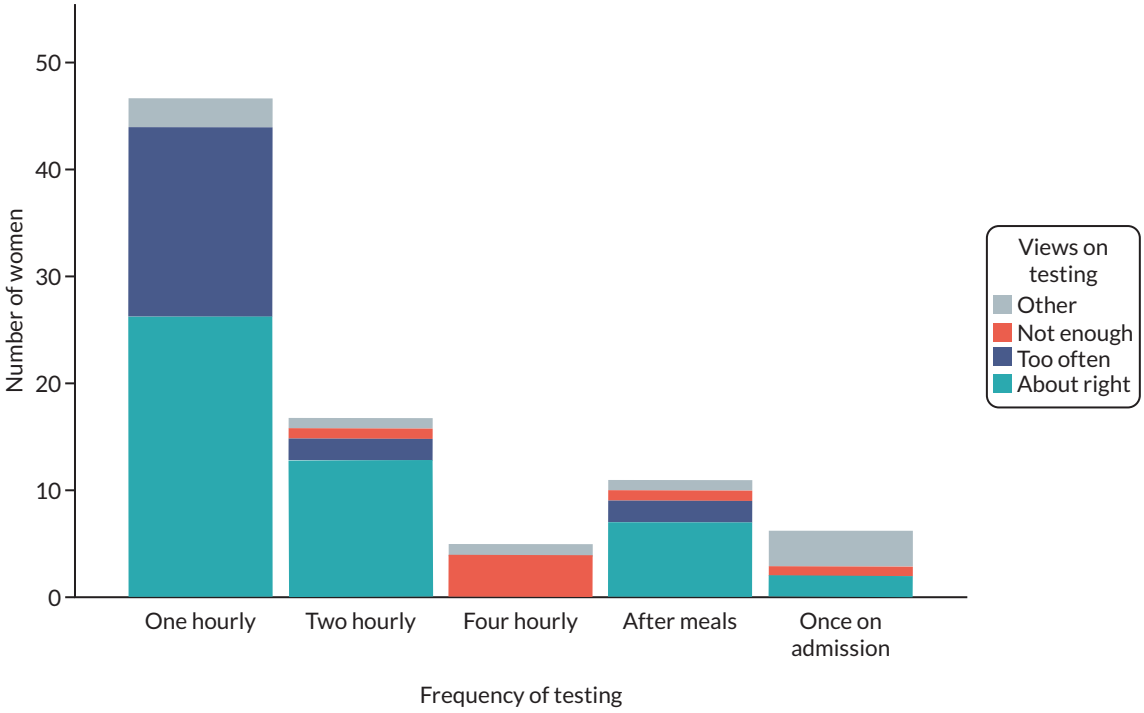

FIGURE 8 Bar chart on views of women on testing frequency grouped by recall of test frequency.

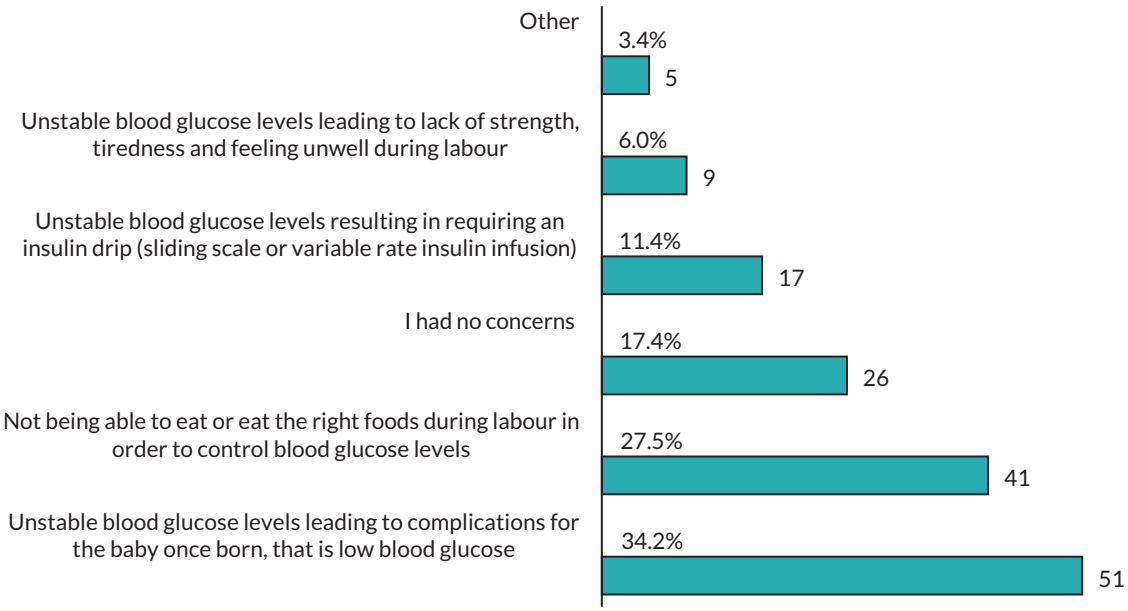

FIGURE 9 Horizontal bar chart of main concern of respondents with respect to blood glucose levels during their labour (absolute numbers and percentages, ordered by frequency of reporting).

The commonest concern women had about their blood glucose in labour was that they would have unstable levels leading to complications in the baby, such as neonatal hypoglycaemia. This was reported by 51 (34%) respondents (*Figure 9*).

In terms of the treatment recommended in response to their glucose level, 13% (n = 20) recall being recommended insulin via an infusion (this was because they were on antenatal insulin in 12 cases and glucose levels were high in 7, and 1 person responded that their unit routinely used insulin in labour). A further 20% (n = 30) recall being asked not to eat anything, while 16% (n = 25) recall being requested to drink or eat a suitable snack. Fifty-eight per cent (n = 86) of women reported that nothing was recommended.

In terms of food intake in labour, slightly more women reported that this was not supported (*n* = 64, 43%) in comparison to those who were allowed (*n* = 54, 36%).

Turning to the views of women on approach of any future trials on glucose control in labour, most women (*n* = 145, 91%) felt that they would want to receive the information during the antenatal period, with 10 (6%) wanting this when they attended for scans and only 3 women (2%) wanting the information at the start of labour. Preference on the format of this information was split between verbal explanation, a paper information sheet and a short information sheet followed by a longer one with the full information. Video information was less popular.

Women were asked the following question about whether they would consider participating in the proposed study:

> We'd like you to imagine a scenario: you are invited to take part in a study comparing different blood sugar monitoring methods during labour. You are provided with all the information to make an informed choice. The information will provide you with benefits and risks of the different strategies that would be compared in the study. For the study to be a fair test, you are not able to choose how you will be monitored, one of the methods being studied will be chosen by a computer. The reason for doing this is because doctors and researchers do not currently know the best way to monitor blood sugar levels during pregnancy. Would you consider participating in the study?

Sixty-six per cent (*n* = 105) of women responded that they would be willing to participate, 23% (*n* = 37) were unsure and 11% (*n* = 17) would decline.

The commonest reason women chose to decline participation was because they would prefer to decide themselves how best to monitor their blood glucose. In free-text responses there were views that studying in labour, when a new life is about to be born, was not the best time, that women felt they wanted to do the safest thing for themselves and their baby, and that they would not wish to take part because of the uncertainty in consequences of participation. Other woman wanted to know if participation might negatively affect her birth plans, for example, more intervention/sliding scale use.

Finally, women were asked to consider what they felt was the most important outcome measure for both mother and baby in a future clinical trial, with the commonest response being low blood glucose in the baby (27%, *n* = 43) and a further 23% (*n* = 36) opting for low blood glucose that made the baby unwell (*Figure 10*).

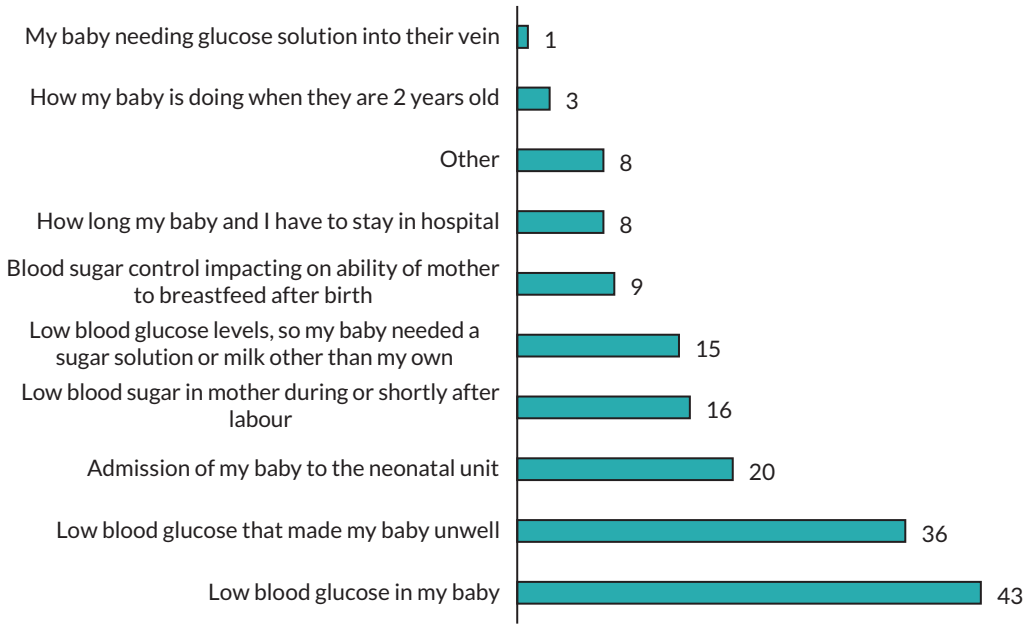

FIGURE 10 Horizontal bar chart of most important outcome measure for mother or baby for any future trial (absolute numbers reported, ordered by frequency of reporting).

Patient and public involvement

The PPI advisory group were involved in the design and dissemination of the national surveys (work packages 1b and 1c). The surveys were drafted by the study team before being shared with the PPI advisory group for comment. In addition to the content, the PPI advisory group considered the language of the surveys to ensure that this was appropriate and would maximise responses from women, including those from seldom-heard communities. One aspect that was adapted following the input made by the PPI advisory group was that questions relating to oral intake in labour were included. The comments and suggestions made by the PPI advisory group were implemented before the surveys were built and disseminated. The answers provided by survey respondents were reviewed by the PPI advisory group in a virtual meeting, and they were provided the opportunity to comment on these before they influenced subsequent work packages.

The PPI advisory group also met to discuss the results of the survey. There was a discussion around the outcomes included in *Figure 10* and their implications. The PPI advisory group felt that areas discussed could be included in a bespoke patient satisfaction survey developed for the purpose of the trial to cover aspects related to glycaemic control that would not be included in current validated questionnaires of childbirth experience. Suggestions for maternal aspects that should be included in a bespoke questionnaire developed by the PPI advisory group and the study team included:

- Impact of maternal hypoglycaemia, in terms of making the woman feel weak or unable to make decisions.
- Impact of neonatal hypoglycaemia on mother – desire for baby not to be taken away but rather stay with the mother and partner; opportunity for skin-to-skin contact immediately after birth.
- Baby being well enough to breastfeed.
- Calm atmosphere in the room – no alarm or chaos due to concerns or uncertainties related to maternal diabetes.
- Confidence of mother in the plan put in place for diabetes control during labour.
- Understanding of the plan put in place for diabetes control during labour.
- No feeling of coercion, rather there was a discussion and choice in the plan put in place for labour.
- How much restriction the plan for diabetes control during labour would have, for example, could they move around, use whatever position they felt comfortable with, ability to use the birthing pool.
- Avoidance of episodes of hypoglycaemia in the first 24 hours postnatal as this would have the potential to influence the quality of time that they had with their baby.

National audit of intrapartum care in pregnant women with diabetes exploring current practice and adherence to clinical guidelines on maternal glycaemic control

Aims

1. To assess adherence to local clinical guidelines in intrapartum glycaemic care in diabetes
2. To determine the incidence of important outcomes, for example, the number of women with diabetes whose term babies had hypoglycaemia or were admitted to the neonatal unit within 24 hours of birth
3. To compare maternal and fetal outcomes in mothers who had 'tight' glycaemic control in labour and mothers who maintained a more permissive/'loose' control
4. To determine the presence of other risk factors (size of the baby/macrosomia/growth restriction, presence of infection/sepsis, hypothermia, third-trimester control) associated with neonatal hypoglycaemia (potential confounders).

Methods

A national UK-based service evaluation of clinical practice investigating the management of glycaemic control in labouring women was performed. We sought responses on patients' demographic characteristics, obstetric history, type of diabetes, antenatal care, ultrasound scan reports, intrapartum care and neonatal outcomes (see *Appendix 3*).

Eligibility criteria

Women with a diagnosis of either T1DM, T2DM or GDM, who had experienced labour from 37 weeks' gestation (confirmed by a first-trimester dating scan) onwards and who laboured on the obstetric-led Delivery Suite were eligible

for inclusion. Women with a planned elective caesarean section or those who laboured to full cervical dilatation (defined as 10 cm on vaginal examination) before admission to the labour ward were excluded from the study.

Data collection

At each unit, obstetric trainees were asked to record the number of women with T1DM/T2DM/GDM who laboured at term (37 or more weeks gestation) over an 8-week period between October and December 2021. Detailed data collection was undertaken on 20 random cases, prospectively collected of women with different forms of diabetes but ensuring that one to two women with T1DM and T2DM were included in the cohort. Additionally, trainees were requested to include women who laboured on weekdays and weekends, days and night.

Data on maternal and neonatal characteristics [including birthweight, neonatal glucose level, admission to the neonatal intensive care unit (ICU) and indication] were collected. Information on deviations from local clinical guidelines was collected.

Detailed data were collected using the REDCap online data-collection platform hosted by the University of Nottingham between 1 November 2021 and 5 January 2022. The data-collection tool was developed by the study team and tested for both feasibility and usability by junior doctors working in Obstetrics and Gynaecology, via the UKARCOG network.

Instructions for participation and a description of the service evaluation were disseminated to UK obstetric units by the UKARCOG. UKARCOG employs a hub and spoke model of regional leads and specialist trainees working in obstetric units throughout the UK, with a nationwide reach, using this model.[21–23] Data were collected by UKARCOG-affiliated specialist trainees in Obstetrics and Gynaecology working within each unit submitting data.

Data analysis

For the purposes of this service evaluation, 'tight' glycaemic control was defined as women whose glucose control was maintained within the target range for that maternity unit. Permissive control was defined where control veered outside this target range, and the duration of the time outside target was recorded where possible.

Statistical analyses were conducted using Statistical Product and Service Solutions version 25 (IBM; Chicago, Illinois). Data were reported using descriptive statistics for quantitative data using frequencies and percentages for categorical data and either means [with standard deviations (SDs)] or medians (with interquartile range) for continuous data depending on the distribution.

The Kruskal–Wallis test was used to compare medians of variables that were not normally distributed between the three groups (T1DM, T2DM and GDM). Ordinal or nominal data were compared using chi-squared tests.

Results

To establish the number of women who experienced labour with different forms of diabetes, 17 participating obstetric units from across England, Scotland and Wales were able to provide information. Over an 8-week period, 824 women with diabetes experienced labour; of these, 92% (n = 759) had GDM, 4% (n = 34) had T1DM and 4% (n = 31) had T2DM.

Detailed data collection using the REDcap software programme included 594 women originating from 33 obstetric units with a further 30 data reports entered for units which were not named. This included 77 (13%) women with T1DM, 52 (9%) with T2DM and 458 (77%) with GDM. There were two other women with other forms of diabetes [Maturity onset diabetes in the young (MODY)] and five with this data missing.

Maternal characteristics

The maternal characteristics of the women included in the study are summarised in *Table 9*. Of the total population, 220 (37%) were primiparous, 176 (30%) had 1 previous child and 156 (26%) 2 or more children (missing data 42; 7%). Of the total population, 44 (7%) women had a history of a previous caesarean section, 318 (53%) had a history of previous vaginal birth and 237 (40%) did not.

TABLE 9 Maternal demographic characteristics

Demographic	Median (interquartile range)
Age	32 (28–36) years
Ethnicity	383 (65%) White British
	78 (13%) Asian
	17 (3%) Black
	6 (1%) Chinese
	69 (12%) other
	41 (7%) missing data
BMI	30.5 (25.5–35.3) kg/m^2
Parity	1 (0–2)
	Range 0–11
DM type	T1DM 77 (13%)
	T2DM 52 (9%)
	GDM 458 (77%)

BMI, body mass index.

Prior to the current pregnancy, 38 (73%) of women with T2DM were on metformin, with 8 using additional (15%) insulin. There were 2 (4%) on insulin alone leaving 12 (23%) on diet only. All women with T1DM were on insulin.

Of those with T1DM 91% (*n* = 70) and those with T2DM 98% (*n* = 51) had a HbA1c taken at the maternity booking appointment. Of those women with GDM, 161 (35%) had booked HbA1c sample (due to COVID-19 changes in testing methods for GDM in pregnancy). The median HbA1c was 51 (44–61) mmol/mol in T1DM, 48 (42–57) mmol/mol in T2DM and 35 (33–38) mmol/mol in GDM. There was a tendency for improvement in the HbA1c across gestation with the last documented HbA1c having a median of 44 (37–50), 44 (38–50) and 36 (33–39) with T1DM, T2DM and GDM, respectively.

United Kingdom NICE HbA1c target at conception is below 48 mmol/mol. This was achieved in 28 (36%) of T1DM and 24 (46%) of T2DM. Booking HbA1c over 86 mmol/mol was seen in two women with T1DM only. Pre-pregnancy complications are included in *Table 10*.

TABLE 10 Pre-pregnancy complications by diabetes type

	T1DM	T2DM
Retinopathy	17 (22%)	0
Nephropathy	0	0
Neuropathy	1	0
Hypertension	2	4
Peripheral vascular disease	0	0
Ischaemic heart disease	0	0
Stroke	0	0

In the group with GDM, the median gestation at diagnosis was 28 + 1 (25 + 3 to 31 + 1) weeks with a range 6 + 6 to 40 + 6 weeks. Two hundred and forty-eight (54%) had a glucose tolerance test (GTT). The median fasting glucose was 5.1 (4.6–5.7) mmol/l and the median 2-hour glucose was 8.3 (7.8–9.3) mmol/l.

Antenatal diabetes treatment

With T1DM, treatment of diabetes in the antenatal period was subcutaneous insulin in 52 cases (68%) and CSII (pump) in 25 (33%) of cases. One patient was also treated with metformin. For those with T2DM, 47 (90%) were treated with metformin and 41 (79%) with insulin as subcutaneous injections (there was no CSII use in this group). For those with GDM, 158 (34%) were treated with metformin alone, 51 (11%) with insulin alone and 62 (14%) with a combination of metformin and insulin. The remainder (n = 187; 41%) were treated by diet alone.

Antenatal complications

On comparing the different types of diabetes, a difference was found in the gestation of the last antenatal ultrasound: T1DM 36 + 3 (35 + 6 to 36 + 5) weeks, T2DM 36 + 2 (36 + 0 to 37 + 6) weeks, GDM 36 + 5 (36 + 0 to 37 + 6) weeks; $p < 0.001$. There was no difference in the sizes of the abdominal circumference (AC) of the babies, $p = 0.19$ (*Figure 11*).

The commonest fetal complication seen in the antenatal period was suspected macrosomia with a significant difference in incidence, ranging from 22% in GDM to 36% in T1DM ($p = 0.04$). There was also a significant difference between groups in the rate of retinopathy ($p < 0.001$). Other antenatal complications are listed in *Table 11*.

Labour characteristics

The median gestation at birth was significantly different between the groups ($p < 0.001$), with women with T1DM delivering at a median gestation of 38 + 0 weeks (37 + 4 to 38 + 2), T2DM at 38 + 2 weeks (37 + 4 to 38 + 5) and GDM at 38 + 6 weeks (38 + 1 to 39 + 4). There was a significant difference between groups in terms of onset of labour with 77%, 81% and 65% of women with T1DM, T2DM and GDM induced, respectively ($p = 0.003$). There was also a

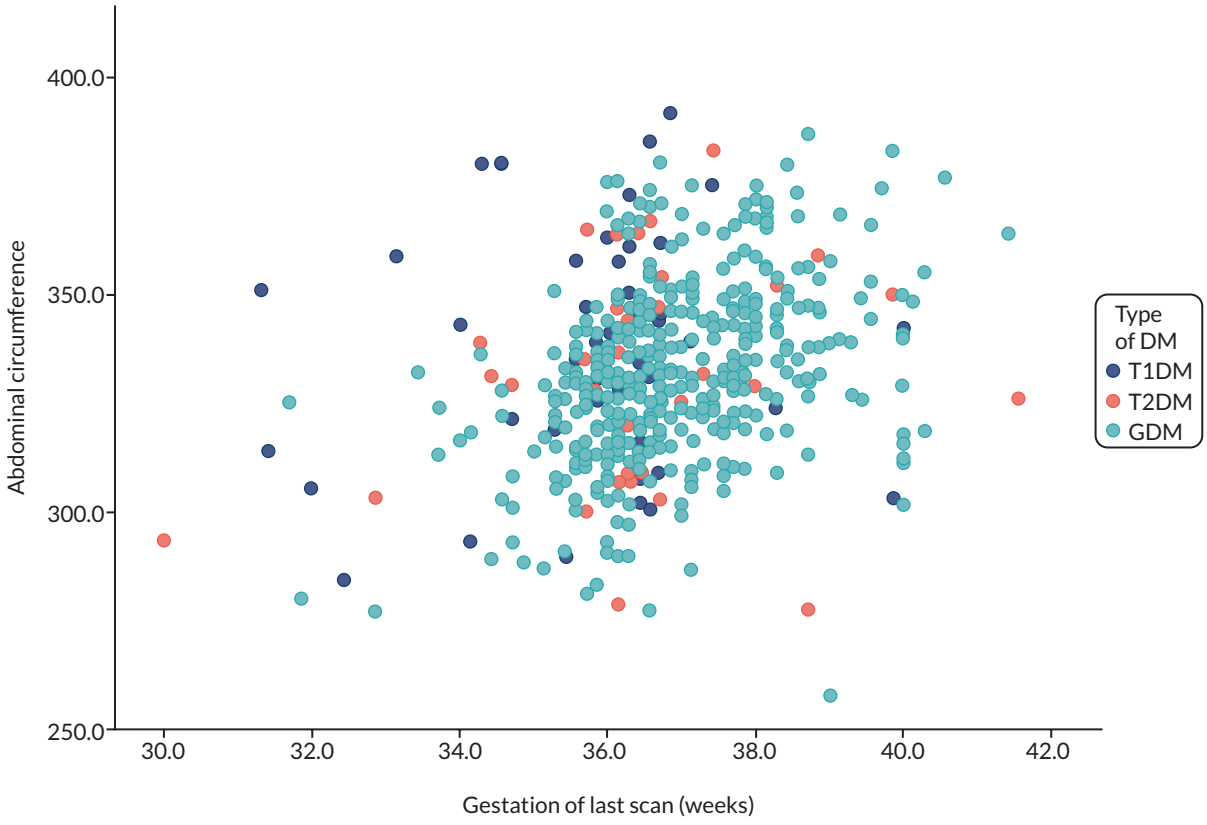

FIGURE 11 Scatterplot of AC plotted against gestation of last scan by type of DM.

TABLE 11 Antenatal fetal and maternal complications by diabetes type

Fetal complications	T1DM	T2DM	GDM
Suspected macrosomia	28 (36%)	15 (29%)	101 (22%)
Pre-eclampsia	4 (5%)	5 (10%)	13 (3%)
Small for gestational age baby	4 (5%)	1 (2%)	20 (4%)
Congenital anomaly	2 (3%)	1 (2%)	5 (1%)
Polyhydramnios	6 (8%)	4 (8%)	29 (6%)
Maternal complications			
Retinopathy	11 (14%)	1 (2%)	0
Nephropathy	1 (1%)	0	1
Neuropathy	1 (1%)	0	1
Hypertension	4 (5%)	5 (10%)	22 (5%)

significant difference in the mode of birth between the types of diabetes, with 32%, 48% and 65% of women achieving a normal vaginal birth in T1DM, T2DM and GDM, respectively ($p < 0.001$). Birthweight was also significantly different between the groups, with a median of 3.53 (3.12–3.82) kg, 3.16 (2.99–3.62) kg and 3.29 (3.04–3.63) kg in women with T1DM, T2DM and GDM, respectively ($p = 0.002$) (*Figure 12*).

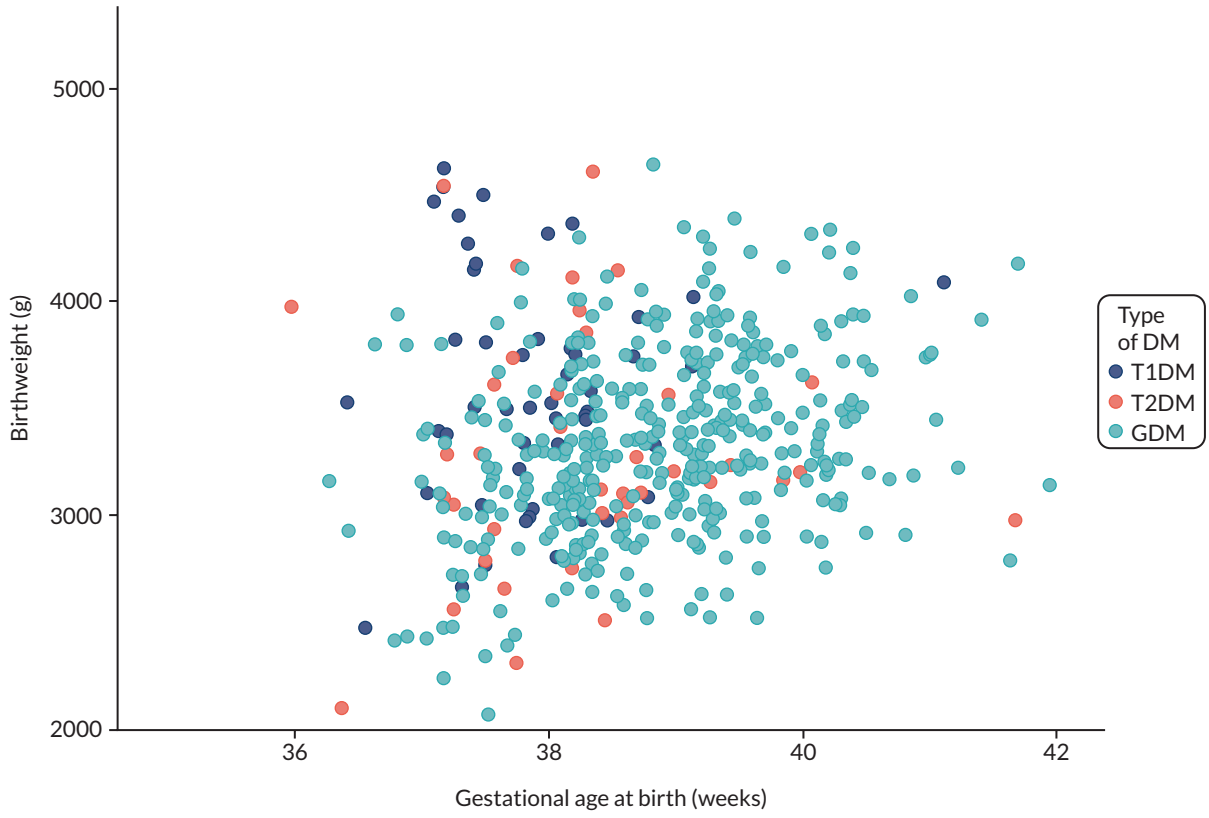

FIGURE 12 Scatterplot of birthweight plotted against gestational age at birth by type of DM.

TABLE 12 Maternal delivery complications by type of DM

	T1DM	T2DM	GDM
Shoulder dystocia	2 (2.6%)	0	9 (2.0%)
Third-/fourth-degree perineal tear	2 (2.6%)	2 (3.8%)	6 (1.3%)
Post partum haemorrhage requiring blood transfusion	4 (5.2%)	2 (3.8%)	13 (2.8%)

The median maternal stay of 2.8 (1.8–4.3) days in T1DM, 2.4 (1.7–3.3) days in T2DM and 1.8 (1.3–2.8) days in GDM was significantly different ($p < 0.001$). Maternal delivery complications were few (*Table 12*).

Maternal glucose control in labour

There were no significant differences between the first and subsequent glucose value with any form of diabetes with a median of 6.2 (5.4–7.6) mmol/l, 5.9 (5.0–6.9) mmol/l and 5.3 (4.6–6.2) mmol/l in T1DM, T2DM and GDM, respectively. These values were statistically significant between the diabetes type ($p < 0.001$). Only 7 women (9%) with T1DM, 7 women (14%) with T2DM and 34 (7%) of women with GDM had a glucose measurement noted within an hour of admission to Labour Suite (8% overall). Similarly, 10 (13%), 9 (17%) and 47 (10%) of women with T1DM, T2DM and GDM, respectively, had glucose measurements recorded within 2 hours of admission to Labour Suite (11% overall).

Glucose values of > 7.0 mmol/l on first testing occurred in 18 (32%) of T1DM, 8 (23%) of T2DM and 24 (8%) of GDM, respectively. The percentages for glucose > 8.0 mmol/l on first testing was 23%, 17% and 3%, respectively. Similarly, glucose < 4.0 mmol/l on first testing occurred in 1%, 2% and 7% of women with T1DM, T2DM and GDM, respectively.

Once testing commenced, repeat testing was undertaken within 1 hour in 34% ($n = 26$) or 2 hours in 52% ($n = 40$) for T1DM, 14% ($n = 7$) and 35% ($n = 18$) in T2DM, and 16% ($n = 74$) and 36% ($n = 163$) in GDM, respectively. Data for 4 hours were 58% ($n = 45$), 50% ($n = 26$) and 42% ($n = 194$) in T1DM, T2DM and GDM, respectively, with 45% overall re-tested within 4 hours. These data were poorly documented, with data missing in 34% of T1DM, 40% of T2DM and 54% of GDM cases. As a result of the fact that the numbers of women whose glucose-testing frequency was managed in line with their unit guidelines were so low, we were unable to compare outcomes based on adherence to these guidelines or compare results between numbers with tight and permissive control.

Women with T1DM using insulin via a CSII (pump) were allowed to continue its use in labour in 72% of cases (18/25). For those who discontinued the reason given was that this was the unit guideline in four cases and the patient was unwell and unable to manage their own diabetes control in three cases.

Of the 17 unit-level responses, only 8 (47%) reported using CGM/sensors in labour in women with T1DM, whereas they all used them in the antenatal period. Whereas 14 (82%) units used CSII (pump) in the antenatal period, this reduced to 65% for the intrapartum period.

Only in 29% of women with T1DM was oral intake in labour documented as permissible. This compared to 29% of women with T2DM and 36% of women with GDM. In terms of the documentation of oral intake in the notes (e.g. fluid balance sheet), this occurred in 49% of women with T1DM, 35% of women with T2DM and 44% of women with GDM.

Neonatal hypoglycaemia

There was a significant difference in the occurrence of both symptomatic and asymptomatic hypoglycaemia ($p < 0.001$), with women with T1DM having more complications than the other groups and the risk being lowest in those with GDM (*Table 13*).

In terms of testing for neonatal hypoglycaemia, the average age of the baby when the glucose was first checked was 4 hours (03 : 03 to 04 : 35) for T1DM, with an average glucose of 2.7 mmol/l (1.9–3.3). For T2DM, the median age was very similar at 4 hours 1 minute (2 : 38 to 5 : 46), with an average glucose of 2.7 (1.9–3.3), while in GDM values of

4 hours 8 minutes (3 : 24 to 5 : 09) and 3.1 (2.7–3.7) were observed. There was between 13% and 20% of missing data for these parameters. Values were statistically significant for the glucose between groups ($p < 0.001$) but not the time of testing ($p = 0.45$).

Due to the low numbers of mothers who had 'tight' control (i.e. glucose values within range according to the schedule of testing recommended in the maternity units), it was not possible to compare fetal outcomes to those mothers who had more relaxed control.

First neonatal glucose result and treatment

Focusing on the documented first glucose levels obtained from the neonate, there were more cases of neonatal hypoglycaemia than those recorded under the binary question of whether there was a documented neonatal hypoglycaemia. The numbers and percentages [and 95% confidence intervals (CIs)] of babies with the first glucose documented as < 2.6, < 2.5 or < 2.0 mmol/l shown together with the treatment recommendations resulting from these results (*Table 14* and *Figure 13*).

Neonatal complications

Focusing on other neonatal complications, there was a significant difference in the number of babies requiring neonatal unit admission between the groups ($p < 0.001$). Length of neonatal unit stay was similar between groups, with a median of 2.6 (1.6–5.1) days for T1DM, 4.4 (1.7–9.1) days for T2DM and 2.0 (0.8–4.9) days for GDM ($p = 0.55$) (*Table 15*).

Patient and public involvement

The study PPI advisory group were not directly involved in the conduct of work package 1d (the service evaluation of the care of women with diabetes in labour). They were indirectly involved in terms of their views on important aspects of their care in labour that they would like to be evaluated, for example, whether women were permitted to eat and drink in labour. The PPI advisory group were aware that the service evaluation was being performed by the study team and informed further study work packages.

TABLE 13 Neonatal hypoglycaemia and incidence of symptoms by type of DM

	T1DM	T2DM	GDM
Asymptomatic neonatal hypoglycaemia	14 (18%)	8 (15%)	41 (9%)
Symptomatic neonatal hypoglycaemia	8 (10%)	3 (6%)	5 (1%)
Jitteriness	6 (8%)	1	0
Irritability	4 (5%)	1	1
Lethargy	0	0	1
Abnormal feeding	1	0	1
Hypotonia/floppy	1	0	2
High-pitched cry	0	0	1
Tachypnoea/respiratory distress	2	2	5 (1%)
Tachycardia/bradycardia	0	0	0
Seizures	0	0	0
Apnoea	1	0	1
Hypothermia	0	0	0
Altered level of consciousness	0	0	0

TABLE 14 Neonatal hypoglycaemia incidence by differing definitions and interventions by type of diabetes

	T1DM (*n* = 59)	T2DM (*n* = 42)	GDM (*n* = 395)
Glucose < 2.6	28 (47%) (95% CI 34.3% to 60.9%)	19 (45%) (95% CI 29.8% to 61.3%)	65 (16%) (95% CI 12.9% to 20.4%)
Glucose < 2.5	27 (46%) (95% CI 32.7% to 59.2%)	17 (40%) (95% CI 25.6% to 56.7%)	55 (14%) (95% CI 10.7% to 17.8%)
Glucose < 2.0	16 (27%) (95% CI 16.4% to 40.3%)	13 (31%) (95% CI 17.6% to 47.1%)	16 (4%) (95% CI 2.3% to 6.5%)
Interventions			
Breast milk	13 (17%)	9 (17%)	44 (10%)
Infant formula	5 (7%)	6 (12%)	29 (6%)
Oral glucose supplement	10 (13%)	7 (14%)	10 (2%)
NG feeding	2 (3%)	0	3 (0.7%)
i.v. glucose	3 (4%)	2 (4%)	3 (0.7%)

i.v., intravenous; NG, nasogastric.

TABLE 15 Neonatal complications by type of diabetes

	T1DM	T2DM	GDM
Neonatal unit admission	21 (27%)	11 (21%)	43 (9%)
Neonatal hypothermia	4 (5%)	0	12 (3%)
Shoulder dystocia	2 (3%)	0	9 (2%)
Fracture	0	0	0
Hypoxic ischaemic encephalopathy	0	0	1
Active cooling of baby	0	0	0
Seizure	0	0	0
Respiratory distress requiring ventilation	1	1	9 (2%)
Respiratory distress requiring surfactant	1	0	2
Respiratory distress requiring neonatal unit admission	6 (8%)	5 (10%)	14 (3%)
Jaundice requiring phototherapy	15 (20%)	7 (14%)	17 (4%)
Congenital anomaly	1	0	6 (1%)
Early-onset neonatal sepsis	1	5 (10%)	14 (3%)
Local infection	1	0	0

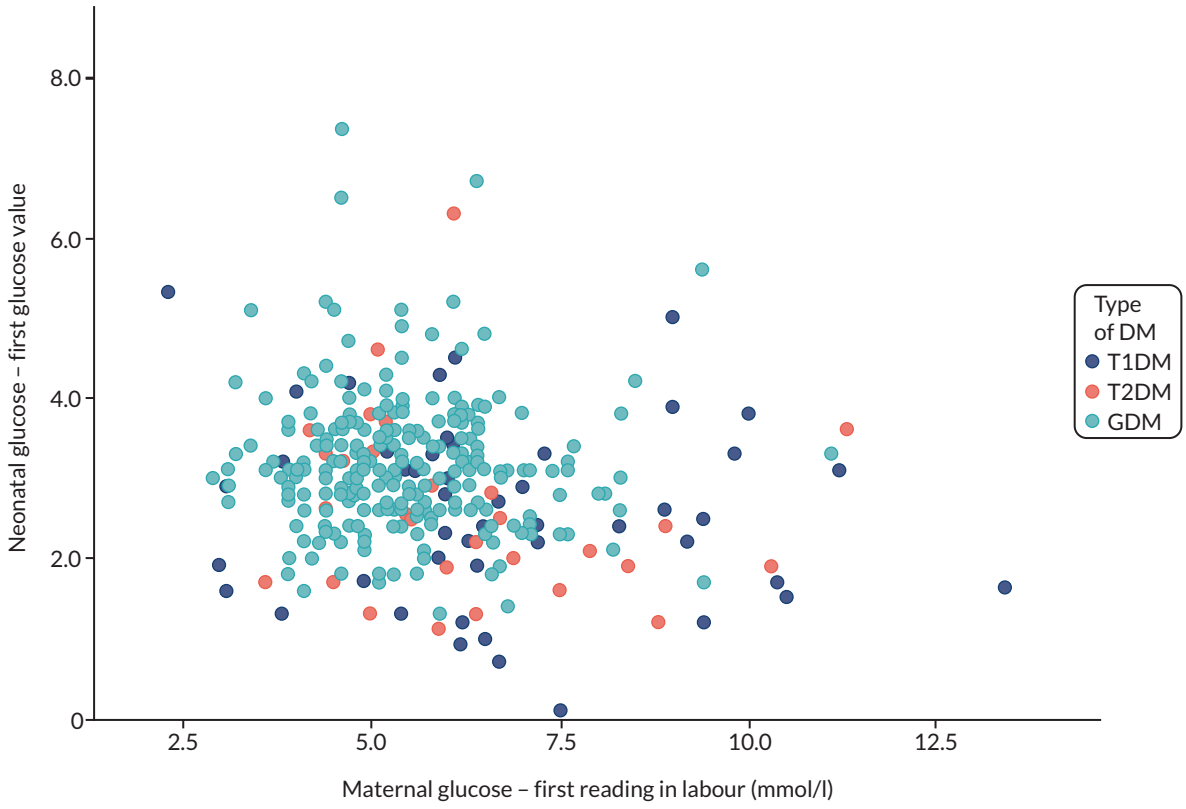

FIGURE 13 Scatterplot of neonatal first glucose value plotted against first maternal glucose reading in labour by type of DM.

Chapter 3 Delphi process and consensus-building

Aim

To reach consensus on the most important clinical components of a future trial of permissive versus intensive intrapartum glycaemic control (types of diabetes to be included, glucose levels, frequency of monitoring, outcomes), in pregnancies complicated by diabetes.

Methods: Delphi process

The previous work packages provided us with information as to which clinical components should be included in the Delphi survey. All available data from the preceding work packages were be used to inform the build of the Delphi process.

Three Delphi rounds were used to steer the groups to consensus, refining the list of components to be used in a trial. We documented the reasons for their decisions.

Panel

A range of expertise within the panel is considered important. The Delphi study surveyed individuals with an interest in the care of women with diabetes in labour. This included women who currently have/have had diabetes in pregnancy, midwives, obstetricians, neonatologists and endocrinologists.

Panel size and recruitment

There is currently no standard method for sample size calculation in Delphi processes, and thus a pragmatic approach was taken. Panel size in other projects has usually been guided by practicality, question scope and time available for analysis.[24] We attempted to recruit as large a panel as possible and encouraged individuals from each stakeholder group to participate. There was no limit to the number of respondents to the Delphi survey.

All groups were alerted to the opportunity to contribute to the Delphi survey through information posted on social media. Obstetricians were additionally invited using the BICS and UKARCOG networks. Neonatologists were identified and invited to participate via the BAPM membership; similarly, endocrinologists via the Association of British Clinical Diabetologists (ABCD) (www.abcd.care). The benefit of using this technique for selection of the panel is that it removes selection bias of an acquaintance with the researchers and, although the level of experience may be less than that from a handpicked panel, the number of responses received are likely to be higher.

Additionally, those who responded to the survey (work packages 1b and 1c) were asked for their permission to contact them again to participate in the Delphi survey. We considered that the individuals who took time to respond to the online survey were those who have demonstrated an interest in the subject and would be more likely to respond to the various rounds of questionnaires.

Anonymity of each panellist's response was maintained throughout the process.

Process

The Delphi survey was managed using the Core Outcome Measures in Effectiveness Trials Initiative Delphi Management software and completed online. The Delphi was designed to ensure that each round was concise and easy to complete

with minimal time commitment. An initial e-mail was sent to potential participants, stating that we were looking for individuals with relevant midwifery, obstetric, endocrine, neonatology, or personal lived experience of diabetes in labour. It contained a brief explanation of the study, emphasising the importance of completing all rounds. An estimate of the amount of time (10–15 minutes) to complete the questionnaires was included and a link to the Delphi survey.

The midwives, obstetricians and endocrinologists were asked to comment on all clinical components of the study and what they considered the most important maternal and neonatal outcomes for any RCT. The neonatologists and women were asked to consider only the maternal and neonatal outcomes, and these two groups are reported together.

Upon registration, participants were asked for their name, geographical location, their primary professional role and if applicable their year of clinical training. Participants' names and contact details were recorded so that personalised reminders to complete the survey could be sent. However, to maintain full anonymity following online registration, the software assigned a unique study identifier to each participant, which was linked to their survey responses but could not be traced to individual names.

It was anticipated that the survey would require three rounds for completion. Each round of the survey was planned to take around 2 weeks, allowing time for responses to be submitted and automated reminder e-mails to be sent to non-responders after 1 week. These reminders were generated automatically by the Delphi Manager software (COMET initiative, University of Liverpool, UK). To encourage participation, maximise response rates and minimise dropouts between rounds, participants who completed all the rounds of the survey were entered into a prize draw.

Round 1

Participants were asked to score questions focused on each of the following four components:

1. Which populations [T1DM/T2DM/GDM (diet)/GDM (on treatment)] require assessment of glucose control in labour?
2. Intensive control is usual in current practice (glucose target 4–7 mmol/l). What upper target would they be willing to recruit into/participate in any future study of more permissive levels, for example, 8, 10, 12 mmol/l? How often should we test glucose levels in those not on insulin?
3. What technologies should be studied in a trial both for monitoring, for example, standard finger prick, CGM/sensors, and treatment, for example, continuous VRIII (or sliding scale), CSII (or pumps), closed loop?
4. What maternal and neonatal outcomes are important to collect in a trial, for example, neonatal hypoglycaemia? What should be the primary outcome(s)?

Participants were asked to rank responses using the Grading of Recommendations Assessment Development and Evaluation scale, which suggests a Likert nine-point scale (1–9) to rank importance.[25] Scores of 7–9 denote outcomes of 'critical' importance, scores of 4–6 are 'important but not critical', and scores of 1–3 are deemed 'not important'. An 'unable to score' option (score 10) and a space to provide optional feedback on reasons for allocating scores were included.

For the first round, a list of outcomes derived from previous studies of intrapartum glycaemic control were included with participants able to suggest other important outcomes to be added to the list.

Analysis of round 1

Additional outcomes or clinical components suggested in round 1 were reviewed and coded by the study team to ensure they represent new outcomes/components. If there is uncertainty then the Delphi development team was consulted, and the collaborators as appropriate. For each outcome or component, scores were summarised using the mean and the number and percentage scoring as unable to score, 'not important', 'important but not critical' and 'critical' using the total number of responses as the denominator. All outcomes and components were carried forward to the

next round. Outcomes and components where all participants have scored 1–3 on the scale were not dropped between rounds, so participants had visibility of decisions for all components. New outcomes and components were added to the list for the next round if two or more participants suggested their inclusion.

Rounds 2 and 3

In rounds 2 and 3, each participant was presented with the number of respondents and distribution of scores for each outcome and component plus their own scores from round 1. They were asked to consider responses from the other members of the group and asked to re-score the outcomes and component considering this. Participants were asked to rate the outcomes and components using the nine-point scale used in round 1.

Analysis of round 2

The total number of participants invited to take part in round 2 was recorded. For each outcome and component, the number of participants who have scored the outcome and component and the distribution of scores were summarised. Any changes to scores were documented.

Analysis of round 3

Each outcome and component were classified as 'consensus in', 'consensus out' or 'no consensus' according to the classifications in *Table 16*. All 'consensus in' outcomes and components were discussed at the consensus meeting.

Definition of consensus

Table 16 describes the classification used to determine whether consensus was reached or not. Inclusion of an item in the subset to be discussed at the consensus meeting required agreement by most survey participants regarding the critical importance of the component, with only a minority considering it unimportant.

Ethical requirements

Individuals participating in the survey gave their details voluntarily. They were sent an introductory e-mail with information about the study including explicit details about what was involved and asked for their consent to participate. Participants were given the option to withdraw from the study at any time. This study was conducted entirely online and was consistent with standard practice in survey research; consent was assumed by agreement to participate and completion of online questionnaires.

TABLE 16 Definition of consensus

Consensus classification	Description	Definition
Consensus in	Consensus that a component should be included	70% or more participants scoring 7–9 and < 15% participants scoring 1–3
Consensus out	Consensus that the component should not be included	70% or more participants scoring 1–3 and < 15% of participants scoring 7–9
No consensus	Uncertainty about importance of the component	Anything else

Results

Data were collected for the three rounds of the Delphi survey between February 2022 and March 2022. Of the 150 participants who registered for the survey, 133 (20 obstetricians, 19 midwives, 5 endocrinologists, 4 neonatologists and 102 parents; 89%) completed round 1. There were 40 (8 obstetricians, 1 midwife, 2 endocrinologists, 1 neonatologist and 28 women; 27%) who completed round 2 and 23 (4 obstetricians, 2 endocrinologists, 1 neonatologist and 16 women; 15%) completed round 3. Stakeholder status was ignored throughout the Delphi survey process and respondents were considered a single panel. We had considered analysis of outcomes by stakeholder group, but insufficient numbers precluded this.

Population

Table 17 summarises the midwives, obstetricians, and endocrinologists round 3 results for which population (T1DM/T2DM/GDM) should be the priority for a RCT. There was consensus that all three populations should be included in a RCT.

Frequency of testing and technology

Table 18 summarises midwives, obstetricians and endocrinologists round 3 results for how often glucose levels should be tested by the different populations (T1DM/T2DM/GDM). For T1DM, there was consensus that 1 or 2 hourly testing should be considered for the trial. For T2DM and GDM, there was consensus that 2 hourly testing should be studied.

Table 19 summarises midwives, obstetricians and endocrinologists round 3 results for which technologies should be studied in the different populations (T1DM/T2DM/GDM) both for monitoring and for treatment. For T1DM, five different technologies reached consensus in: finger prick, VRIII, continuous flash/glucose monitoring (CGM), CSII (pump) and closed loops were close to the threshold value at 66%. For T2DM, two different technologies reached consensus in: finger prick and VRIII. For GDM, there was consensus that finger prick should be used.

Maternal outcomes

Midwives, obstetricians and endocrinologists

Twenty-two maternal outcomes were included in round 1. One new maternal outcome (percentage time glucose in target range) was added after round 1, following participant nominations. Twenty-three maternal outcomes were included in round 2. All 23 maternal outcomes were carried forward into round 3. Six maternal outcomes reached the criterion for consensus in at the end of round 3 (see *Table 20*) and were carried forward to the consensus meeting. *Table 21* describes the six maternal outcomes.

Women and neonatologists

Twenty-two maternal outcomes were included in round 1. One new maternal outcome (mothers' mobility in labour) was added after round 1, following participant nominations. Twenty-three maternal outcomes were included in round 2. All 23 maternal outcomes were carried forward into round 3. Ten maternal outcomes reached the criterion for consensus in at the end of round 3 (*Table 20*) and were carried forward to the consensus meeting. *Table 21* lists the 10 maternal outcomes.

TABLE 17 Summary of round 3 results for population of diabetes to be included in a future RCT

Type of diabetes	Round 3 mean score	*N* (%) participants scoring 7–9	*N* (%) participants scoring 1–3
GDM	7.5	5 (83)	0
T1DM	9	6 (100)	0
T2DM	9	6 (100)	0

TABLE 18 Round 3 scores for frequency of testing by different populations (T1DM, T2DM and GDM)

Testing for diabetes	T1DM			T2DM			GDM		
	Round 3 mean score	*N* (%) participants scoring 7–9	*N* (%) participants scoring 1–3	Round 3 mean score	*N* (%) participants scoring 7–9	*N* (%) participants scoring 1–3	Round 3 mean score	*N* (%) participants scoring 7–9	*N* (%) participants scoring 1–3
No testing in labour	1	0	6 (100%)	1	0	6 (100%)	1	0	6 (100%)
On admission and if normal no further testing required in labour	1	0	6 (100%)	1.5	0	5 (83%)	1	0	6 (100%)
Pre-meal glucose	1.7	0	5 (83%)	1.5	0	5 (83%)	1.8	0	5 (83%)
Post-meal glucose	2	0	5 (83%)	2.2	0	5 (83%)	2.3	0	4 (66%)
Hourly glucose	7.5	5 (83%)	0	6.5	4 (66%)	1 (16%)	4.2	1 (16%)	3 (50%)
2 hourly glucose	7	6 (100%)	0	7.2	5 (83%)	0	6.3	5 (83%)	0
4 hourly glucose	3.2	0	3 (50%)	3.2	1 (16%)	3 (50%)	3	1 (16%)	3 (50%)
Other; please specify via the feedback box	1	0	4 (100%) 2 scored '10'	1	0	5 (100%) 1 scored '10'	1	0	5 (100%) 1 scored '10'

TABLE 19 Round 3 scores for technology to be used for monitoring and treatment by different populations (T1DM, T2DM and GDM)

Technology	T1DM			T2DM			GDM		
	Round 3 mean score	*N* (%) participants scoring 7–9	*N* (%) participants scoring 1–3	Round 3 mean score	*N* (%) participants scoring 7–9	*N* (%) participants scoring 1–3	Round 3 mean score	*N* (%) participants scoring 7–9	*N* (%) participants scoring 1–3
Finger prick	8.6	6 (100%)	0	8.2	5 (83%)	0	8.3	6 (100%)	0
Continuous flash/ glucose-monitoring sensors	7.7	4 (66%)	0	6.2	3 (50%)	0	3.7	1 (16%)	3 (50%)
Continuous VRIII	8.5	5 (83%)	0	7.3	5 (83%)	0	6.7	4 (66%)	0
CSII (pump)	7.7	4 (66%)	0	3.5	1 (16%)	3 (50%	2.5	4 (66%)	0
Closed loops (integrated sensor and pump system)	7.3	4 (66%)	0	2.5	0	5 (83%)	1.7	0	6 (100%)

There was overlap in three of the maternal outcomes between the two groups (see *Table 21*); therefore 13 maternal outcomes were taken forward to the consensus meeting.

Neonatal outcomes

Midwives, obstetricians and endocrinologists

Twenty-one neonatal outcomes were included in round 1. All 21 neonatal outcomes were carried forward into round 3. Nine neonatal outcomes reached the criterion for consensus in at the end of round 3 (*Table 23*) and were carried forward to the consensus meeting. *Table 22* includes the nine neonatal outcomes.

TABLE 20 Round 3 scores for maternal outcomes by group (1) midwives, obstetricians and endocrinologists and (2) women and neonatologists

Maternal outcome	Midwives, obstetricians, endocrinologists			Women[a], neonatologists		
	Round 3 mean score	*N* (%) participants scoring 7–9	*N* (%) participants scoring 1–3	Round 3 mean score	*N* (%) participants scoring 7–9	*N* (%) participants scoring 1–3
Mode of birth	6.8	4 (66%)	0	8.5	13 (76%)	0
Reason for caesarean birth	7.2	3 (50%)	0	7.9	13 (76%)	0
Maternal admission to HDU/ICU	8.3	6 (100%)	0	8.1	17 (100%)	0
Maternal satisfaction	8.2	6 (100%)	0	8.5	17 (100%)	0
Estimated blood loss	6	2 (33%)	0	7.2	13 (76%)	1 (6%)
Third/fourth-degree perineal tear	6	2 (33%)	0	7.1	12 (71%)	1 (6%)
Post partum infection	6.7	3 (50%)	0	6.8	8 (47%)	0
Maternal food intake in labour	5.3	1 (16%)	1 (16%)	7.5	13 (76%)	1 (6%)
Maternal fluid intake in labour	5.2	2 (33%)	1 (16%)	7.5	13 (76%)	1 (6%)
Length of maternal hospitalisation	6.3	5 (83%)	1 (16%)	7.1	10 (59%)	1 (6%)
Adverse emotional status	5.7	2 (33%)	0	6.6	9 (53%)	3 (18%)
Anxiety	5.8	2 (33%)	0	6.5	8 (47%)	3 (18%)
Eating behaviour	4	0	1 (16%)	6.5	8 (47%)	1 (6%)
Mental health status	5.3	0	0	6.9	11 (65%)	1 (6%)
Postnatal depression	5.5	0	0	7.3	13 (76%)	1 (6%)
Quality of life	5.3	3 (50%)	0	6.4	8 (47%)	1 (6%)
Return to work after pregnancy	3.8	0	4 (66%)	3.7	2 (12%)	9 (53%)
Sleep quality	3.5	0	3 (50%)	4.4	3 (18%)	5 (29%)
Social support	3.8	0	3 (50%)	4.4	2 (12%)	4 (24%)
Breastfeeding initiation	6.7	5 (83%)	0	6.4	8 (47%)	2 (12%)
Breastfeeding at 1 month	6.7	5 (83%)	0	6.2	7 (42%)	2 (12%)
Maternal mortality	8.7	6 (100%)	0	8.5	16 (94%)	0
Percentage time glucose in target range	7	5 (83%)	0			
Mobility in labour				7.1	10 (59%)	0

HDU, high-dependency unit.
a Women who have previously given birth with diabetes or who are currently pregnant with diabetes.

Women and neonatologists

Twenty-two neonatal outcomes were included in round 1. All 22 neonatal outcomes were carried forward into round 3. Twelve neonatal outcomes reached the criterion for consensus in at the end of round 3 (see *Table 23*) and were carried forward to the consensus meeting. *Table 22* reports these 12 neonatal outcomes.

There was overlap in 5 of the neonatal outcomes between the 2 groups (see *Table 22*); therefore 16 neonatal outcomes were suggested for to the consensus meeting.

TABLE 21 Maternal outcomes reaching consensus in by group (1) midwives, obstetricians and endocrinologists and (2) women and neonatologists and a final combined list

Midwives, obstetricians, endocrinologists	Women, neonatologists	Combined final list
Maternal admission to HDU/ICU	Mode of birth	Mode of birth
Maternal satisfaction	Reason for caesarean birth	Reason for caesarean birth
Breastfeeding initiation	Maternal admission to HDU/ICU	Maternal admission to HDU/ICU
Breastfeeding at 1 month	Maternal satisfaction	Maternal satisfaction
Maternal mortality	Estimated blood loss	Estimated blood loss
Percentage time glucose in target range	Third/fourth-degree perineal tear	Third/fourth-degree perineal tear
	Maternal food intake in labour	Maternal food intake in labour
	Maternal fluid intake in labour	Maternal fluid intake in labour
	Postnatal depression	Postnatal depression
	Maternal mortality	Breastfeeding initiation
		Breastfeeding at 1 month
		Percentage time glucose in target range
		Maternal mortality

HDU, high-dependency unit.

TABLE 22 Neonatal outcomes reaching consensus in by group (1) midwives, obstetricians and endocrinologists and (2) women and neonatologists and a final combined list (overleaf)

Midwives, obstetricians, endocrinologists	Women, neonatologists	Combined final list
Stillbirth	Stillbirth	Stillbirth
Neonatal death (within 28 days of birth)	Neonatal death	Neonatal death
Neonatal hypoglycaemia	Neonatal hypoglycaemia	Neonatal hypoglycaemia
Seizure	Hypothermia	Hypothermia
Respiratory distress requiring ventilation	Shoulder dystocia	Shoulder dystocia
Respiratory distress requiring surfactant	Fractured skull	Fractured skull
Respiratory distress requiring admission to neonatal unit	Hypoxic ischaemic encephalopathy	Hypoxic ischaemic encephalopathy
Neonatal unit admission	Active therapeutic hypothermia (cooling) required	Active therapeutic hypothermia (cooling) required
Length of neonatal hospital stay	Early-onset neonatal sepsis	Early-onset neonatal sepsis
	Neonatal unit admission	Neonatal unit admission
	Transitional care	Transitional care
	Length of neonatal hospital stay	Length of neonatal hospital stay
		Seizure
		Respiratory distress requiring ventilation
		Respiratory distress requiring surfactant
		Respiratory distress requiring admission to neonatal unit

TABLE 23 Round 3 scores for neonatal outcomes by group (1) midwives, obstetricians and endocrinologists and (2) women and neonatologists

	Midwives, obstetricians, endocrinologists			Women[a], neonatologists		
Neonatal outcome	Round 3 mean score	*N* (%) participants scoring 7–9	*N* (%) participants scoring 1–3	Round 3 mean score	*N* (%) participants scoring 7–9	*N* (%) participants scoring 1–3
Stillbirth	8.3	6 (100%)	0	8.9	17 (100%)	0
Neonatal death (< 28 days)	8.5	6 (100%)	0	8.9	17 (100%)	0
Neonatal hypoglycaemia	8.6	6 (100%)	0	8.5	17 (100%)	0
Hypothermia	5.2	3 (50%)	2 (33%)	7.1	12 (71%)	1 (6%)
Shoulder dystocia	7	5 (83%)	1 (16%)	7.8	12 (71%)	0
Fractured clavicle	5.3	1 (16%)	1 (16%)	7.1	11 (65%)	2
Fractured long bone	4.8	0	1 (16%)	7.0	10 (59%)	2
Fractured skull	5.3	1 (16%)	1 (16%)	7.4	15 (88%)	0
Hypoxic ischaemic encephalopathy (grade specified)	7	5 (83%)	1 (16%)	8.0	13 (76%)	0
Active therapeutic hypothermia (cooling) required	6	4 (66%)	2 (33%)	7.8	13 (76%)	1 (6%)
Seizure	8.2	5 (83%)	0	7.2	11 (65%)	1 (6%)
Respiratory distress requiring ventilation	8.3	6 (100%)	0	7.5	11 (65%)	0
Respiratory distress requiring surfactant	8	6 (100%)	0	7.2	9 (53%)	0
Respiratory distress requiring admission to neonatal unit	8.3	5 (83%)	0	7.4	10 (59%)	0
Jaundice requiring phototherapy or other treatment	7.7	4 (66%)	0	7.2	10 (59%)	0
Brachial plexus injury	6	3 (50%)	1 (16%)	7.4	11 (65%)	0
Early-onset neonatal sepsis	7.2	4 (66%)	0	7.5	12 (71%)	0
Neonatal unit admission	7.8	5 (83%)	0	7.9	13 (76%)	0
Transitional care	6.8	4 (66%)	0	7.5	12 (71%)	1 (6%)
Length of neonatal hospital stay	7.8	5 (83%)	0	7.5	12 (71%)	1 (6%)
2-year neurodevelopmental outcomes	7.5	3 (50%)	0	7.4	10 (59%)	0

a Women who have previously given birth with diabetes or who are currently pregnant with diabetes.

Consensus workshop

Prior to the meeting, the core members of the study team reviewed all the components of the Delphi and considered the appropriateness of different variables to be included within the consensus meeting. A decision was made that all components in the Delphi would be voted upon:

1. priority of type of diabetes to be included in any future trial
2. frequency of testing with each type of diabetes
3. upper target range for glucose in the permissive arm

4. technology to be included in any future trial (for both testing glucose and treatment of hyperglycaemia)
5. outcome(s) considered important as either primary or composite primary outcome.

In terms of outcome, the study team considered if ones that reached 'consensus in' would be potentially altered by glycaemic control in labour or not (a future RCT would not be exploring glycaemic control in the antenatal or postnatal period). For neonatal outcomes, it was considered that respiratory distress requiring admission to the neonatal unit, requiring surfactant or requiring ventilation would be more reflective of practices of individual neonatal units rather than glycaemic control in labour (admission policies to neonatal units vary, some units have a low threshold for surfactant use and others rarely use it). It was also agreed that while seizures were an important possible consequence on neonatal hypoglycaemia, this outcome would be rare and unfeasible to run as a primary outcome. It was agreed that the outcomes that were dropped from the outcomes that were voted on would be included in a list of secondary outcomes.

An online consensus-building workshop was held via Microsoft Teams (Microsoft Corporation, Redmond, WA, USA) on the 25 April 2022. Individuals who completed the online surveys were asked if they wanted to participate within the consensus workshop, and it was additionally publicised via social media. The first half of the meeting comprised a summary of results from work packages 1 and 2 being explained to the participants to enable them to use this information to inform their views on the voting in the second half of the meeting (see *Appendix 4*). Participants were provided with the opportunity to express their views, hear different perspectives and think more widely about which components are most suitable at each point at which voting was required. The aim of the meeting was to use the information available primarily from the Delphi survey to establish consensus on important aspects of any future trial. Participants were requested to vote on any aspect they felt comfortable with and were able to choose not to vote if they felt the question was outside of this (e.g. not all neonatologists voted on maternal outcomes).

Results

A total of 30 participants attended the meeting. In order to ensure that representation was diverse, attendees included obstetricians (7), endocrinologists (4), neonatologists (3), midwives (6), trialists/methodologists (2), health economists (2), health psychologist (1) and women with lived experienced of labour with diabetes through the inclusion of members of the PPI advisory group and women who completed the Delphi survey (5).

All types of diabetes were equally prioritised by the respondents.

Testing frequency and upper target level

Participants were asked to vote on whether testing should be 1 or 2 hourly with each diabetes type. The majority of respondents (77%) felt that the testing in T1DM should be hourly. For T2DM, there were equal responses for 1 hourly (50%) and 2 hourly (50%) testing. For GDM, the majority selected 2 hourly (85%).

A discussion around the upper target glucose level to use in a future trial was opened prior to voting. It was agreed that usual care should be that recommended by NICE or JBDS. The recent pragmatic change (rather than as a result of any new evidence) in the JBDS guideline, to increase the upper target to 8 mmol/l to avoid maternal hypoglycaemia, was highlighted. Participants realised that the decision for the upper limit was a balance between there being a clear separation between randomised groups in terms of their glucose values and the upper target being considered 'too high' for either women or clinicians to be in equipoise regarding participation. The endocrinologists expressed that maternal health glucose levels of between 4 and 11 mmol/l would not be a concern, but one respondent explained that any glucose above 10 mmol/l would activate a pathway where women should be tested for ketones in the antenatal period. Neonatologists felt that overall there was insufficient evidence that a glucose of < 11 mmol/l would be more detrimental to the baby than a glucose of < 8 mmol/l. There was also the realisation that an upper target means that at times values would overshoot this value which made some people anxious about its risks to the participant. One endocrinologist suggested that an upper target of 10 mmol/l would be an appropriate compromise as this is the upper target range often recommended in the post partum period.[3]

Following this discussion, the permissive target of 4–10 mmol/l achieved most votes, followed by 4–11 mmol/l and, lastly, 4–9 mmol/l for all forms of diabetes (*Figure 14*).

Technology

Results for technology used for testing suggested that there was support for using CGM/sensors with all forms of diabetes in labour and that CSII (pump) were supported for T1DM only, with a VRIII being the treatment consensus for T2DM and GDM. Respondents were allowed to choose up to five types of technology when voting (*Figure 15*).

Maternal and neonatal outcomes

These are summarised in *Table 24*, with the most popular neonatal outcome being neonatal hypoglycaemia and maternal outcome being mode of birth. Respondents were asked to vote for the outcomes as either a primary outcome or a component of a composite primary outcome and were allowed to select multiple outcomes.

Patient and public involvement

Members of the PPI advisory group were invited to participate in both the Delphi study and the consensus meeting. Women were also offered the opportunity to participate in the Delphi study itself so that their views were considered alongside those of HCPs. The PPI advisory group supported the study team in the use of appropriate language so that although similar outcomes were considered by both women and HCP, the wording was such that women would be able to understand, and technical terms were avoided or explained. They also supported the study team in deciding if appropriate outcomes were taken forward to the consensus meeting.

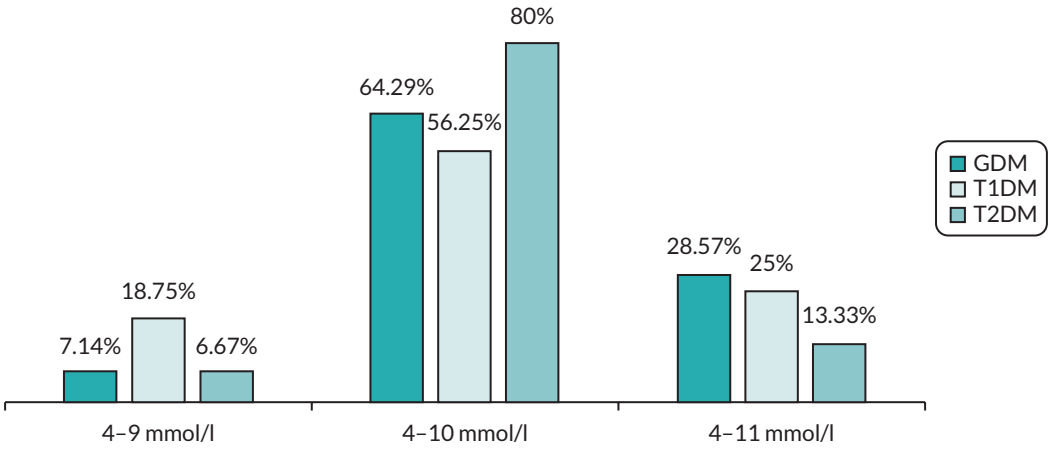

FIGURE 14 Bar chart of consensus meeting voting results of which permissive target should be used in a trial for all types of DM (*y*-axis: percentages of total votes for each glycaemic target).

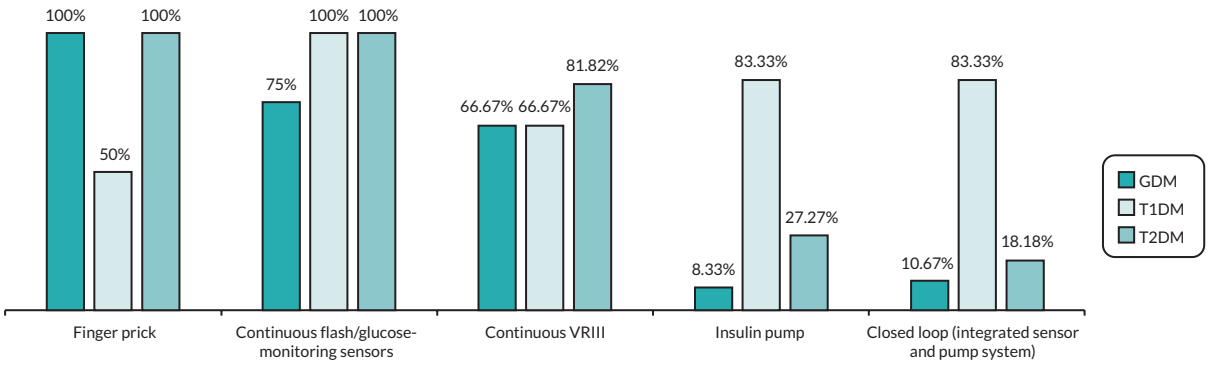

FIGURE 15 Bar chart of consensus meeting voting results of which technology respondents thought should be used for monitoring blood glucose in a trial for all types of DM (*y*-axis: percentages of total votes for each technology).

TABLE 24 Voting results showing the percentage of each outcome to be included in a trial for all types of DM

Maternal outcome	Voting result (%)	Neonatal outcome	Voting result (%)
Mode of birth	94	Stillbirth	63
Reason for caesarean birth	47	Neonatal death	69
Maternal admission to HDU/ICU	65	Neonatal hypoglycaemia	94
Maternal satisfaction	59	Hypothermia	31
Estimated blood loss	18	Shoulder dystocia	69
Third/fourth-degree perineal tear	29	Fractured skull	19
Maternal food intake in labour	47	Hypoxic ischaemic encephalopathy	44
Maternal fluid intake in labour	35	Active therapeutic hypothermia (requiring cooling)	38
Postnatal depression	29	Early-onset neonatal sepsis	19
Breastfeeding initiation	53	Neonatal unit admission	81
Breastfeeding at 1 month	35	Transitional care	38
Percentage time glucose in target range	47	Length of neonatal hospital stay	69
Maternal mortality	65		

HDU, high-dependency unit.

The consensus meeting also included PPI representation, with two members of the study PPI advisory group and other women who completed the Delphi survey attending. Co-applicant Plachcinski also attended the consensus meeting to ensure wider PPI views were represented. The members who attended voted on the items discussed in the consensus meeting where they felt they had knowledge or experience and offered feedback on the trial design components discussed by the study team.

Chapter 4 Design of a randomised clinical trial

Aims

1. Through assimilation of information collected in earlier work packages, to design a clinical trial of intensive versus permissive intrapartum glycaemic control for women with diabetes in labour.
2. To determine the components of a health economic assessment in a future clinical trial.

Methods

Following the stakeholder consensus meeting, three trial design meetings were held to discuss all elements of a future trial in this area. These meetings were attended by members of the research team with clinical and trial design and conduct expertise. One meeting was held in person, with the subsequent two being held virtually, via Microsoft Teams. Subsequent discussions and decisions were on ad hoc meetings and/or e-mail.

The first meeting, held on 26 April 2022, focused on the most appropriate trial design to use, the PICO (population, intervention, control, outcomes), how best to approach potential participants and sample size estimations. Data gathered in previous work packages and the subsequent consensus-building meeting informed discussions and decision-making in these meetings.

Meeting 2 was held on 16 May 2022. The focus of this meeting was to discuss, in further detail, the proposed outcomes for the trial.

A third meeting was held on 20 June 2022. This meeting specifically focused on the health economic component of a future trial, and therefore only involved a subgroup of the research team (NJ, KW, EM, SP, ES).

The discussions and, importantly, decisions taken during these meetings will now be described in the *Results* section.

Results

Meeting 1

Trial design

Due to the substantial differences in the intervention (permissive or tight control of blood glucose levels during labour), in women with pre-existing diabetes (T1DM or T2DM) or GDM, it was agreed that two clinical trials were needed. For efficiency, and to ensure adequate statistical power for the different types of diabetes, a master protocol design[27,28] was chosen. As the aim was to evaluate whether a less intense (i.e. permissive) monitoring strategy was not inferior to the current tight control monitoring strategy, a non-inferiority design was chosen. For feasibility of recruitment and generalisability of participants, the trial would need to be multicentre. A cluster RCT was briefly considered but not taken further as this would reduce choice for women and be fraught with other complications which could potentially introduce bias.

The final proposed design is a multicentre, non-inferiority RCT, using a master protocol design.

Population, intervention, comparison, outcomes

Population

For inclusiveness, all pregnant women with any type of diabetes, who are delivering in a consultant-led maternity unit in a participating recruiting site in the UK aiming for a vaginal birth, are offered the opportunity to participate in the trial. Given the nature of the trial design, using a master protocol design, women will be split into subgroups:

- women with pre-existing diabetes (T1DM or T2DM)
- women with GDM, stratified at the time of randomisation by:
    - GDM, treated with insulin antenatally
    - GDM, treated with oral hypoglycaemics or diet alone antenatally.

The decision to group T1DM and T2DM together was taken as we felt that a similar glucose target level should be aimed for in both groups and the numbers of women planning vaginal births would be similar (see *Discussion* for further information). This would make the trial more feasible to run at sites, as a three-arm parallel design trial would be much more complicated.

Intervention (permissive control)

Significant discussion took place about the length of time between monitoring blood glucose during labour, and the target levels. Permissive control could be interpreted in terms of increasing the intervals between tests or having a wider target range of values. From the perspective of patient safety, all women on insulin administered either via CSII (pump) or VRIII would require monitoring of their blood glucose 1 hourly, so considering increasing the frequency of testing would only be applicable to those not on insulin (i.e. women with GDM with capillary glucose within the target range). In order therefore to design a trial with a master protocol it was deemed more suitable for the intervention to be a wider target range, and this could be consistent for all forms of diabetes. Two different monitoring strategies will be used, depending upon the type of diabetes:

- For women with pre-existing diabetes (T1DM or T2DM), hourly blood glucose monitoring during labour, with the intention to control blood glucose levels between 4 and 10 mmol/l.
- For women with GDM (irrespective of antenatal treatment type), blood glucose monitoring will be every 2–4 hours during labour, with the intention to control blood glucose levels between 4 and 10 mmol/l.
    - Women start on a VRIII, when their blood glucose is above the upper target range, will then follow their unit guidelines on frequency of testing, which is likely to be 1 hourly.

Control (tight control)

For women randomised to the control arm in a future clinical trial, the following monitoring strategy will be used:

- For women with pre-existing diabetes (T1DM or T2DM), hourly blood glucose monitoring during labour, with the intention to control blood glucose levels between 4 and 8 mmol/l.
- For women with GDM (irrespective of antenatal treatment type), blood glucose monitoring every 2–4 hours during labour, with the intention to control blood glucose levels between 4 and 8 mmol/l.
    - Women start on a VRIII, when their blood glucose is above the upper target range, will then follow their unit guidelines on frequency of testing, which is likely to be 1 hourly.

Figure 16 illustrates the population, intervention and control arms of the proposed randomised trial.

Outcomes

During the first trial design meeting, it was agreed, based upon previous work packages, that the most appropriate primary outcome would be neonatal hypoglycaemia. Further detailed discussions about this outcome were held during trial design meeting 2 a month later.

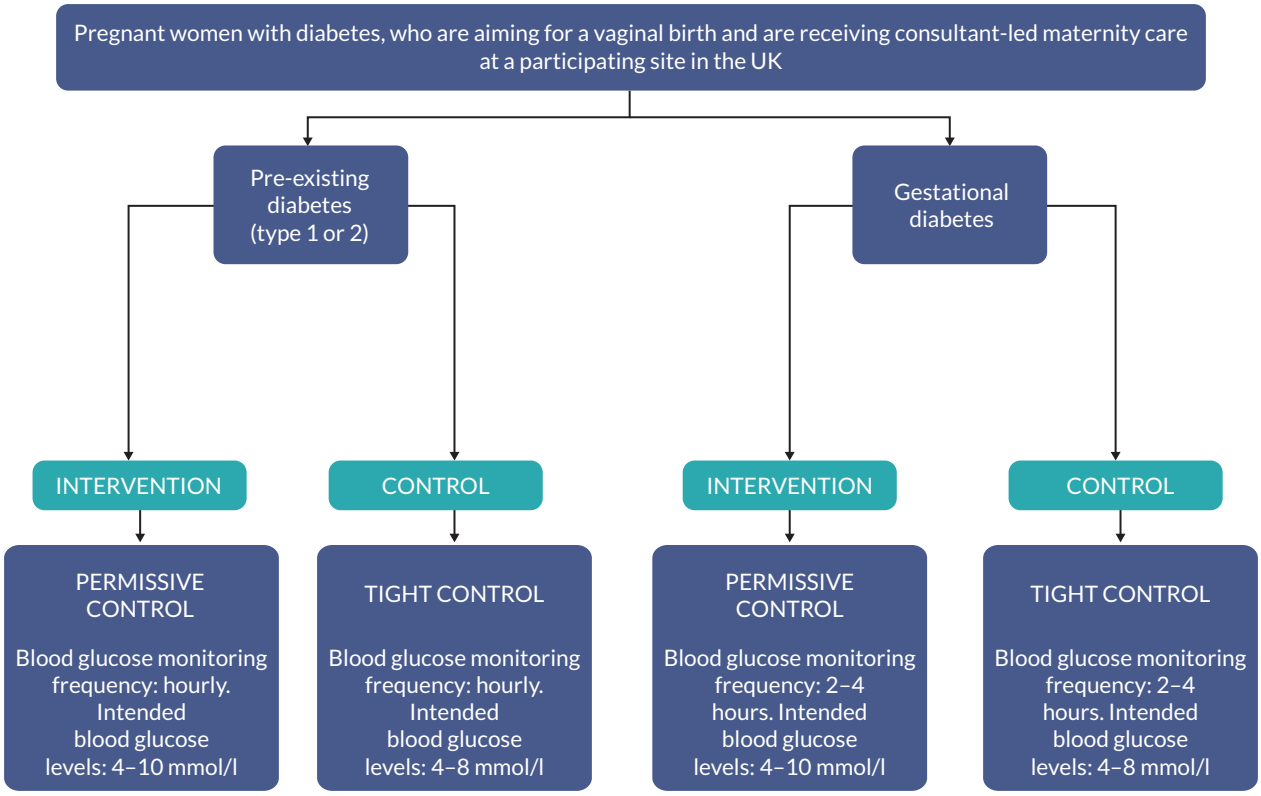

FIGURE 16 Schematic representation of proposed trial design.

During the first trial design meeting, discussions were held about potential secondary outcomes. It was agreed that outcomes that scored 'consensus in' within the Delphi survey and consensus meeting would be included as secondary outcomes unless there was a strong rationale for not including them. These were further discussed at the subsequent meeting. All agreed, and with strong PPI input, that maternal satisfaction would be a key secondary outcome. It was agreed this would be measured by the Childbirth Experience Questionnaire Version 2,[29] in addition to the Edinburgh Postnatal Depression questionnaire[30] and a bespoke study specific questionnaire, to summarise satisfaction related to diabetes-associated intervention and care that would not be captured through the other questionnaires. It was noted that some of the secondary outcomes, such as maternal mortality and hypoxic ischaemic encephalopathy, would be very rare but were important to collect for safety.

Though it did not score highly in the Delphi survey and subsequent consensus meeting, the research team agreed it would be important to include longer-term outcomes to assess whether permissive glucose control may have a longer-term effect on the baby. It was agreed that neurodevelopmental outcomes, collected via parent-completed questionnaire at around the time of the child's second birthday, would be important specifically to assess cognitive, visual and spatial neurodevelopment since these can be associated with severe neonatal hypoglycaemia.

Approaching potential participants

Important aspects of trial conduct, including how to approach women, method and timing of consent and randomisation, were discussed during this meeting. The following decisions were agreed, and subsequently ratified by the PPI advisory group:

- Women will be approached between 28+0 and 36+6 weeks' gestation, during a routine hospital antenatal clinic appointment, by a research midwife or other member of the research team. Plans for vaginal delivery or caesarean birth are usually made before 37 weeks' gestation, the point at which delivery is routinely recommended in women with uncomplicated T1DM or T2DM. Similarly, 28 weeks is a common point in time at which women attend the hospital antenatal clinic, coinciding with a scan to estimate the fetal size. An early time point to approach and discuss the study would then allow women adequate time to consider if they wanted to participate. Plans for birth are unlikely to be formulated by clinicians or women prior to this point in time.

- An information leaflet and a link to a short video will be given to the woman, explaining that the trial is taking place and the research midwife will ask if she would be interested in participating.
- Written, informed consent will be taken at least 1 week before the woman's expected due or planned delivery date.
- One week before the expected delivery or planned delivery date, the research midwife, or other member of the research team, will randomise the woman using an electronic randomisation system, and contact the woman (contact method to previously be determined between woman and research midwife) to inform her of her blood glucose-monitoring strategy during labour.

Sample size considerations

The sample sizes for the two component trials would be determined separately to ensure adequate power to answer the research question for the two groups of women (pre-existing diabetes or GDM). The following considerations were debated during the first trial design meeting, ahead of subsequent discussions and decision-making at future meetings:

- The most appropriate non-inferiority margin and whether this would be defined based upon the relative risk or difference in risk. It was agreed that PPI input into the non-inferiority margin would be important.
- Adherence with the randomised blood glucose-monitoring strategies (permissive and tight control), and to consider whether sample size adjustments may be required, depending upon expected adherence rate.
- Ability to capture primary outcome data, and whether sample size adjustments may be required depending upon estimated missing primary outcome rate.
- Comparative analysis would be planned based on both the intention-to-treat population and the per-protocol population to assess the robustness of the results, given the possible increased risk of falsely claiming non-inferiority (type I error) in the intention-to-treat population.

Meeting 2

Meeting 2 focused entirely on discussions about the primary and secondary outcomes for a proposed future trial.

The agreed primary outcome is:

- The number of infants with hypoglycaemia, as defined as any blood glucose level < 2.6 mmol/l (confirmed by a laboratory-analysed blood glucose test), in the first 24 hours of life, or until blood glucose monitoring is no longer required as per the BAPM framework,[3] whichever is sooner.

Neonatal hypoglycaemia was reported to be the most popular neonatal outcome within the womens' survey ('low blood glucose in my baby' scoring higher than 'low blood glucose that made my baby unwell' – *Figure 10*). While this may initially be counterintuitive, our understanding of women's beliefs is that neonatal hypoglycaemia (any definition) increases the risk of admission of the baby to the neonatal unit, mother–baby separation, impacts upon feeding of baby and increases anxiety for the family.

In terms of the Delphi survey, the most popular neonatal outcome was neonatal hypoglycaemia. During voting on outcomes, it was not specified whether this should be symptomatic hypoglycaemia or based on a biochemical level.

While the preferred primary outcome is, technically, a biochemical marker, the understanding of 'low blood sugar' is easily comprehensible to most non-experts. The link between having low blood sugar and becoming unwell, needing treatment and being at risk of long-term problems is not unfamiliar to people outside of medicine due to the general awareness about hypoglycaemia, especially among a group that has been exposed to these concepts in the course of their own care as people with diabetes during pregnancy.

Discussions during the trial planning meeting included that the diagnosis of 'symptomatic neonatal hypoglycaemia' was subjective with many of the symptoms being non-specific. It is much less common than biochemical hypoglycaemia, and the sample sizes for any trial would need to be significantly larger (more than double the sample size with the non-inferiority margin requiring modification), and, in the view of the study team, this was unfeasible and challenging to standardise. Additionally, babies born with biochemical but asymptomatic hypoglycaemia are at risk of future harm to the baby. For example, there are concerns at the long-term impact on neurodevelopment.

The feasibility and practicalities of confirmation of the blood glucose level by a laboratory-analysed sample were discussed. It was agreed that this would be the preferred gold standard, rather than using a blood gas analyser. However, some practical issues were identified including that in some hospitals confirmatory laboratory samples are not sent. Women may also not wish such additional blood sample to be performed, as treatment would be commenced on the result from the blood gas analyser rather than waiting for the results of a subsequent laboratory sample, to reduce the potential morbidity for the baby. There is also potential for discrepancy in the results between the blood gas analyser glucose level and the laboratory-confirmed test. In addition, the timing of the test may vary, as indicated by the audit data. Finally, since few hospital guidelines specifically indicate that a laboratory sample should be taken, this would result in additional costs and complications for participating sites. These issues require further exploration at the time of seeking funding for a future trial.

Table 25 lists all proposed secondary outcome measures and the proposed data-collection methods. The following data-collection time points were agreed:

- baseline
- immediately after birth
- before maternal discharge from hospital
- while infant is receiving neonatal care in hospital
- 6 weeks after birth
- 6 months after birth
- 12 months after birth
- 24 months after birth.

Parent-completed questionnaires would be sent by e-mail, with a link to an online questionnaire, or post if that were preferred.

Neurodevelopment of the child was considered an important secondary outcome for the study, looking at the longer-term outcome for the child. The Children with HYpoglycaemia and their Later Development (CHYLD) study reported 2-year outcomes of infants born at 35 weeks or more with risk factors for neonatal hypoglycaemia (using the definition of neonatal hypoglycaemia of < 2.6 mmol/l), some of whose mothers had diabetes.[31] It found very little difference in the mean glucose concentration (0.2 mmol/l) between those who did and did not have adverse outcomes, raising the possibility that the risk factors were more important than the glucose level itself. Large-scale follow-up studies of babies born to mothers with diabetes where their intrapartum control is well documented is lacking.

The proposal for a future trial is to include an assessment at 24 months and ask for consent to approach for longer-term follow-up should this be funded separately.

Follow-up of the CHYLD study at 4.5 years did demonstrate a dose-dependent increased risk of visual–motor function (integration between visual perception and motor skills) and poor executive functioning but not neurosensory impairment, with the highest risk in babies exposed to severe, recurrent, or clinically undetected hypoglycaemia.[32] Longer-term follow-up of any future trial should thus be considered, although difficult to justify within the main trial as this would delay reporting of results.

Between meetings 1 and 2, indications of likely sample sizes of the proposed trial were circulated to the team to support discussions about the feasibility of the trial in the two different populations. Assumptions about the percentage of babies with neonatal hypoglycaemia in the tight control group were based around the UKARCOG audit where around 50% of babies in mothers with T1DM or T2DM diabetes and 20% with GDM had neonatal hypoglycaemia (based on a first glucose value of < 2.6 mmol/l). The statistician selected differing non-inferiority margins as examples. Sample size estimates were based on a one-sided 2.5% significance level and assumed that the actual percentage of babies who develop hypoglycaemia is the same in the permissive and tight control groups. *Tables 26* and *27* give the information presented to the team for the pre-existing diabetes trial and the GDM trial with the non-inferiority margin based on the difference in risk. In the meeting, the team acknowledged that the proposed trials would need to be large

TABLE 25 Proposed secondary outcome measures with the proposed data-collection methods

Outcome	How data will be collected	Additional notes
Maternal satisfaction	• Childbirth Experience questionnaire • Edinburgh Postnatal Depression questionnaire • Study-specific questionnaire administered by research nurse/midwife, postdelivery, before discharge home	One questionnaire for completion which includes various components
Maternal mortality	Research nurse/midwife to record in electronic clinical research form (eCRF)	
Maternal admission to critical care	Research nurse/midwife to record in eCRF	High-dependency or ICU
Breastfeeding initiation and subsequent feeding	• Research nurse/midwife to record in eCRF (i.e. whether BF initiated) • 6-week questionnaire (online/postal) to include breastfeeding questions • 6-month questionnaire (online/postal) to include breastfeeding questions • 12-month questionnaire (online/postal) to include breastfeeding questions	
Mode of delivery	Research nurse/midwife to record in eCRF	If mode of birth is caesarean section, reason to be recorded in eCRF
Maternal food and fluid during labour	Research nurse/midwife administered questionnaire, shortly after birth	To record hunger/thirst levels, whether offered food/fluids. No need to capture specific volumes of fluid/food
Symptomatic neonatal hypoglycaemia	Research nurse/midwife to record symptoms relating to hypoglycaemia in eCRF	Symptom list to be determined at a later date
Length of neonatal unit admission	Admitted for neonatal care (yes/no) and admission/discharge date to be recorded in eCRF by research nurse/midwife	
Neonatal mortality	Research nurse/midwife to record in eCRF	
Infant outcome	Live or stillbirth to be recorded in eCRF by research nurse/midwife	
Hypothermia	Research nurse/midwife to record in eCRF	To be agreed length of time to record – any episode of < 36.5 °C
Hypoxic ischaemic encephalopathy	Research nurse/midwife to record in eCRF	
Active therapeutic hypothermia, where cooling is required	Research nurse/midwife to record in eCRF	
Maternal and neonatal adverse events	To be determined, but list likely to include: Infants: shoulder dystocia, fractured skull Mother: hypoglycaemia requiring secondary assistance	
Neurodevelopment at 2 years	24-month questionnaire (online/postal)	To be agreed (PARCA-R/ASQ)

ASQ, Ages and Stages Questionnaire; BF, breastfeeding; PARCA-R, Parent Report of Children's Abilities – Revised.

but that it would be feasible to recruit such numbers in a reasonable time frame, given the number of women who have diabetes in pregnancy annually in the UK. The team agreed to put together an infographic to use in the qualitative interviews with information about the potential pros and cons of permissive and tight control and taking these into account what increase in neonatal hypoglycaemia levels women would accept for permissive control in labour compared to tight control to inform a non-inferiority margin for any future trial.

TABLE 26 Indications of sample size required for pre-existing diabetes trial with non-inferiority margin of 3%, 5% or 10%

Percentage with hypoglycaemia in tight control group	Non-inferiority margin (difference in % with hypoglycaemia)	Sample size for analysis for 90% power	Sample size for analysis for 80% power
45%	3%	11,692	8768
50%	3%	11,808	8854
55%	3%	11,692	8768
45%	5%	4242	3188
50%	5%	4284	3220
55%	5%	4242	3188
45%	10%	1080	818
50%	10%	1092	826
55%	10%	1080	818

TABLE 27 Indications of sample size required for GDM trial with non-inferiority margin of 3%, 5% or 10%

Percentage with hypoglycaemia in tight control group	Non-inferiority margin (difference in % with hypoglycaemia)	Sample size for analysis for 90% power	Sample size for analysis for 80% power
15%	3%	6088	4582
20%	3%	7606	5714
25%	3%	8890	6674
15%	5%	2224	1682
20%	5%	2770	2090
25%	5%	3232	2436
15%	10%	578	438
20%	10%	712	540
25%	10%	828	630

The percentage of women likely to have higher blood glucose values which would be managed differently using the permissive strategy should be considered when setting the non-inferiority margin, as the percentage of babies with hypoglycaemia in mothers whose glucose values stay in the range 4–8 mmol/l will be similar to that in the tight control group. There are limited data on the percentage of women whose blood glucose values are > 8 mmol/l during labour, given that treatment has been recommended for most women when they have a glucose value of > 7 mmol/l until very recently. In the national audit, 32% of women with T1DM and 23% of women with T2DM had glucose values of > 7 mmol/l on first testing, and 26% of women with GDM with blood glucose values recorded had at least one values > 7 mmol/l. Based on this, *Table 28* (pre-existing diabetes) and *Table 29* (GDM) present the overall percentage of babies that would be observed with neonatal hypoglycaemia in the permissive control group according to the percentage of babies with hypoglycaemia whose mother's blood glucose levels run between 8 and 10 mmol/l during labour assuming that:

- 45% of babies in mothers with pre-existing diabetes have hypoglycaemia and
- 15% of babies in mothers with GDM have hypoglycaemia

if their mother's blood glucose levels are controlled between 4 and 8 mmol/l during labour.

Information such as presented in *Tables 28* and *29* could be used to inform the overall non-inferiority margin for the main trial. For example, in the pre-existing diabetes trial based on *Table 28*, if an increase from 45% of babies having hypoglycaemia where their mother's blood glucose levels are controlled between 4 and 8 mmol/l during labour to 55% of babies where their mother's blood glucose levels are controlled between 8 and 10 mmol/l is considered acceptable, then the overall non-inferiority margin would need to be 3%.

TABLE 28 Hypoglycaemia rates expected in permissive control group in pre-existing diabetes trial

Percentage of babies with hypoglycaemia in permissive control group where maternal blood glucose levels run between 8 and 10 mmol/l during labour[a] (%)	Overall percentage of babies observed with hypoglycaemia in permissive control group[b] (%)
47	45.6
50	46.5
55	48
60	49.5
70	52.5
80	55.5

a Assuming that 30% of women will be maintained between 8 and 10 mmol/l during labour in the permissive control group.
b Assuming that 45% of babies have hypoglycaemia when their mother's blood glucose levels are controlled between 4 and 8 mmol/l during labour.

TABLE 29 Hypoglycaemia rates expected in permissive control group in GDM trial

Percentage of babies with hypoglycaemia in permissive control group where maternal blood glucose levels run between 8 and 10 mmol/l during labour[a] (%)	Overall percentage of babies observed with hypoglycaemia in permissive control group[b] (%)
20	16.25
25	17.5
30	18.75
35	20
40	21.25
50	23.75
60	26.25

a Assuming that 25% of women will be maintained between 8 and 10 mmol/l during labour in the permissive control group.
b Assuming that 15% of babies have hypoglycaemia where their mother's blood glucose levels are controlled between 4 and 8 mmol/l during labour.

Meeting 3

Meeting 3 focused entirely on the health economic component of a future trial.

Feasibility for the design of the economic evaluation

Aim

The overall aim of the health economic component of the GILD was to provide early evidence on the economic aspects of glycaemic control in labour and an assessment of the best possible ways to estimate and express cost-effectiveness within a larger subsequent trial.

Economic evaluation perspective and time horizon

The economic evaluation would be conducted from a health system perspective and consequently only direct costs to the NHS would need to be included. The time horizon would primarily mirror the duration of trial follow-up, identified for women randomised at the start of their care in labour and completed at 6 weeks postnatal care, irrespective of whether the mother or baby are at home or hospital. If higher-level care following the birth was required for either the mother or the baby, or both, this would be included in the economic evaluation.

Methods

The broader scope and design for the economic evaluation was developed during May and June 2022.

The methodological approach included:

1. an early assessment of the economic costs associated with GILD
2. an assessment of the broader resource use and health-related quality outcomes associated with GILD
3. identification of appropriate sources of unit costs for potential resource consequences and an assessment of how much primary costing research will be required for the main study
4. identification of available routine health and social data sources that could be used to complement and validate self-reported resource utilisation data
5. an assessment of the best possible way of expressing cost-effectiveness for mothers and infants separately and a composite measure for cost-effectiveness for a mother–infant dyad.[33]

The approach for identifying, measuring and valuing resource use for the within-trial analysis, the associated data-collection strategy, and identification of appropriate unit costs was developed across the months of June–November 2022. Research meetings comprised the GILD research clinicians, PPI representatives and the health economists.

In an iterative process, the list of variables to be collected in a subsequent trial were defined across three categories proposed as secondary outcomes process outcomes, and birth characteristics. This list was used this to inform the framework for the data-collection approach. It was decided that due to likely differences in intrapartum care practices and service configuration by participating hospitals and in the NHS more broadly, data collection would primarily be undertaken through a detailed electronic clinical research form (eCRF) to be completed by the trial's research midwives.

Economic costs associated with GILD

An economic evaluation embedded into a future trial should aim to estimate the broader resource use of delivering the intervention and should include of all of the 'downstream' resource use and costs generated across the trial's lifespan. Resource use should be identified for all women receiving intrapartum care in hospital from study randomisation until the primary endpoint, which is planned to be at 6 weeks post partum. This approach also provides an opportunity to explore the additional care the mother and her baby are likely to receive in the community following discharge from hospital.

An assessment of the broader resource use and health-related quality outcomes associated with GILD

Identification and measurement of resource use

Table 30 presents the resource use items identified to inform the economic costs of the intervention, and the proposed methods of documentation and measurement. Data would be collected from primary sources, either directly captured in eCRFs or from hospital administrative systems. eCRFs would be designed to be completed by the attending or research midwife at the time of each labour episode. In addition, maternal and neonatal morbidity forms would be completed during or after maternal or neonatal discharge.

Table 30 presents the intrapartum and postbirth resource use categories identified for the mother and baby, from randomisation until hospital discharge. These categories include resource use items specific to the trial's research

TABLE 30 Intrapartum and postbirth resource use identified for the mother and baby, from randomisation until hospital discharge

Mother or baby	Category of resource use	Specific data to be captured	Mode of data capture
Mother	Blood glucose tests	Number of capillary blood glucose tests Number of venous blood glucose test	eCRF
	<the intervention> • Lower: administration of glucose gel (glucogel) to gum • Administration of 10% dextrose i.v. • Lower: glucagon intramuscular • High: sliding scale insulin titrating rate		eCRF
	Diagnostic tests and procedures	Number of ultrasound scans Number of EEGs Number of MRIs Number of Echos Number of ECGs Number of CT scans Number of X-rays List of any other diagnostic tests, procedures or reviews carried out	eCRF
	Intrapartum clinical care – staffing by grade	Intrapartum activity, staffing levels, and related resource use	eCRF
	Mode of delivery	Birth with no intervention Birth assisted with ventouse or forceps caesarean section	Hospital Data System and/or electronic healthcare record database, and/or research midwife
	Length of stay by hospital (original or transfer) by level of care[a]	Intensive care High dependency Critical care Postnatal care	Hospital Data System and/or electronic healthcare record database, and/or research midwife
	Surgical procedures	All surgeries	Hospital Data System and/or electronic healthcare record database, and/or research midwife
	Mode of transport (if transferred)	Air ambulance Road	Hospital Data System and/or electronic healthcare record database, and/or research midwife
	Death	Post-mortem carried out Hospital Coroner's office unknown	Hospital Data System and/or electronic healthcare record database, and/or research midwife
Baby	Blood glucose tests	Number of capillary blood glucose tests Number of venous blood glucose test	eCRF
	Diagnostic tests and procedures	Number of ultrasound scans Number of EEGs Number of MRIs Number of Echos Number of ECGs Number of CT scans Number of X-rays List of any other diagnostic tests/procedures/ reviews carried out	eCRF
	Clinical care – staffing by grade (if separate to the mother)	Postbirth activity, staffing levels, and related resource use	eCRF

TABLE 30 Intrapartum and postbirth resource use identified for the mother and baby, from randomisation until hospital discharge (*continued*)

Mother or baby	Category of resource use	Specific data to be captured	Mode of data capture
	Length of stay by hospital (own or transfer) by level of care[a]	Intensive care High-dependency unit Special care General paediatric ward	Hospital Data System and/or electronic healthcare record database, and/or research midwife
	Surgical procedures		Hospital Data System and/or electronic healthcare record database, and/or research midwife
	Mode of transport (if transferred)	Air ambulance Road	Hospital Data System and/or electronic healthcare record database, and/or research midwife
	Death	Post-mortem carried out Hospital Coroner's office Unknown	and/or electronic healthcare record database, and/or research midwife

ECG, electrocardiogram; EEG, electroencephalogram; i.v., intravenous; MRI, magnetic resonance imaging.
a BAPM Categories of Care 2011.

objectives, such as numbers of glucose tests, and generic resource use associated with perinatal events, such as diagnostic tests and mode of birth.

In a broader discussion of the table above, it was identified that there may be additional resource use items or activities that will influence costs and require consideration.

The trial may consider providing a Libre device to all women, and the approach to apportioning costs for the Libre device will change depending on its intended use. In the first instance, if employed for the trial's research purposes only; that is for universal monitoring of all women, or where limited to documenting target glucose measurements, then it will accrue as a research cost. If instead, it is viewed as a potential tool for glucose monitoring to be introduced into the NHS, then the full acquisition cost of the Libre devices should be included as part of the intrapartum cost data to be collected in *Table 30*.

Capillary testing may be used to diagnose neonatal hypoglycaemia, with additional venous (blood glucose) test samples required for verification. Venous tests are sent to clinical chemistry laboratories for analysis, and the additional tests imposed by the trial will likely impact on the laboratories' service capacity. Estimating the impact of additional testing for hypoglycaemia was out of scope for this research, but a rigorous costing approach should be considered for the trial. This will require primary mixed-methods data collection, to include formative interviews with laboratory managers and follow-up surveys with all clinical chemistry services in the trial. Data collection will need to consider current test-response capacity and the potential service reconfiguration that would be required to accommodate a greater demand for venous tests, and a cost estimation of the expanded service. The estimation of service model costs can be split into two components, which when combined will provide an estimate for comprehensive service costs resembling the format of service costs within the Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care compendium.[34] Direct service costs include the operational and overhead costs of running the service. Additional staffing costs would include, for example, total wages to deliver services, direct contact, management, supervision, total salary on-costs, training and if relevant, travel costs.

Serious adverse events are not included in the table because they are very rare. Diabetic ketoacidosis may cause an obstetric emergency or admission to high dependency or intensive care, although frequent monitoring means this is likely to be avoided. Mothers with pre-existing diabetes and glucose levels that are difficult to manage may require a caesarean section and this would be documented by mode of birth.

If the baby struggles with early feeding, then the baby will likely be admitted to the neonatal unit. Any neonatal admission and stay will also likely extend the duration of the postnatal admission for the mother.

Care pathways

Differences in the frequency and nature of intrapartum monitoring activities for the management of glycaemic control by midwives may affect staff to patient ratios. A pragmatic trial design will accommodate the use of pre-existing hospital management protocols; variability in intrapartum ratios of staff to patient time will likely be influenced by hospital protocols and procedures, will impact on resource use and thus costs. An example of variability due to differences in hospital policy is the changeable definition of 'critical care'. It is defined in some hospitals by a patient's location (ward), and in other hospitals by the intensity of nursing care irrespective of ward, and thus a mother may receive a version of critical care while still on the labour ward. Variation in staffing care between the participating sites would need to be assessed to identify the generalisability of the cost parameters. A working document similar to a labour care audit could capture the generalisability and variability in the management of glycaemic control, or related events through interviews with a sample of maternity ward managers. In each scenario, the respondent would be asked to describe the 'standard procedures' that would be undertaken for specific labour events and, where possible, the typical ratios of 'staff to mother' care. Scenarios will then be varied between the least and the most complex to include a description of the associated change in activity, staffing levels, and related resource use. Prior research designs developed by the researchers[35] suggest that each interview would be approximately one and a half hours of structured time plus an additional hour of discussion and clarification. The interviews could be recorded and transcribed to inform proportional staff costs.

Resource use identified for the mother and baby, from posthospital discharge until 6 weeks post partum

Table 31 (overleaf) shows the resource use items identified for the mother and baby between discharge from hospital and 6 weeks post partum.

Table 31 identifies resource use items from hospital discharge to 6 weeks post partum that can inform costs by trial arm for the mother and baby. This includes all hospital admissions for the mother and baby, by date of admission, ward type, reason for admission and duration of stay. Outpatient consultations can be estimated via numbers of contacts by type of health care. Medication costs would be estimated by multiplying the unit cost of the medication by its dosage and number of courses. For the sample of patients providing self-report data, this would likely best be captured through online or postal questionnaires; however, most of the data required to estimate costs could be sourced from linked electronic healthcare record databases.

TABLE 31 Posthospital discharge resource use identified for the mother and baby

Mother or baby	Category of resource use	Specific data to be captured	Mode of data capture
Mother	Hospital admissions – inpatient	>Date of admission >Type of ward >Reason for admission >Number of nights Surgery type if applicable	Linked electronic healthcare record databases
	Types of health care – outpatient community	>Types of health care >Number of contacts GP appointments Practice nurse appointments Community nurse appointments Hospital community counselling Hospital accident and emergency Department Hospital outpatient clinic appointments Other	Online or postal questionnaire

TABLE 31 Posthospital discharge resource use identified for the mother and baby (*continued*)

Mother or baby	Category of resource use	Specific data to be captured	Mode of data capture
		Medications *Type of medication>Number of courses>Name of medication* Antibiotics Pain killers Antidepressants Contraception Other	Online or postal questionnaire
Baby	Baby's admission to hospital	*>Date of admission* *>Type of ward* *>Reasons for admission* *>Number of nights type of ward* > ICU/HDU/special care baby unit/General Ward/Other	Linked electronic healthcare record databases
	Additional health care in the Community	*>Type of Health care* *>Number of contacts* GP appointments Practice nurse appointments Health visitor Contacts Community nurse appointments Community paediatrician appointments Physiotherapy appointments Hospital accident and emergency appointments Hospital outpatients clinic appointments Other	Online or postal questionnaire
	Prescription inhalers	*>Number of months prescribed*	Online or postal questionnaire
	Baby's use of other medicines and drugs	*>Type of medication* *>Number of courses* *>Name of medication* Antibiotics Steroid/tablets Other	Online or postal questionnaire
	Feeding	>Breast milk or put the baby to the breast, even if only once >Baby ever been prescribed formula milk	Online or postal questionnaire

GP, general practitioner; HDU, high-dependency unit.

Availability of routine-linked data sets to support the collection of resource use data

It is anticipated that the trial research nurses/midwives will collect the majority of hospital data for the trial. Identifiers of women receiving care during the study could be entered into a bespoke, secure database. Irrespective, linked electronic healthcare record databases can support the identification, measurement and valuation of resource use. Routine databases can provide a rich source of information for both resource use and clinical outcomes, without relying on records from patients or study participants.[26] Information extraction from such sources is therefore extensively conducted as part of clinical trials today. This section explores research considerations around the use of routine data collection for a definitive trial.

Using routine data for economic evaluations

There are several advantages of using routine data in a future trial-based economic evaluation. Linkage with routine data can provide information about the medical history of patients, when self-reported questionnaires provide insufficient information. Routine-linked data can additionally be used for modelling parameters of costs where an economic analysis starts after patient or participant follow-up is completed. Thus, routine data can be used to inform long-term epidemiological models of disease or health status progression.

Routine data can also be used to validate and complement resource use data from the trial data-collection instruments. This enables researchers to collect a broader set of retrospective or prospective data items than identified in the health economic questionnaires completed by trial participants, especially where supplementing incomplete or missing resource use information.[26]

Based on the advantages of using routine-linked data and in view of the data that might be required to inform the incremental cost-effectiveness for a unit of change in neonatal developmental outcome at 2 years post partum, a future trial-based economic evaluation of GILD may consider extracting key resource use items from a variety of maternal and neonatal data sets.

Potential data providers and their data sets

Table 32 summarises potential data sources of interest for a future trial, to inform resource use data for longer-term follow-up. Identifiers that include the NHS number and date of birth could be sent to the relevant data providers to request data extraction for the trial population. These are NHS Digital for the Maternity Services Data Set (MSDS), Hospital Episode Statistics (HES) and the Office for National Statistics (ONS), the National Neonatal Research Database (NNRD) and Clevermed for BadgerNet Maternity and Neonatal data sets.

The MSDS is a patient-level data set capturing maternity care activity for a mother and baby(s), from the point of the first booking appointment until mother and baby(s) are discharged from maternity services.[36]

BadgerNet UK is another patient-level data set that collects data for more than 180 sites in the UK and categorises data into a shorter clinical summary version, which reports pregnancy and labour delivery details and includes admission and discharge details. The extended data set collects variables that include trend monitoring from nursing observations, timing of staff shift handovers, and baby diaries.[37]

The NNRD maintains clinical data captured during treatment and care, on all admissions to NHS neonatal units, with around 1 million babies and 10 million days of care included. Neonatal units in England, Isle of Man, Scotland and Wales submit data through electronic patient record systems.[38]

Hospital Episode Statistics is a database containing details of all presentations at accident and emergency, inpatient and day case admissions and appointments at outpatients departments in NHS hospitals in England. HES data cover a wide range of information about patients admitted to NHS hospitals in England (e.g. protected characteristics of the patient including age, gender, race and ethnicity, geographical information on their location, medical information regarding diagnoses and types of admission and discharge). HES data, hypothetically, should include all secondary care attendances in England. Devolved country equivalents are available for Scotland, Wales and Northern Ireland.[39]

The ONS provides data for live births, as well as stillbirths, family composition, life expectancy and deaths.[40]

Data received from each data provider could be safely stored and processed and linked, and the researchers would be granted remote access to perform analyses.

Timelines for accessing data

One of the main challenges of using routine data is the time it takes to apply and receive approval for access. One example is that this research team previously experienced more than a year's delay in accessing hospital data from NHS Digital.[41] The length of time to access routine data can exceed expectations as the application approvals often rely on other parts of the research process, such as ethics approvals and other requirements (e.g. legal approvals), for data linkage. Management of the trial to facilitate completeness of data and timeliness of data for analysis will need to be considered within the constraints of the data access process.

TABLE 32 Linked electronic healthcare record databases to support the identification and measurement of resource use

Database	Resource use variables identified in the data dictionary
Maternity Services Data Set	Labour and delivery Labour or delivery onset method code: start date (mother labour and delivery hospital provider spell) Admission method code: (mother labour and delivery hospital provider spell) Discharge date: (mother post labour and delivery hospital provider spell) Discharge time: (mother post labour and delivery hospital provider spell) Discharge: method code: (mother post delivery hospital provider spell) Care activity (labour and delivery) Clinical contact Duration of care activity Baby's demographics and birth details Pregnancy outcome Person death date (baby) Discharge date (baby post delivery hospital provider spell) Neonatal admission <All> Hospital provider spell Admission method code [Hospital discharge date (hospital discharge time) (hospital provider spell)] Ward stay <All>
Badgernet Data Set	Baby episode index Episode type admit time date time (local) Discharge time date time (local) Neonatal intensive care Admission reason Transfer: Transfer timing: transfer hospital: transfer date Growth and discharge Medical diagnostic services Surgery Chronic care Extra-corporeal membrane oxygenation Other Death/discharge: Died within 12 hours Discharge NNU: discharge destination postnatal ward/other ward: Discharge destination hospital name Discharge feeding tube Discharge treatment Death cause Choices withdrawal of care Congenital malformation Inpatient admission: Level 1 care Level 2 care Level 3 care Normal care level Surgery: Major surgery Surgery details Discharge: Discharge time Discharge status

continued

TABLE 32 Linked electronic healthcare record databases to support the identification and measurement of resource use (*continued*)

Database	Resource use variables identified in the data dictionary
	Critical care: Start date Critical care start time Critical care discharge date Critical care discharge time
NNRD (Categories of care)	Neonatal unit episodes Demographics and birth information (baby) Labour and delivery Admission details Discharge details General information Respiratory Cardiovascular Gastrointestinal Blood transfusions Neurology Ophthalmology Fluids and feeding Infections Jaundice Medication Abdominal X-rays Retinopathy of prematurity screening Cranial ultrasound scan Biochemical screening Augmented period
HES (Categories of care)	Maternity Clinical care Admissions; period of care Psychiatric care Discharge care Neonatal care Critical care by level

Valuation of resource use – identification of sources for unit costs

Intrapartum and postbirth resource use identified for the mother and baby, from randomisation until hospital discharge

A combination of primary and secondary sources could be employed for identifying sources of unit costs depending on the availability of reliable data.

Table 33 presents the sources for unit costs for intrapartum and postbirth care identified for the mother and baby, from randomisation until hospital discharge, and *Table 34* presents the sources for unit costs for the mother and baby in the community post birth.

TABLE 33 Sources for unit costs for intrapartum and postbirth care identified for the mother and baby, from randomisation until hospital discharge

Mother or baby	Category of resource use	Specific data to be captured	Unit cost (£, 2021)	Metric	Source of unit cost
Mother	Blood glucose tests	Number of capillary blood glucose tests Number of venous blood glucose test	–	Per test	Primary data required from trial clinical chemistry laboratories
	Diagnostic tests and procedures	>Number of ultrasound scans >Number of MRIs >Number of ECHOs >Number of CT scans >Number of other diagnostics	52.45 37.82 86.78 32.41 64.62	Per ultrasound Per MRI Per ECHO Per CT scan Per diagnostic image	National Schedule of NHS Costs – Year 2019–20 www.england.nhs.uk/publication/2019–20-national-cost-collection-data-publication/ IMAGING, row 69 DIAGNOSTIC IMAGING row 9 DIAGNOSTIC IMAGING row 15 DIAGNOSTIC IMAGING row 6 DIAGNOSTIC IMAGING row 32
	Intrapartum clinical care – staffing by grade	Intrapartum activity, staffing levels, and related resource use	51	Per hour	Jones K, Burns A. *Unit Costs of Health and Social Care 2021*. Canterbury: Personal Social Services Research Unit, University of Kent; 2021. Band 6, hospital-based nursing/midwifery Page 138, section 13 hospital-based nurses www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/#sections
	Mode of delivery	Birth with no intervention Birth assisted with ventouse or forceps caesarean section	1707.54 1812.75 1898.30	Per birth Per birth Per birth	Normal Delivery with CC Score 0 Normal Delivery with CC Score 1 Normal Delivery with CC Score 2 + NON ELECTIVE SHORT STAY, rows 1793–5 National Schedule of NHS Costs – Year 2019–20 www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/
	Length of stay by hospital (original or transfer) by level of care*	Intensive care High dependency Critical care Postnatal care	2729.24 2388.26 2171.74 653.34	Per day/episode Per day/episode Per day/episode Per day/episode	CRITICAL CARE CCU1XC02Z row 74Adult Critical Care– obstetric CRITICAL CARE CCU1XC02Z row 63Adult Critical Care– obstetric CRITICAL CARE CCU1XC02Z row 64 Adult Critical Care– obstetric NON ELECTIVE SHORT STAY Postnatal CC Score 0–1 row 1791
	Surgical procedures	All surgeries	Example 1421.17	Example per procedure	NZ27Z Postnatal Procedures row 1680 www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ DAY CASE

continued

TABLE 33 Sources for unit costs for intrapartum and postbirth care identified for the mother and baby, from randomisation until hospital discharge (*continued*)

Mother or baby	Category of resource use	Specific data to be captured	Unit cost (£, 2021)	Metric	Source of unit cost
	Mode of transport (if transferred)	Ambulance Road	292.09	Per journey	ASS02 See and treat and convey Ambulance row 9 www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/
	Death		824.32	Per death	Primary costing. *BMJ* 2012;344:e2292, updated to current prices
Baby	Blood glucose tests	Number of capillary blood glucose tests Number of venous blood glucose test	-	Per test	Primary data required from trial microbiology labs
	Diagnostic tests and procedures	Number of ultrasound scans Number of MRIs Number of ECHOs Number of ECGs List of any other diagnostic tests/procedures/reviews carried out	52.45 95.79 103.76 32.41 64.62	Per ultrasound Per MRI Per ECHO Per CT scan Per diagnostic image	National Schedule of NHS Costs – Year 2019–0 www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/IMAGING, row 69 DIAGNOSTIC IMAGING Magnetic Resonance Imaging 5 years and under row 42 Echocardiogram, 5 years and under DIAGNOSTIC IMAGING row 81 DIAGNOSTIC IMAGING row 32
	Clinical care – staffing by grade (if separate to the mother)	Postbirth activity, staffing levels, and related resource use	51	Per hour	Jones, K. and Burns, A. (2021) Unit Costs of Health and Social Care 2021, Personal Social Services Research Unit, University of Kent, Canterbury. Band 6, hospital based nursing/midwifery Page 138, section 13 hospital-based nurses www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/#sections
	Length of stay by hospital (own or transfer) by level of care*	Intensive care High dependency Special care General paediatric	1706.65 1058.82 709.86 469.15	Per day/episode Per day/episode Per day/episode Per day/episode	CCU13 Neonatal ICU row 6 CCU13 Neonatal Critical Care, High Dependency row 9 CCU13 Neonatal Special Care, row 12 CCU14 babies on a transitional care, row 19 National Schedule of NHS Costs – Year 2019–0 www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ critical care
	Surgical procedures	Example	945.72	Per procedure	Specialised Procedures NZ71Z row 1829 National Schedule of NHS Costs – Year 2019–20 www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ NON ELECTIVE SHORT STAY
	Mode of transport (if transferred)	Ambulance Road	292.09	Per journey	ASS02 See and treat and convey Ambulance row 9 www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/

ECG, electrocardiogram; ECHO, extra-corporeal membrane oxygenations; MRI, magnetic resonance imaging
*note, higher costs are incurred for emergency care, for example, emergency caesarean section with complications

TABLE 34 Sources for unit costs for postbirth care identified for the mother and baby, in the community

Mother and/or baby	Category of resource use	Specific data to be captured	Unit cost (£, 2021)	Metric	Source of unit cost
	Types of health care – outpatient community	General practitioner appointments	39.23	Per surgery consultation lasting 9.22 minutes	Jones K, Burns A. *Unit Costs of Health and Social Care 2021*. Canterbury: Personal Social Services Research Unit, University of Kent; 2021. www.pssru.ac.uk/pub/uc/uc2021/communitybasedhcstaff.pdf page 110
		Practice nurse appointments	44	Per hour	as above page 109
		Hospital/Community counselling	88	Per hour	as above, Band 8b, page 104
		Hospital accident and emergency department	600.76	Per episode	Emergency, Any Investigation -National Schedule of NHS Costs – Year 2019–20 www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ A and E, row 7
		Hospital outpatient appointments	372.20	Per episode	Postnatal Day admission, Emergency, Any Investigation National Schedule of NHS Costs – Year 2019–20 www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ DAY CASE row 1679

The National Schedule of Reference Costs can be used to attribute costs for diagnostic tests. Average costs could be assigned for common groups of tests including clinical chemistry and diagnostic imaging. For tests that do not fall within these 'commonly used' lists, individual unit costs could be assigned to each diagnostic test using primary research directly conducted in clinical chemistry laboratories. The NHS Supply Chain Catalogue could additionally be used to capture the costs of resource items such as medical supplies where it is not possible to collect these comprehensively from maternity units.

The NHS reference costs provide per diem costs for admissions to a neonatal ICU, high-dependency care unit or special care baby unit. A per diem cost is also available for adult intensive and high-dependency admissions, and for admissions to a specialist ward. The cost of a higher-level care provided within the labour ward immediately after labour is also included. These per diem costs do not include the costs of surgical procedures and high costs drugs and interventions, and therefore these would need to be recorded and valued separately.

The PSSRU compendium of Unit Costs of Health and Social Care and the Department of Health Reference Costs both include detailed costing of emergency and non-emergency transfers, including obstetric and neonatal ambulance transfers. Primary data collection may be required for the estimation of costs of other modes of transfer, such as transfer in a helicopter. Only medical staff time needs to be attributed to helicopter transfer, as the NHS does not fund the cost of the service.

Midwifery and clinician staff time is considered the main cost driver for birth and can be allocated directly to the duration of contact hours of the labour episode. The duration variable could be calculated directly from eCRFs. Midwifery staff costs could be calculated from the PSSRU Unit Costs of Health and Social Care compendium.[34] It would include the midpoint salary for both a Band 6 and 7 midwife, including salary on-costs, indirect and direct overheads and contribution to qualifications adjusted for working hours per week, study and leave days. Medical staffing might include consultant obstetricians, paediatricians, neonatologists, anaesthetists, obstetric registrars and foundation year doctors and should be allocated per patient contact hour. Medical staffing costs could be calculated in a similar way, using the costs allocated to direct person contact from data in the Unit Costs of Health and Social Care compendium.

Sources of unit costs for the period following hospital discharge until 6 weeks post partum can primarily be derived from secondary sources. Costs could be allocated to each resource use item using standard methodologies outlined below.

Primary care consultations would be defined as events to include face-to-face or telephone contacts in surgery or home settings with a general practitioner, practice nurse or other professional. More than one appointment held on the same date would be defined as one consultation. Costs could be attributed to these consultations using the PSSRU Unit Costs of Health and Social Care compendium based on the setting of the consultation (e.g. home, hospital, surgery) and the type of HCP providing the consultation.[34] Prescription items can be valued according to the *British National* Formulary (BNF).[42]

Secondary care service use would include admitted care (inpatient and day case admissions) and outpatient attendances and procedures. For inpatient encounters, each admission would be assigned an appropriate reference cost using the national tariff prices, based on the national average unit service provision costs from the National Schedule of Reference Costs.[43] Inpatient stays could be considered as short stays for day-long admissions and long stays for admissions lasting 2 or more days in line with NHS reference costs calculations. Inpatient costs can be analysed at the spell level by summing Full Consultant Episode (FCE) costs within spells to generate total costs per inpatient spell.

For outpatient encounters, each encounter could be costed using treatment speciality average costs from the relevant NHS reference cost schedules. Any outpatient encounters that cannot be attributed to a treatment speciality could be attributed an average outpatient cost. The HRG4 + 2022–23 Reference Cost Grouper[44] can be used to generate Health Resource Group (HRG) codes for each outpatient attendance, day case and inpatient admission, at the FCE level. HRG codes will be matched to the appropriate costs in the 2022–23 Reference Costs Main Schedules[43] based on the clinical specialty, inpatient length of stay (short stay vs. long stay) and type of admission (elective vs. non-elective).

The prescription cost analysis (PCA) could be used to assign all prescription costs, and these could be obtained from the PCA database, electronic searches of the BNF and where required searches of the literature.[42]

All costs should be expressed in pounds sterling discounted to current prices using the NHS Hospital and Community Pay and Prices Index.

An assessment of the broader health-related quality outcomes associated with GILD

The primary research objective for the GILD Economic Evaluation is to estimate the incremental cost-effectiveness per neonatal hypoglycaemia prevented at birth. Secondary outcomes proposed for the economic evaluation include an estimation of maternal health-related quality of life outcomes at baseline and 6 weeks post partum, and neonatal developmental outcomes at age 2 years. This would capture the longer-term sequelae of GILD on neonatal hypoglycaemia.

In the first instance, maternal and neonatal costs and outcomes would be reported separately with outcomes expressed in natural or physical units for the estimation of cost-effectiveness, though methodological and modelling-related approaches that combine the presentation of cost-effectiveness and/or cost–utility for a mother–baby dyad could be explored.

Preference-based measures are reported in the literature for maternal health-related quality of life and validated instruments are regularly used, at baseline pre-birth and after birth.

Maternal health-related quality of life

Data to inform maternal health-related quality of life outcomes can be collected using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), at baseline and at 6 weeks post partum.

The EQ-5D-5L is a multiattribute generic instrument widely used in the conduct of cost–utility analysis of healthcare interventions. It has been translated into more than 150 languages and is recommended by reimbursement organisations, such as the NICE.[45] It identifies different health states that can be converted into a preference-based score using a value set obtained from a representative sample of the UK general population.

Another validated instrument that could be used is the Short Form questionnaire-12 items (SF-12). The SF-12 has eight dimensions, which explore limitations in physical activities, physical or emotional problems, and/or usual role activities because of physical or mental health problems. More broadly, it also considers bodily pain, general mental health, vitality and health perceptions. The Short Form questionnaire-6 Dimensions utility algorithm can be applied to SF-12 responses to allow the analyst to obtain quality-adjusted life-years (QALYs) for use in cost–utility analysis.

Health-related quality of life for the baby

Translating the potential benefits of GILD into QALY metrics for the baby is currently constrained by lack of validated preference-based measures in the perinatal and early childhood contexts, though a systematic review of published utility values for childhood health states has been undertaken.[46] The Child Health Utility-9D is a paediatric generic preference-based measure of health-related quality of life suitable for 7- to 17-year-olds. It has been used in outcomes measurement for pre-school aged children as young as 3 years of age, though as yet is not validated for the preschool age group or younger.

At present, the Paediatric Quality of Life Inventory is validated to capture outcomes for babies at 2 years of age through parent-rated report. The broad instrument, which is validated from ages 2 to 18 years, has 23 items across four Generic Core Scales that address physical function, emotional function, social function and school function and could be used to derive health outcomes for the baby.

Health-related quality of life for a mother–baby dyad

It is anticipated that QALY-based approaches are not yet sufficiently developed to capture the disparate effects of GILD for both mothers and children, partly because of an absence of an available validated multiattribute utility measure for infancy and partly because of methodological challenges surrounding aggregation of disparate benefits for both mothers and children in a single metric. At this stage, there is not a UK preference-based measure validated for use in infancy that permits the estimation of QALYs amenable to cost-effectiveness decision-making. To combine disparate outcomes for mothers and children in a single preference-based outcome measure will be a challenge for a future economic evaluation; however, this trial would provide an excellent vehicle for postdoctoral research to collect and explore modelling approaches to examine this in terms of the parameter estimates required and the design of a model structure.

Representation of cost-effectiveness

Cost-effectiveness can be expressed in terms of incremental cost per unit change in a primary clinical outcome measure. It is estimated via an incremental cost-effectiveness ratio (ICER). The ICER would be estimated using the following formula:

$$\text{ICER} = \text{Difference in mean costs/difference in mean effects}$$

which calculates the ICER. The ICER reflects the additional cost of one additional unit (i.e. one additional improved case) of health outcome improvement associated with the intervention compared with control. For the QALY outcome and cost–utility analyses, the ICER reflects the additional cost of one additional unit of health effect (i.e. an additional QALY) associated with the intervention compared with control. All ICER estimates could be simulated using non-parametric bootstrap analyses with between 1000 and 10,000 replications to generate robust estimates of the standard errors, CIs, and measures of uncertainty.

The full analysis would include all cost and outcomes variables, in accordance with the 'intention to treat' principle. Utilisation of resource use items should be summarised by trial allocation group and differences between groups should be analysed using *t*-tests for continuous variables and Pearson chi-squared (χ^2) test for categorical variables. Mean differences in costs and outcomes between the intervention and control arms could be estimated using *t*-tests and the bootstrap 95% CI that will be computed based on 1000 (or more) replications.

Measures of uncertainty (standard errors and CIs) should also be reported for the mean cost-effectiveness estimates. The data could be combined to calculate an ICER and net monetary benefit (NMB) statistic from a health perspective. In addition, NMBs[47] could be estimated for a range of different cost-effectiveness (willingness to pay) thresholds. Based

on the NMB framework, cost-effectiveness acceptability curves (CEACs) could be constructed to identify the optimal intervention at different cost-effectiveness thresholds. Decision uncertainty characterised by estimating the probability that GILD is cost-effective at different cost-effectiveness thresholds should be explored using CEAC.

Subgroup analyses would mirror those undertaken for the main analysis. Several sensitivity analyses will be undertaken to explore uncertainties surrounding key parameters, including the key cost drivers, and the variables for which there emerges the most uncertainty surrounding the resource use parameters. The cost-effectiveness outcomes would be re-estimated after these sensitivity analyses.

In the case of GILD, the economic evaluation would estimate the incremental cost per neonatal hypoglycaemia prevented at birth. Secondary analyses would explore the incremental cost per maternal QALY gained between baseline and 6 weeks post partum. An additional secondary analysis would estimate the incremental cost of a unit change in neonatal developmental outcomes at 2 years of age and would explore cost–utility for the baby through collaborative methodological and modelling approaches; this would capture the longer-term sequelae of GILD on neonatal hypoglycaemia.

Patient and public involvement

Throughout this phase of the study, PPI advisory group members were informed and helped to shape discussions and make decisions. Documentation to describe the proposed trial design was produced and to explore the most appropriate non-inferiority margin, in anticipation of subsequent qualitative interviews.

The Chief Investigator had a meeting with the PPI advisory group to discuss the trial design and their views on the PICO. It was noted that some women with GDM, controlled by diet, may continue their pregnancy under midwifery-led care; thus, the necessity for a woman to be consultant-led to be eligible to participate in the trial would mean that women with mild GDM may not be able to participate. A suggestion was therefore made and agreed to change this to women delivering in a consultant-led maternity unit.

There was agreement that neonatal hypoglycaemia should be the primary outcome for the trial and that if this was based on a numeric definition, rather than one additionally based on symptoms, that this would be appropriate. Their reasoning was that a low glucose value in the baby would impact the mother in terms of anxiety and pressure over making sure baby was feeding. Additionally, if the baby had a numerically low glucose value, this would also risk the baby being taken to the neonatal unit and impact on bonding. The general feeling was that maternal satisfaction should be the most important maternal outcome.

A draft participant information sheet (PIS) was coproduced with the PPI advisory group to help guide discussions within the qualitative interviews for women and HCPs to give their opinion about acceptability of the proposed trial. Further details are included in *Chapter 5*. The PPI advisory group also thought that in the information developed for the trial it would be important to explain to women what would actually happen if they agreed to participate. Some felt that if participation would potentially change their labour experience, women may choose not to participate, and that if joining in would not change most aspects of their labour experience, it was important to highlight this.

Chapter 5 Determining the acceptability of our proposed randomised trial

Aim

To understand facilitators or barriers (feasibility) of conducting a trial comparing permissive to intensive glycaemic control for women with diabetes.

Methods

Design

A qualitative interview study of women with experience of diabetes and labour and HCPs with experience of managing diabetes in labour to explore their views on the acceptability and feasibility of conducting a trial comparing permissive to intensive glycaemic control.

Ethical approval

Ethical approval was obtained from the University of Nottingham Faculty of Medicine & Health Sciences Research Ethics Committee (ref: 304-0621).

Participant identification

Eligibility criteria were that women were aged 16 years or older (no upper age limit), were currently pregnant or experienced the birth of a baby involving active labour in the past 3 years, and had T1DM, T2DM or GDM. They also needed to speak adequate English and be able to provide informed consent. Purposive sampling was used to ensure that women with different types of diabetes (T1DM, T2DM, GDM) were represented, as well as women from ethnic minority groups. This ensured that this study population would be representative of populations eligible to participate in any future trial. We wanted to explore if there were different views on the acceptability of different intrapartum tests or techniques and participation in a future trial between different populations.

Women were recruited to this work package by national and local publicity including social media, websites, advertisements and posters. The networks that supported with publicity included Gestational Diabetes UK, National Childbirth Trust, Mumsnet and Maternity and Neonatal services for Derbyshire. Personal contacts of the study team also supported with recruitment.

Similarly, HCPs were also interviewed. Eligibility for HCPs were that they were employed in the UK as an obstetrician, endocrinologist, or midwife and had experience in planning or caring for women who have diabetes during labour. They also needed to be able to speak adequate English and be able to give informed consent. Purposive sampling was used to ensure that HCPs from relevant disciplines were represented (midwifery, obstetrics, endocrinology) as well as differing levels of experience. HCPs were identified from national publicity (e.g. BICS, UKARCOG, Royal College of Midwives and associated Twitter accounts), clinical contacts, networks and snowball sampling.

Invites were made in person, by e-mail or through social media.

Measures

Participants' experiences and views on acceptability and feasibility of a future trial were explored using a semistructured interview schedule (see *Appendix 5* and *Appendix 6*) developed from a theoretical framework of acceptability.[48] The interview schedule explored participants' experiences of intrapartum glycaemic control; the acceptability of the proposed trial (e.g. methods and frequency of testing, glycaemic targets); maternal or clinical barriers to implementing and conducting the trial; site-specific contextual barriers and facilitators to implementing and conducting the research; perceived benefits and challenges of the trial; and whether women would be willing to take part in a future trial. The

interview schedule was developed by the research team and sense-checked by the PPI advisory group. At the end of the interview, a few questions were asked about sociodemographic or professional characteristics.

Information on the proposed trial and design was developed by the PPI advisory group in consultation with the wider research team. Three versions were created: one for women with GDM (see *Appendix 7*); one for women with pre-existing diabetes (T1DM or T2DM) (see *Appendix 8*); and one for HCPs (see *Appendix 9*). These outlined the purpose and rationale for the trial, gave a flow chart outlining trial procedures, and a visual summary of what would be used in the tight (intensive) and loose (permissive) arms of the trial. These were given to the women prior to the interview so that they could familiarise themselves with what the study would entail and the advantages and disadvantages of the intervention and control arms.

Participant recruitment

Women and HCPs who expressed an interest in participating in the study were sent a letter of invitation, PIS and consent form electronically via e-mail. If they were interested in participating, they returned their consent form to the researcher, indicating their interest and providing contact details. The researcher explained the details of the study, was available to answer any questions, and ensured participants had sufficient time to consider whether to take part. A written paper or online consent form was completed depending upon participant preference. All participants taking part in the qualitative interviews provided informed consent prior to the interview. The researcher then contacted participants to arrange a suitable time to conduct the interview. Before the interview, participants were sent the relevant information on the proposed trial (see *Appendices 7–9*).

Data collection

Interviews were done by Dr CG (PhD) a health psychologist and an experienced qualitative researcher. Participants were not known to the researcher before they expressed a wish to join the study. The information brief for participants included the interviewer's name and that she was a research fellow. A few brief screening questions were undertaken at the beginning of the interview to confirm eligibility. Interviews started by looking at the information about the trial (see *Appendices 7–9*), so the interviewer could answer any questions and/or offer further information to ensure every participant had a reasonable understanding of the proposed trial. Then confidentiality was outlined, and consent was verbally re-confirmed prior to the interview. It was explained to all participants that entry into the study was entirely voluntary and, for women, that their treatment and care would not be affected by their decision. It was also explained that they could withdraw at any time. Similarly, if a participant no longer wanted their interview transcript to be used, they could request this after the interview. After participants re-confirmed their consent, the interview was conducted. At the end of the interview, participants were asked to provide basic sociodemographic information, such as age, ethnicity and diabetes (for women) or type/job role, years practising (for HCPs). Interviews were conducted via telephone or online software by an experienced qualitative research fellow using the semistructured interview schedule at a location selected by the participant (home or workplace). After the interview, women were sent a £10 gift voucher as a token of appreciation for taking part.

Interviews were recorded using an encrypted digital recorder. Only one interview was undertaken by each participant. To protect participants' personal information, audio recordings were identified by participant number. At the end of the interview, audio files were uploaded to a secure password-protected server and deleted from the digital recorder. Transcription was done by a transcription service under a data-sharing agreement with City, University of London which is General Data Protection Regulation (GDPR) compliant. Audio recordings, interview transcripts and data analysis files were stored on a password-protected, encrypted computer at City, University of London. Digital audio recordings were transcribed verbatim, checked for accuracy and de-identified prior to analysis. Transcripts were not sent to participants for comment/corrections due to time constraints.

Reflexive statement

The qualitative research team consisted of two research psychologists who were not working clinically and had no prior knowledge or beliefs about diabetes management during pregnancy or birth. Interviews were conducted by CG who has an interest in maternal and child health but no biases or assumptions related to diabetes in pregnancy. We anticipated women would have individual views and preferences about diabetes management during their labour. Field notes were kept during and after interviews to help maintain reflexivity. Our awareness of these prior beliefs and their potential

impact on our analysis were monitored to ensure that we were not over-interpreting data that supported our prior beliefs, or overlooking disconfirming data.

Data analysis

Transcripts were analysed using systematic thematic analysis.[49,50] A combined inductive–deductive approach was used to enable the specific research questions to be addressed as well as identifying unexpected or new themes related to acceptability and feasibility of the proposed trial.

Field notes were made throughout the data collection and analysis process to facilitate reflexivity and monitor the saturation of the experiences shared. As the data analysis was ongoing, this enabled the researcher to monitor when data saturation was achieved, that is where major themes were re-occurring from previous participants and no new major themes were being discovered. When the researcher thought data saturation was achieved, one further interview was carried out to confirm this.

Initial coding was done by one researcher (GC). All transcripts were read to become familiarised with the data, and then re-read and coded until no further codes were identified. After this, the codes were examined by two researchers (GC, SA) to extract the most salient and frequent codes which could be integrated into main themes – themes were derived from the data. Data were examined for confirming and disconfirming information for each theme. Regular meetings of the research team where problematic issues were discussed and resolved ensured credibility. A structured summary of the findings was used to present the themes of the study in relation to the acceptability and feasibility of the trial.

Interviews for women were analysed together, followed by interviews with HCPs. Similar themes were identified in both groups, so the results are presented together. Analysis was conducted using NVivo 12 (QSR International, Warrington, UK) qualitative analysis software[51] and presented in line with consolidated criteria for reporting qualitative research 32-item guidance. Sample size was determined by data saturation in each group. Participants did not provide feedback on the findings.

Results

Sample characteristics

A total of 19 women are included in this study. Sample characteristics for women are shown in *Table 35*. Thirty women expressed an interest in participating and 19 (63%) consented to take part. Four women who volunteered were not eligible for participation as they had no experience of active labour or were not currently pregnant. Three did not have time to complete the interview. The number of volunteers with GDM and saturation of themes from the experiences of women with GDM meant four volunteers with GDM were not invited to interview. No participants withdrew from the study.

The average age of women was 34.3 (SD 4.4) years. Most participants were White British, married, post partum, and had a diagnosis of GDM in their current or previous pregnancy. Three participants (16%) were from an ethnic minority background. Four participants had pre-existing diabetes (T1DM, T2DM or mitochondrial diabetes). Time since their last birth was between 2 months 12 days and 2 years 7 months. The only non-study participants present during the interview were that some of the mothers were caring for a child.

A total of 16 HCPs were recruited into the study. Twenty HCPs expressed an interest in participating and 16 (80%) consented to take part. Reason for dropout was mostly lack of time to be interviewed. Sample characteristics for HCPs are given in *Table 36*. This shows that half of HCPs interviewed were obstetricians and just under half were midwives; one participant was an endocrinologist. Average years practising was 13.5 (SD 6.2) years. Exposure to diabetes management in pregnant women varied, with half the sample having frequent exposure. The other half had some or little experience managing women with diabetes during their labour. Participants who reported little experience were all involved in discussions about diabetes management during antenatal care, rather than management during labour.

TABLE 35 Sample characteristics for women (*N* = 19)

Characteristic		*N* (%)
Pregnancy status	Pregnant	2 (11)
	Post partum	17 (89)
Ethnicity	White British	14 (74)
	White European	2 (11)
	Black British	1 (5)
	Asian British	1 (5)
	Sri Lankan Tamil	1 (5)
Experience with diabetes	GDM	15 (79)
	T1DM	1 (5)
	T2DM	2 (11)
	Mitochondrial	1 (5)
Number of pregnancies	1 (first pregnancy)	6 (32)
	2	9 (47)
	3	3 (16)
	4	1 (5)
Occupation	Administration	3 (16)
	Education	2 (11)
	Accounting/finance	3 (16)
	Health or social care	7 (36)
	Other	4 (21)
Marital status	Married	15 (79)
	Cohabiting	3 (16)
	Single	1 (5)
Education level	Postgraduate	8 (43)
	Graduate	7 (36)
	A-levels	4 (21)

Thematic analysis

Interviews took an average of 34 (SD 7.2) minutes for women and 31 (SD 10.7) minutes for HCPs. Analysis of the interviews with women and HCPs identified four main areas for consideration: (1) previous experiences of diabetes management in labour; (2) acceptability of the proposed trial; (3) trial design considerations; and (4) implementation factors. The themes within each of these areas are given in *Table 37* and outlined in more detail below with illustrative quotes.

I: Previous experiences of diabetes management in labour

The first area for consideration was the previous experiences of women and HCPs of diabetes management during labour. Women shared their experiences of diabetes monitoring during labour, detailing feeling confused over whose

TABLE 36 Sample characteristics for HCPs (*N* = 16)

Characteristic		*N* (%)
Profession	Obstetrician	8 (50)
	Endocrinologist	1 (6)
	Specialist diabetes midwife	4 (25)
	Midwife	3 (19)
Professional grade	Consultant	9 (56)
	Band 8	2 (13)
	Band 7	5 (31)
Years practising	5–10	5 (31)
	11–15	6 (38)
	16 or more	5 (31)
Exposure to intrapartum diabetes control	Frequent	8 (50)
	Sometimes	3 (19)
	Rarely (antenatal care)	5 (31)

TABLE 37 Main areas for consideration and themes

Main areas for consideration	Themes
I: Previous experiences of diabetes management in labour	Current practices of diabetes monitoring during labour[a,b] Confusion and worry[b]
II: Acceptability of the proposed trial	Contributing to improving care[a] Tweaking care during labour[b] Informed choice[a] Being able to change their mind[a] Tight vs. loose control/target ranges[a]
III: Trial design considerations	Outcomes relevant to women and professionals[a,b] Recruitment for the trial[a,b] Confounding factors[b] Taking a blood sample[a] Target ranges[a]
IV: Implementation factors	Approach and consent[a,b] Barriers to the trial[b] Facilitators to the trial[b] Selling it to HCPs[b] Training[b]

a Theme arose from women only.
b Theme arose from obstetricians only.

responsibility it was to measure blood glucose during their labour. Some women shared experiences of managing their own glucose throughout because this role was not adopted by the team caring for them.

> *No, no one ever just said, oh right so we're going to have someone check it, dah, dah, dah. They were just sort of, well, you look after your own diabetes don't you? And I'm like, well, yeah I test, and I inject, yeah, and that was it really.*
>
> *Woman Pre-existing DM, P003*

> *When I went in, no one discussed diabetes with me … so, I asked, myself, 'How am I managing my diabetes while I'm here?' and they said, 'Well, just do what you usually do, but to be honest, it doesn't really matter now you're here.' Which I thought was very strange.*
>
> *Woman Pre-existing DM, P006*

Others were not able to recall being tested at all or very frequently and some reported experiencing misunderstandings between HCPs over whether they should be testing the woman's glucose now that they were at the hospital.

> *There is no information and, also at the hospital, there is complete inconsistencies in what healthcare professionals tell you, depending on who you speak to. So, one midwife might tell you, 'Yes, you need to be testing like you would at home', another professional might tell you 'To check every hour'. It's, there's no consistency.*
>
> *Woman Pre-existing DM, P006*

In addition to experiences of staff providing conflicting information on testing during labour, women shared experiences of staff not understanding their diabetes needs around food intake during labour. Those women who did experience frequent testing explained that they were not hourly as they had expected, and that finding a midwife who was available to test their glucose hourly was very difficult.

> *I offered to do it myself because I knew it would be a pain trying to get somebody to come in every hour to do it, that's why I offered to do it.*
>
> *Woman GDM, P002*

Some of the women experienced lots of intervention during their labour and were put on a variable-rate intravenous insulin infusion (referred to as a 'sliding scale') which is an intravenous drip with insulin and glucose administered via an intravenous cannula in the hand or arm. The sliding scale had a negative impact on these women's birth experiences particularly because it limited their movement.

> *So that meant that I was ended up with a sliding scale and I was completely stuck to the bed in the same position, which meant that I then ended up with an epidural.*
>
> *Woman Pre-existing DM, P014*

Some women felt that adhering to a tightly controlled approach during labour was too regimented and described experiences of 'clock watching' to adhere to this time frame which took away from their birth experience.

> *like just dealing with the contractions and just trying to pass a bit of time, but then when you're constantly clock-watching it just made it more stressful to be honest.*
>
> *Woman GDM, P002*

Healthcare professionals also talked about their experiences of current practice, with many sharing the view that hourly testing between 4 and 8 mmol/l is too labour intensive and intrusive, discussing that it does not always have the 'net gain' expected.

> *I think that it's very intrusive, and I think it's labour-intensive, and you have got to action what you find. I think the current regime that we certainly have at our Trust is that we want blood sugars between four and seven in labour, and I think it's too tight personally, and I think it's too much of an intrusive thing for women with no net gain particularly.*
>
> *Specialist Diabetes Midwife, P001*

The time-consuming nature of tight control for both women and midwives was an issue, and HCPs also described tight control as unnecessarily anxiety provoking for midwives.

> *I think that we are probably overly, my gut feeling is we're overly, strict anyway and it's quite a time consuming and unnecessarily anxiety provoking thing.*
>
> *Consultant in Diabetes and Endocrinology, P007*

As already highlighted by the women, HCPs also felt hourly testing can take away from other aspects of birth, particularly the use of a sliding scale being intrusive and restrictive for the woman. They also thought sliding scales added stress, medicalised the birth experience and increased the workload of the HCP.

> *Sliding scale is restricting because the woman is connected to a series of POMS whereas it is restrictive and it medicalises their birth experience which is what most people don't want. And finally in terms of the workload of the midwifery staff, that increases the workload on the midwifery staff.*
>
> *Consultant Obstetrician, P013*

Healthcare professionals highlighted this as an issue particularly for GDM women who were diet or metformin controlled and typically had 'good control' antenatally. As the current guideline manages both pre-existing DM and GDM women in the same way, HCP detailed that 'tightly' controlled does not feel necessary for GDM women. One professional described tight control for GDM women as 'overkill', with others also feeling tightly controlled is not as important managing GDM women in labour as it is for pre-existing DM.

> *Because they are less likely to require a variable rate intravenous insulin infusion if they are diet or Metformin controlled. So, it almost feels like a bit overkill really to be checking hourly, when it's very … I don't actually know what the figures are. But from my experience they are unlikely to require while in labour.*
>
> *Specialist Diabetes Midwife, P010*

For many, the reasoning behind this was the lack of flexibility in the guidelines which meant that if a woman's glucose levels were just over the target range it led to intervention which seemed unnecessary.

> *But gestational, often you do it because the guidelines say it …. But when I look after people in labour, often it stays normal, and sometimes it just goes 8.1 or something just slightly over, and an hour later it can be normal. We're testing that 1 hour later, but it just seems like overkill sometimes.*
>
> *Specialist Diabetes Midwife, P012*

It was recognised that the current approach in guidelines is often not followed consistently or viewed as equitable due to these kinds of issues. However, it was also recognised that the current 'one size fits all' approach gives clarity to staff at difficult times and having different procedures for staff may be confusing for them to follow.

> *So I think it works well in the sense that it's not confusing for the people who are actually operating it on the Labour Suite, the Labour Suite is a very difficult place to be at the moment. It's very understaffed and having a one size fits all approach that feels safe, I can see as being well received.*
>
> *Consultant Obstetrician, P016*

Experiences of managing women's diabetes in labour also highlighted the variation between different NHS trusts' guidelines for target ranges. Where the proposed trial design is for a target range of 4–8 mmol/l, different trusts used 4–7 mmol/l, 4–7.5 mmol/l or 4–7.8 mmol/l. It was also reported that there can be difficulty actioning the glucose levels between 4 and 7 mmol/l, particularly at night. Finally, HCPs raised concerns over women having their own CGM devices which HCPs then might rely on for monitoring during the woman's labour. Specialist HCPs stressed that relying on CGM readings can be dangerous.

> *I'm talking about the Type 1s, Type 2s. I think it's just fraught with danger. I've got mixed feelings about CGM. I really like the idea of CGM, but I worry about its accuracy from some of my experiences. And so with all the will in the world, no matter how much I say it: do not go off the CGM reading; in a rush people do. They rely on it, and they might start something off where they shouldn't be starting something off. Personally, I think four to seven is too strict. That's my feeling.*
>
> *Specialist Diabetes Midwife, P001*

In addition to experiences of current practice, a key area of concern for obstetricians and specialist diabetes midwives was experiences of some HCPs finding management of women with diabetes leading to *confusion and worry*, with many

midwives being fearful of caring for women with pre-existing diabetes. This worry about managing women with pre-existing diabetes could then impact the rest of the Labour Suite activity.

> *I've had three (labouring women) on Labour Suite all at the same time the other day. The impact to Labour Suite is massive, it's a ripple effect. My woman is there, and being a midwife, labouring midwife, you can be bobbing in between rooms and managing a couple of different women. When you've got a woman with pre-existing diabetes, the fear element is quite large. So, the impact to the entire Labour Suite and all the other women is significant. It's not just about the safety of that one woman and that one baby, it's all the other midwives and all the other women on Labour Suite at the same time.*
>
> *Specialist Diabetes Midwife, P001*

These experiences highlight the complexity in managing women with diabetes and burden of meeting current care guidelines, with support from more senior professionals important in relieving these fears.

> *I remember being that midwife going, oh God, don't give me the diabetic. Oh God, I've got a diabetic …. It's painful for people. They didn't come into midwifery to run a variable rate on some woman. They don't like it. So as long as I'm supporting them, I think they'll be fine.*
>
> *Specialist Diabetes Midwife, P001*

These experiences were thought to stem from some midwives not having a detailed understanding of diabetes, and so they might worry about getting the right approach for the right woman. In addition, misunderstandings over what is trying to be achieved when using sliding scales were also thought to contribute to these experiences, particularly when midwives already feel overloaded and overwhelmed with caseloads and procedures.

II: Acceptability of the proposed trial

The second area for consideration was the acceptability of the proposed trial. Women's views about the trial were highly positive. They spoke about the prospect of being involved in this type of trial as enabling them to *contribute to improving care* for other women in the future. They were keen to be involved in research that could lead to change and recognised that the care provided cannot be improved if research like this is not done.

> *I think it's important that you do research with women during their labour, (yes) especially when it will improve things for both their outcomes and the baby … Well I just think you're not going to make things better if you don't do research, (yes) you're not going to improve things for people.*
>
> *Woman GDM, P002*

This was discussed in relation to previous experiences of birth and women thought this trial might contribute to reducing intervention such as the use of sliding scales which some felt strongly about.

> *Like I say I think this is something that I do feel fairly strongly about because I did kind of get swept along with my first baby and it did kind of add to things because it was a very long, very hard labour and when you can't eat because you've got a sliding scale in on top of everything else then…It's just another layer of stress adding to an already stressful situation, well it can be.*
>
> *Woman Pre-existing DM, P014*

Women also thought the trial itself was acceptable as it still closely monitors women in either arm of the trial.

> *They're still saying they're going to be testing every hour to make sure you're in that box. I suppose, personally I suppose I'd be like, cool, they're still keeping an eye on it.*
>
> *Woman Pre-existing DM, P003*

Some women also said that being involved in a trial like this would provide reassurance over the care they would receive. However, it was important to women that the trial did not affect pregnancy care.

> *I think it's that reassurance to know that, okay this is. I get freaked out about it, okay someone's doing it for me, and telling me it's fine. Yeah, your sugars are fine, it will be okay.*
>
> *Woman Pre-existing DM, P003*

While women were highly positive towards the prospect of a trial, they also discussed the importance of *informed choice* as a key factor in conducting trials. As long as women are fully informed and agree to be involved, the trial is acceptable. However, they recognised that personal choice might be a contributing factor.

> *If a woman is happy and volunteering, saying okay, yes I'm happy to do that, then yeah. I don't see why there should be a problem.*
>
> *Woman Pre-existing DM, P003*

> *I don't think they wouldn't be acceptable. No, it's just a personal choice. If they are fully aware of what's happening and the implications and the benefits to everybody and obviously they agree to it, then I think it's absolutely fine.*
>
> *Woman GDM, P004*

For a few women it was discussed that the word 'trial' is scary because it may be viewed as new.

> *I think just the fact that it's called a trial makes you think, oh, God, this has never happened before, this is new. Yeah, I think.*
>
> *Woman GDM, P004*

When discussing their views on the trial, women stated the importance of being able to change their mind. This referred to women knowing they were able to opt out of the trial at any time during labour if they changed their mind.

> *During labour, if there are any complications? At any point can I withdraw from it once I'm in labour?*
>
> *Woman GDM, P004*

The circumstances they felt were important to be recognised were if they felt unwell or wanted extra diabetes testing during the trial. Having this control was an important part of whether the trial was deemed acceptable to them. However, they thought it was important to recognise that not all women may be comfortable saying they feel unwell.

> *I think just giving you that reassurance really that you can have your bloods tested if you need to it's not that we're not going to leave you, (yes) so if people are worried. Because not everybody will stand up and say something as well, (yes) some people can be quite quiet, they're not going to make themselves more worried.*
>
> *Woman GDM, P002*

Sensitive and family-centred care was important within this, with one woman stating that she felt like just a patient not a person.

> *Remember that each person is just becoming a mother and having a child. We're not just patients, we're people and our job is not just to be there and push a baby out and then be sent away, so I guess sensitivity.*
>
> *Woman GDM, P004*

Many women felt there was not a lot of difference between the two monitoring strategies or target ranges proposed in the trial with both the tight versus loose control viewed as acceptable.

> *Because really when you compare them from a risk point of view there's not a lot of difference, (no) if you know what I mean, you're just looking at the difference if it's just not as tight.*
>
> *Woman GDM, P002*

However, loose control was deemed more favourable, with women reporting that loose control would be better for longer labours and if the labour was difficult.

> *If I go again and it was going to end up being longer I'd probably want that wider range just for, it's like a bit of slack isn't it, I suppose? It's a bit more forgiving I'd say.*
>
> *Woman GDM, P004*

> *But I think anything, you're focusing on having a child, you're in labour, I don't think at that time, it should, there should be that pressure. I think it should be obviously, checked, to make sure that your wellbeing, you're okay, but I think, a less intrusive method would be a lot better.*
>
> *Woman GDM, P006*

Some women also had previous experience of their blood glucose levels going over 10 mmol/l in labour and felt their midwives were not overly concerned.

> *When I was in. like seeing my midwife and stuff, she would say that they were happy, there was times with me when I was going over ten, but it wasn't a problem*
>
> *Woman Pre-existing DM, P003*

The benefit of loose target ranges was that they were viewed as making things more relaxed.

> *Actually sounds so much better, because if you're not as tight it's a lot more relaxed, because you can get a nine with blood sugars and you'd be okay.*
>
> *Woman GDM, P002*

There was however some confusion about why the target ranges were chosen to be 4–8 mmol/l for the trial when women's previous experience was under 7 mmol/l.

> *(I) know that in your trial it said that they needed to be under, did it say that they had to be under eight, I was told that mine had to be under seven?*
>
> *Woman Pre-existing DM, P014*

Professionals justified the acceptability of the trial as allowing care to be 'tweaked' during labour to improve what they already do. This 'tweaking' of care was defined as adjusting the targets and time frame in which monitoring is done, and therefore the trial does not remove or add anything new. This made it more acceptable in the opinion of most HCPs interviewed.

> *We're not taking anything away. We're not, it's not that some people are getting one treatment and another getting others, we're tweaking timings and we're tweaking trigger points for things, rather than saying that you're never going to get that treatment. They just, I think that's easier for clinicians and also for patients to accept because there'll be an amount of trust in what we already do.*
>
> *Consultant Obstetrician, P016*

The simplicity of the trial was also discussed alongside the expectation that making these 'tweaks' to the guidelines used would not make much difference to outcomes for women.

> *It's not going to be much of a difference to be honest … What you are trying to see is that whether having a tight control with 4–8 as nationally recommended compared to what you are suggesting up to 10, is going to make a significant difference in the outcome for the babies and for mum. My answer is no. Because I have worked in different Trusts where I know that patients won't get started on insulin infusion if the levels are not above 10.*
>
> *Consultant Obstetrician, P015*

Healthcare professionals agreed that reducing unnecessary intervention is an important aspect of the trial's acceptability, emphasizing that HCPs should not medicalise birth if they do not need to, with hopes that it could reduce the number of women ending up on sliding scales unnecessarily.

> *People with diabetes, they're pregnant first and diabetic second. And I think that there is too much of a medicalised arm or control in their pregnancy, without the rationale behind it. It's very dictatorial.*
>
> *Specialist Diabetes Midwife, P001*

> *Anything that we can do that's going to improve the experience for women, I'm all for it. These are life changing times, and we need to give control to the women as much as we can. We shouldn't be medicalising where we don't need to medicalise so much. We're putting fear into women when, do we need to?*
>
> *Specialist Diabetes Midwife, P001*

This was thought to inform practice and therefore improve the experiences of women and the team providing their care. However, a few HCPs raised the need for further robust evidence on which the trial would be designed upon, with queries about whether observational research has been conducted in locations where loose control is already being used before running a trial in the UK.

> *I wondered whether we should do a cluster randomisation and by clusters, I mean find countries where we have, if there is some such practice around the world, countries where they might have a bit of loose control over those that have tight control over here. (Yes) So do cluster randomisation or a simple observational study, if you do have already health system that is already doing loose control and one that is doing tight control over here, just have much cases in control.*
>
> *Trainee Registrar, P011*

Another important consideration was that although both women and HCPs may benefit from loose control, it should not be used as a fix for understaffing.

> *We shouldn't use it as a fix for understaffing, right. We must still do what evidence tells us is best for the patient so if the evidence comes back and says that we can have loose control and that is without harming the patient then good to go. Happy to have that on board.*
>
> *Trainee Registrar, P011*

III: Trial design considerations

Important design considerations were women's and HCPs' views on trial outcome measures. Outcomes relevant to women included: incidence of neonatal hypoglycaemia, mothers' experiences of birth, stillbirth, women's health during labour, interventions used during labour, neonatal unit admission, and extended stay in hospital after birth. Outcomes relevant to HCPs included: neonatal hypoglycaemia, maternal hypoglycaemia, women and partners' experiences of birth, staff experiences of providing care, Apgar scores, feeding and surveillance needed after birth, neonatal unit admission, calcium levels in the baby, intravenous glucose, jaundice, interventions during labour, separation of the mother and baby. Additionally, three HCPs also discussed the importance of follow-up, recognising that the proposed 2-year time frame for developmental follow-up may be better conducted between 3 and 5 years.

> *The other concern about that one, maybe I would chat to the developmental paediatrician because most of the neuro-developmental outcomes don't become clear until 3 to 5 years of age. So the last seminar I attended about this I think people would be keen to know what the figures are doing at 3 years at least, not 2 years.*
>
> *Trainee Registrar, P011*

> *Yes, because I think most of the other studies that have looked at the milestones have used 2 years and some have later extended it to 5 years.*
>
> *Consultant Obstetrician, P013*

In addition to discussing outcome measures, participants also discussed the need for clearer information on sampling of specific subgroups of women with diabetes. For women, their concerns were around their *suitability for the trial*. Participants recognised that some women may not be as suitable to take part in a trial like this one, for example, women who are anxious about their diabetes or first-time mothers.

> *I think some people might prefer that rigidity of knowing that everything's okay, especially if somebody's really anxious about their blood sugar levels.*
>
> *Woman GDM, P002*

> *I think first time mums is going to be a bit more sceptical about it, than probably if you went to a mum that's probably had a couple of pregnancies.*
>
> *Woman Pre-existing DM, P003*

Women also thought that women whose diabetes was diet-controlled might be more relaxed about loose control compared to women who required insulin.

> *I think as someone who only had diet control (I) would've been happy to go for the looser, definitely, had I been insulin dependent then I think maybe that would've been a bit different but as diet control, I definitely would only have gone for that.*
>
> *Woman Pre-existing DM, P014*

Women also wondered whether women with other known complications for themselves or their baby would be safe to take part. They thought factors such as poor control of diabetes in pregnancy or preterm birth might prevent them from being able to take part.

> *I guess it depends how well controlled the diabetes was during their pregnancy … what their risk level is, whether it's their first baby … whether they've experienced it before … Yeah, haven't been able to get it under control or diagnosed very late. So, if they didn't have a chance to get it under control.*
>
> *Woman GDM, P004*

Healthcare professionals also discussed *recruitment*, with many stating they would be more concerned about recruiting women with pre-existing diabetes as they perceived that more could go wrong.

> *I would feel uncomfortable with them having a looser range compared to a woman on GDM diet controlled, who I would feel more relaxed about. Yeah, because if they are diet controlled their baby's risk of having neonatal hypoglycaemia compared to a Type 1 diabetic, is much lower. So, I guess that's why I feel more at ease.*
>
> *Specialist Diabetes Midwife, P010*

Related to this, HCPs wondered whether pilot research with lower-risk women with GDM and good control would be a safer alternative.

> *Perhaps for this study I would say we go for women who have GDM but have quite good results (management).*
>
> *Trainee Registrar, P011*

Some HCPs also felt that the trial would be improved if the time frames for testing were different for diet, metformin and insulin controlled regardless of diabetes type as opposed to dividing the trial into pre-existing and GDM women.

> *So, ideally what we would like to do at this Trust is to change the frequency of blood glucose monitoring for women who are diet controlled to 4-hourly. And women who are Metformin controlled to 2-hourly. And insulin controlled to hourly*
>
> *Specialist Diabetes Midwife, P001*

In addition to this, HCPs raised whether some professionals may have a bias when randomising women with insulin control.

> *Like I understand the benefits and the improved quality of research when it is a randomised controlled trial. But my concern would be that maybe I would have a bias for women who are insulin controlled. Like I would be more concerned if they fell into the looser target range. Like I know it would be out of my control, or women with Type 1 diabetes for example. I would feel uncomfortable with them having a looser range compared to a woman on GDM diet controlled, who I would feel more relaxed about.*
>
> *Specialist Diabetes Midwife, P010*

Professionals in this study also discussed the confounding factors that could influence the trial results and listed key factors they thought should be controlled for. These were factors such as diabetes management in pregnancy, use of steroids and other medications, other complications for the mother (comorbidities and diabetic ketoacidosis risk) and baby, and the woman's food intake during labour.

> *Does a value of 9.9 increase the women's risk of ketoacidosis if they have got type 1 diabetes?*
>
> *Specialist Diabetes Midwife, P010*

Another factor which was mentioned under previous experiences of care was whether women's use of continuous monitoring devices would be included in the trial and whether the trial testing methods would be performed in these cases. Similarly, it was important to know whether women who wanted to test their own blood glucose during birth could continue doing so and how their blood glucose would be tested/recorded in these instances.

One HCP was concerned that taking part in the trial might impact on care through confusion of the different approaches used in the trial compared to standard practices for other women not involved in the trial.

> *Yeah, so if … word gets around very quickly. So, if someone is saying well this patient she had a blood glucose level of 9.6, and she didn't need the sliding scale. It almost like demeans the guidelines that we have been working on so hard to implement. So, it might mean that the midwife caring for that woman might be like, oh well they are doing that trial and it's only 9. So, let's just give it a bit longer.*
>
> *Specialist Diabetes Midwife, P010*

The final aspect of the trial design discussed by women was taking a blood sample from the baby after birth. The interview asked women whether this would influence their views on the trial. For the majority of women they did not think this would change their perspective, either because the baby would typically have samples taken anyway or that they had already experienced this with a previous birth.

> *No, because they take blood anyway from the baby.*
>
> *Woman GDM, P002*

> *No, that's fine. Well, only because. I only say, yeah because (baby's name) had to have loads of bloods samples when she was a baby, and it all had to go into that little tube. It wasn't very nice to watch, but I don't think it would bother me, no.*
>
> *Woman Pre-existing DM, P003*

Others had the view that although it was not perceived to be pleasant for themselves or baby, it was necessary that the baby's glucose levels are checked to prevent complications. One mother claimed it would cause her more stress if she did not know the baby's glucose levels were okay therefore justifying the unpleasantness of the test.

> *I wouldn't mind at all, because obviously, I would want to know that my baby was okay, so, it wouldn't make any, in fact, I'd be more stressed, and anxious if nobody checked my child's blood sugar.*
>
> *Woman GDM, P006*

Many of the women asked whether this blood test would be the same as the heel-prick test, saying they would prefer it if the blood test could be done at the same time and with the same blood sample taken in the heel prick test because it is less invasive than venepuncture.

> *I know my daughter definitely had to have a blood sample taken from her after birth because the first blood sugar test that they did they weren't happy with it so then they did it with a different machine where you actually physically needed to get blood out rather than just a little drop. It can be quite traumatic having blood taken from a newborn though, not for me personally but I think some women would find it a little bit traumatic because they don't tend to like it very much, it's not painful but they don't tend to like it very much because it has to be done in a very particular way.*
>
> *Woman Pre-existing DM, P014*

Overall, while most women (*n* = 17; 89%) found the blood test acceptable, they recognized that the nature of venepuncture blood tests might be stressful for some women. Only two women said the blood test would change their view on taking part. However, of the 17 who said the blood test was acceptable, 6 (35%) said they would decide on participation based on the type of sample being taken.

IV: Implementation factors

How to successfully implement the trial was discussed by women and HCPs. One important aspect was the *approach and consent* process. *Women's perspectives* on the important aspects to consider when approaching women included whether or not this was a woman's first pregnancy since having been diagnosed with diabetes because they might need longer to come to terms with the diagnosis and adhering to management of their diabetes before they would be able to take on more information about a potential trial.

> *I found it a huge shock to have, even at twenty-eight weeks knowing that I still had another ten weeks. Well, yeah, we delivered at thirty-eight, but potentially had another twelve weeks of having to take medication off the nurses (ph). It's a lot and it takes an emotional toll when you're thinking that your body's trying to not do. Well, yeah, your body's unable to do what you want it to do or what it should do. So, I guess throwing extra testing into the mix, yeah, maybe too much to deal with.*
>
> *Woman GDM, P004*

Consequently, women advised that potential participants should not be approached too soon about the trial. However, this did not apply to women with pre-existing diabetes who they thought would be happy to know earlier as they would have already come to terms with their diabetes and be confident with managing it.

> *I would even have been happy earlier to talk about it in my second pregnancy that would've been fine.*
>
> *Woman Pre-existing DM, P014*

> *I'd say straightaway, definitely, I think … Yeah, because I suppose I would like to know everything. I'd want to know then, than someone saying it to me right at the end, I suppose. I think I'd rather know at the beginning.*
>
> *Woman Pre-existing DM, P003*

Most women felt approaching potential participants between 28 and 36 weeks of pregnancy would be appropriate. However, variation in time since diagnosis and type of diagnosis was important to consider within this. Most agreed that approaching women in the appointment before their birth-planning consultation (36 weeks) would be a good time to recruit women as they are ready to start thinking about the birth and can finalise their birth plans.

> *Yes, yes, yes because it's thirty-six weeks is when you have to write up your birthing plan or that's when you normally have your appointments looking over your birthing plan.*
>
> *Woman Pre-existing DM, P014*

For consent, women discussed this being done 1 or 2 weeks after information about the trial is provided, with follow-up within a couple of weeks or at the next appointment seeming reasonable to women. It was important that the follow-up did not happen too close to the birth as some women thought they may feel differently or potentially would have said 'yes to anything' at that time so it would not be an informed decision.

> *I guess a week before I was due to give birth I was absolutely desperate for her to come out, so at that point I would have consented to anything, I think.*
>
> *Woman GDM, P004*

A key factor when collecting consent is that women should be given the opportunity to re-affirm their consent when they come into hospital to give birth, providing a reminder which clarifies what will happen during their labour and reassure women that they have a choice to take part.

> *At the end of your pregnancy you're then not the same as you were at the beginning … So, I suppose it's good to know that if you did that re-consent, I suppose you give them the chance to still say yes or no.*
>
> *Woman Pre-existing DM, P003*

Healthcare professionals' perspectives also raised that the time of approach should be different for women with pre-existing diabetes, GDM and first-time pregnancies. with earlier approaches appropriate for women with pre-existing diabetes.

> *I think it depends on whether they've got gestational diabetes or pre-existing. I think pre-existing, yes, that's absolutely fine for a 28–36 week mum. I do a gestational diabetes clinic and there's an awful lot of information that those people are trying to take in, at the 28 week mark, that's the time that the vast majority of our patients are being diagnosed.*
>
> *Consultant Obstetrician, P016*

The HCPs' views also supported women's views in stating that 28–36 weeks is the appropriate time to approach women and that 36 weeks is optimal to finalise and consent while discussing birth plans. One HCP also mentioned that this is a time when it is clear whether the fetus has complications that might preclude the woman from taking part in the trial.

> *So for example in our Trust we see them at 36 weeks, that is where we finalise timing of delivery. So that is the time to re-emphasise whether they accept to be part of the study or not.*
>
> *Consultant Obstetrician, P013*

Recognition of potential language barriers was deemed important and a potential influence on accessibility of certain groups of women being recruited to the trial, with concerns that some professionals may have a bias as to who they would discuss the trial with, particularly if it is more difficult due to language difficulties. This highlighted the importance of having study materials available in appropriate languages.

> *I think also the accessibility of the materials that you know, it's, I think, especially the hospital I work at now, if you don't have materials available in Bengali, you're going to miss a huge proportion of the patients that you could have recruited.*
>
> *Consultant Obstetrician and Gynaecologist, P004*

All HCPs emphasised the time pressure they face, especially if expected to approach women in clinic. However, they thought a short video explaining the trial and/or apps used in certain hospitals to provide information to women would be effective tools for approaching women about the study and providing detail in a way that is accessible.

Women also spoke in detail about how information is provided about the trial to help recruitment of women. They also thought a video would be useful and more accessible for certain women; it would also provide a way for women to share information about the trial with their partners before deciding whether to take part.

> *Yes, a perfect idea, because again, your brain is so scattered sometimes, when you're trying to think about everything, you have all these appointments, if you've got a video to reference back to, that would be really useful.*
>
> *Woman GDM, P006*

Women had varying views on who would be the best person to share information about the trial with them. Many decided that their specialist diabetes midwife would be best placed to give information and answer their

questions in detail. Some were concerned that non-specialist midwives might not be able to answer their questions as comprehensively.

> *I definitely would have ruled out my midwife because she didn't know a lot about my diabetes … I suppose if I. the diabetic. I suppose because I had a lot of faith with my diabetic midwife, and she knew everything about diabetes, she knew everything about mine, I suppose if she said to me, then I think then yeah.*
>
> *Woman Pre-existing DM, P003*

For lots of women having a good relationship and knowing the HCP approaching them would help recruitment, regardless of whether this was an obstetrician or midwife. Particularly if the HCP was familiar with the women's diabetes specifically and was able to identify whether they are suitable for the study.

Women discussed a range of things they would want to know when deciding whether to take part in the trial. These included:

- the impact on the woman and her labour
- risks to the baby as well as the anticipated benefits
- whether it would change her birth plan
- physical implications of having their blood glucose tested and treated (if required) including what would happen if they do not stay between the target ranges
- information and statistics behind why the trial is being done and the design chosen.

Similarly, HCPs spoke in detail about selling it to HCPs, discussing that successful implementation of the trial would depend on the engagement of the healthcare team.

> *Start with the why. Always explain what you're trying to do, and what the net results are hoping to be. Which isn't just about woman and baby focused, it's about the impact on the whole team. So you've got to sell it to them and they'll go, oh yeah, okay, brilliant, we don't have to put a variable rate up so quickly, because actually we can give her a bit more room, so therefore the impact is less.*
>
> *Specialist Diabetes Midwife, P001*

The concept of needing HCPs to 'buy in' to the trial was thought to be critical in the success of the trial. To do this, HCPs felt that 'winning hearts and minds' through information on the importance of the trial and potential benefits to women and the HCPs themselves was important.

> *Think it's winning hearts and minds with what the end game is … I guess reaching out to the midwifery perspective the impact on Labour Suite. If you can sell it that way, that's where you'd win hearts and minds. Because it's that poor midwife on a Friday evening on a Bank Holiday weekend when nobody's around, and you think, oh God, what do I do now?*
>
> *Specialist Diabetes Midwife, P001*

Healthcare professionals made suggestions for information they would like to know in order to engage in the trial including providing predictions of reductions in intervention if the trial was successful.

> *if you had any data where you could calculate like what reduction in percentage of women who end up needing intravenous you know, the variable dosing insulin. You know, if you, if you had an idea of how many fewer women you think would end up needing insulin because of implementing this, then that I think, you know, might be quite attractive because I, I, you know, I can tell that the midwives find it irritating to have to do that.*
>
> *Consultant Obstetrician and Gynaecologist, P004*

Emphasis on how the trial might reduce HCPs' hourly commitments, workload and the potential to simplify care was welcomed as their previous experiences suggested many HCPs already think testing is too frequent in some cases.

Healthcare professionals also identified potential barriers to the trial they envisaged within their own Trust. The first was needing to have all the necessary teams on board and being able to get different teams outside of maternity care to agree to the trial, for example, endocrine and neonatal teams. This is in the context that engaging antenatal and intrapartum teams may also be challenging and a key factor in the success of the trial.

> *How do we generate that awareness for the whole Labour Ward team. Because I, as a lead for antenatal care, most of my time got spent in the antenatal clinic, you know, and that is why I was very keen to bring on those trials that involved just talking and liaising with the antenatal team because I sit very closely with them and most of my sessions were based in that setting. Whereas if this trial is going to be on the Labour Ward I will have got think a few times how am I going to do it?*
>
> *Consultant Obstetrician, P015*

Another barrier was time pressure in services, especially in the context of the staffing crisis facing these services, which might affect the data-collected intrapartum. Having enough time in clinics to discuss the trial with potential participants was a similar barrier that could stop engagement with the trial.

> *So, the staff … like all maternity units we are short staffed and to have something else extra to do, we might have poor compliance or poor uptake with the research … Yeah, so for midwives they are completely overworked, burn out and then to be told well we have got this extra thing to look at.*
>
> *Specialist Diabetes Midwife, P010*

In relation to this, data collection through electronic and paper records was discussed with worries that different sites using different systems may increase workload if needing to transfer details from paper to electronic records or vice versa. In addition, needing to retrieve information may also create double workload, which HCPs were keen to avoid.

> *Some people will still be doing it on paper, some people will be able to pull it very easily from their electronic patient records. So, it's about thinking really carefully about what Trust does what. And those that are still using paper or different electronic patient records for maternity and neonatal, which is what we … prior to our switchover this year … The easier data collection is the more you will get out of your Trusts.*
>
> *Consultant Obstetrician and Gynaecologist, P008*

> *But I mean I don't know if you're planning to collect the data prospectively or retrospectively because if you're expecting the, the midwife in the room to fill out a table for you, with what the blood sugar is every hour, then she's duplicating the work that she's already doing.*
>
> *Consultant Obstetrician and Gynaecologist, P004*

There was some discussion over the number of people involved in data collection. It was thought that bigger teams would be more challenging in terms of consistency of implementation and data collection. A related factor was the change-over of staff during a woman's labour and the involvement of agency staff, which was also anticipated to create confusion and impact on data collection.

> *A hurdle would be for example having different people on different shifts, so and also dependent a lot on agency staff who locum, consultant, locum midwives, and whether they are keen to facilitate the trial or just go the other way. I think that would be a challenge there.*
>
> *Trainee Registrar, P011*

Timing of the study was deemed important, with longer data-collection time frames making it harder for HCPs to maintain.

> *Maybe the timescale as well, because I think any, any study where you're having to recruit for a long time, again you just lose momentum and people lose interest.*
>
> *Consultant Obstetrician and Gynaecologist, P004*

The feasibility of this trial was thought to be largely influenced by the sample size aimed for.

> *I think, you know, having a realistic number that you're hoping to recruit from each place probably helps as well, so that you're not having to recruit for a very, very long time.*
>
> *Consultant Obstetrician and Gynaecologist, P004*

Conversely, HCPs were aware of several facilitators to the trial including the importance of leadership from the diabetes midwives and consultants. This was expected to encourage those midwives working within their teams and would be strengthened by discussion at MDT meetings.

> *I think we would have to look at it as an MDT with the neonatal team as well as the obstetric team, to whether we felt that was safe for our women.*
>
> *Specialist Diabetes Midwife, P010*

Leadership and stakeholder engagement were particularly important. HCPs felt that having strong 'backing' from the Trust and clinical governance at the site was important particularly when a change in guidelines is necessary to action the trial design.

> *It would need the backing of a Trust, because clinical governance, risk management guise, because we would be going against the guideline and, at the end of the day, if there is any poor outcomes then we usually, our practice is gauged against the guidelines, so the Trust needs to buy the idea; and the other thing is whether we need to be very careful as well about the women and the babies that could participate.*
>
> *Trainee Registrar, P011*

The phrase 'champions' was used repeatedly to describe the approach needed to encourage HCPs to engage with the study.

> *Also champions, you need to trust they are research champions who will get you the results as well. The worst thing is to come to work and you find there's a trial going on that you've not been aware about and then suddenly you are being told, oh, this patient is eligible but you don't even know about the trial. So invest a lot of time in preparing staff about it.*
>
> *Trainee Registrar, P011*

Healthcare professionals also reported that the support of nationwide diabetes groups would facilitate engagement with the trial by team members and provide reassurance of its importance.

> *I think there are some nationwide groups like the MacDonalds Obstetric Society for example, there's a Diabetes Care Society or the Obstetrician Maternal and Fetal Medicine Society. I think if we use these groups of professionals it will be easier to spread the word out about this trial.*
>
> *Consultant Obstetrician, P013*

For those based in university hospitals, some viewed the study as feasible in their Trust because they are part of a research hospital, with experience managing these types of trials and available research staff. However, HCPs highlighted paid time to facilitate leading the study as essential.

> *I think if, if there's someone who is, has paid time that is working on this … or if you've got someone who's coming from your study who's, you know, got an honorary contract or whatever, who's going to attend the site on a regular basis, to support the project from the perspective.*
>
> *Consultant Obstetrician and Gynecologist, P004*

Keeping the paperwork needed to complete the data collection simple was flagged as important in a trials success to minimise the amount of work that needs to be done intrapartum.

> *I suppose that if the amount of data that you want us to collect intrapartum, that's the other thing, because you know, you're, you're already, you're studying this because there's already a lot of work that has to happen intrapartum, to look after these women … I think that has to be simplified and you have to think about what's realistic, that they will actually collect for you.*
>
> *Consultant Obstetrician and Gynaecologist, P004*

Another consideration surrounding implementation of the trial was the training needed to carry out the trial. The overall perception of HCPs was that no additional training would be needed surrounding testing women as the skills are already available.

> *I don't think any extra training in terms of skill set, no.*
>
> *Specialist Diabetes Midwife, P001*

However, it would be beneficial to provide more training on sliding scales as misunderstandings were recognized.

> *I think that there is sometimes a bit of a misunderstanding about whose responsibility is the sliding scale, how often do you need to be checking, who is responsible for doing what and understandably midwives are, they're not all … It's rare for an individual midwife to have to set up a sliding scale. Even though I see it all the time, given the number of midwives I work with, each individual person may only do it once or twice a year. I think being able to train all the midwives that would need to be trained in order to run the study would be the biggest challenge but actually it's already stuff that they are supposed to know how to do so I think it would support what's already an educational issue.*
>
> *Consultant in Diabetes and Endocrinology, P007*

While it was acknowledged that minimal skills training would be required, it was noted that education about the trial would be important, in particular how to respond differently in the two arms.

> *I think video style training would be adequate it's not actual things that we do need to are not new to us. And it really is just a change in the targets. So, I think more to just to familiarise people with the trial and what the targets are.*
>
> *Consultant Obstetrician, P006*

How to discuss the trial with women was essential, preparing HCPs to answer women's questions effectively. Those recruiting needed to feel confident in what they were asking women to sign up to and why. In addition, training on how to generate awareness of the trial so that women are aware of it in pregnancy was required.

> *Just on what to say to women really … Yeah, just so that you can answer all the questions, and you answer the questions in the same way to everybody. Because you don't want to be influencing in terms of getting their consent, or in terms of how they perceive it. You don't want to say the wrong thing in terms of risk.*
>
> *Specialist Diabetes Midwife, P012)*

Ethical approval was also an important facilitator of the trial though confirmation and reassurance that the trial was safe for participants.

Patient and public involvement

The study PPI advisory group informed the development of all the study materials and helped with recruitment. The PPI group were instrumental in developing and informing the PIS, recruitment materials, information sheet on the proposed trial design and interview schedule. They were involved in recruitment of participants (women) through their peers and local network groups.

Chapter 6 Discussion

Main findings of study

This study was designed to explore practice and views solely on intrapartum diabetes care, has not focused on antenatal care, and makes no recommendation for changes in antenatal practice.

The study has shown variation in care of women with diabetes in labour and finds that a trial of glycaemic control in labour is feasible for all forms of diabetes. The local guidelines of NHS maternity units included in this study unanimously recommended 1 hourly glucose testing for women with T1DM and, with the exception of one guideline, for T2DM too. The significant variation in testing frequency of GDM suggests that some units believe that the 1 hourly frequency recommended by NICE[2] is too frequent as only 58% of units follow this recommendation, while some units did not recommend testing at all, or only on admission if the patient had GDM. The variation in the frequency of intrapartum maternal glucose testing in women with GDM was reinforced by the HCP survey, with 69% recommending 1 hourly glucose testing. There was also a lack of agreement between units with an upper target range varying from 6 to 9 mmol/l, suggesting that there is uncertainty about what this upper reference range should be. T1DM was also variably managed with some units allowing CSII (insulin pump) use to continue in labour and others recommending discontinuation and conversion to a VRIII. In the HCP survey, 45% of respondents would test glucose in labour using flash sensors or CGM.

Regarding testing for neonatal hypoglycaemia, the timing was commonly recommended to be 2–4 hours after birth or prior to the second feed. There was greater variation identified in the number of glucose levels and target level aimed for, with the latter ranging between > 2.0 and > 2.6 mmol/l. A blood gas analyser was the commonest device used to test the neonatal glucose level, with only 9% of units stating that neonatal hypoglycaemia required confirmation with a laboratory-processed sample, which is what is recommended in the BAPM guidance.[20]

The confidence of HCP in the intrapartum maternal glucose management demonstrated that only just over a half (57%) were fairly or extremely confident in caring for women with T1DM. This increased to 62% and 72% for T2DM and GDM, respectively. Only 44% acknowledged that they had received training on the control of diabetes for women in labour, with only 1 in 10 having received training on CGM and CSII (pump) in labour. Theoretical training was more common than practical training. Ninety-eight per cent of respondents felt that training would be helpful or necessary prior to any future RCT; this would be incorporated into the site training package prior to opening the trial. Eighteen per cent of respondents felt not confident in the diagnosis and treatment of neonatal hypoglycaemia, and training in this area was deemed fairly or extremely important by 72% of respondents.

The women's survey responses were from women with GDM in the majority (95%), with women having hourly glucose testing feeling that they were being tested too often. The commonest concern women had in labour was that their glucose levels would be unstable and lead to complications for the baby (neonatal hypoglycaemia) once it was born. Women seem willing to consider participation in a future trial in principle to guide future practice, with two-thirds of respondents responding positively, 23% unsure and only 11% would decline. Women would prefer information about any study in the antenatal period, using a combination of verbal and paper information. Women felt that the most important outcome measure for the mother or baby in any future study was neonatal hypoglycaemia (27%) with symptomatic hypoglycaemia (23%) being the second most important outcome.

Seventeen obstetric units in the UK responded to our request to record the number of women with different types of diabetes aiming for vaginal births over an 8-week period. It is well known that there is a higher rate of elective caesarean section in women with T1DM, and we wanted to establish if the percentages of women with T1DM and T2DM aiming for a vaginal birth, therefore eligible for participation in any future trial, were similar. This demonstrated that, in comparison to the percentage of women with diabetes in pregnancy, there was a reduction in women with T1DM and a greater number of women with GDM in the population aiming for vaginal birth and the numbers of women with T1DM and T2DM aiming for a vaginal birth were similar (92% GDM, 4% T1DM, 4% T2DM). This will

make recruitment into the arm for women with pre-existing diabetes easier if the number of women eligible are equally balanced.

We undertook a service evaluation of 594 women with diabetes in labour at term over an 8-week period, with purposive sampling to ensure that all forms of diabetes (T1DM, T2DM and GDM) were included from submitting units. Cases comprised of 13% women with T1DM, 9% with T2DM and 77% with GDM.

In the antenatal period, the only difference in outcomes identified between types of diabetes was that women with T1DM were more likely to have babies with suspected macrosomia (T1DM 36%, T2DM 29%, GDM 22%; $p = 0.04$). In line with national guidance, women with T1DM and T2DM were likely to deliver earlier than those with GDM and more likely to be induced (T1DM 77%, T2DM 81%, GDM 65%; $p = 0.03$). Mode of birth varied between groups, with 32%, 48% and 65% of women achieving a normal vaginal birth in T1DM, T2DM and GDM, respectively ($p < 0.001$).

Information on the frequency of testing demonstrated that data were recorded far less commonly than expected by the guidelines in use in the units surveyed. Only 7 women (9%) with T1DM, 7 women (14%) with T2DM and 34 (7%) of women had a glucose measurement taken within an hour of admission to Labour Suite. Once testing commenced, repeat testing was undertaken within 1 hour in 34% or 2 hours in 52% of T1DM, these figures were 14% and 35% in T2DM and 16% and 36% in GDM, respectively. These data may reflect that women are not having glucose measurements checked, or alternatively that if they are checked, then they are poorly documented in the maternity notes. Such knowledge is useful in the conduct of a pragmatic trial of glycaemic control in labour as the documentation of glucose values will be fundamental in the conduct of any future trial. The binary outcome asymptomatic neonatal hypoglycaemia was reported in 18% of babies born to women with T1DM, 15% with T2DM and 9% with GDM. The values for symptomatic hypoglycaemia were 10%, 6% and 1%, respectively. Focusing on actual glucose values, 47%, 45% and 16% of babies born to mothers with T1DM, T2DM and GDM, respectively, had a first blood glucose level < 2.6 mmol/l. The corresponding values for a glucose level of 2.0 mmol/l or less were 27%, 31% and 4%, respectively. Comparison with other studies is discussed in the subsequent section. With the exception of jaundice, all other neonatal complications were uncommon.

Our Delphi study obtained input from key stakeholders including midwives, obstetricians, neonatologists, endocrinologists and women who currently have/have had diabetes in pregnancy. There was consensus among participants that all three populations (T1DM, T2DM, GDM) should be included in a RCT. The outcomes that reached consensus, by having 70% or more participants scoring 7–9 and < 15% participants scoring 1–3 in the third round of the Delphi, were then voted on at the consensus meeting. For T1DM, there was consensus that 1 or 2 hourly testing should be adopted. For T2DM and GDM, there was consensus that 2 hourly testing should be adopted. Finger prick, continuous flash/glucose-monitoring sensors, VRIII, CSII and closed loops were technologies that were voted on; all reached consensus for T1DM while only finger prick reached consensus for GDM, and finger prick, CGM, VRIII reached consensus for T2DM. All were discussed again at the consensus meeting. For maternal and neonatal outcomes, midwives, obstetricians and endocrinologists responded in one survey, while neonatologists and women responded in a second survey (as the latter group only voted on outcomes). A total of 13 maternal outcomes and 16 neonatal outcomes reached consensus in.

At the consensus meeting, all types of diabetes were equally prioritised for inclusion in a future RCT with consensus that glucose testing should be 1 hourly in T1DM and 2 hourly for GDM (no longer interval than 2 hourly was voted upon). For T2DM, an equal number of respondents voted for 1 hourly and 2 hourly glucose testing. Results for technology used for testing suggested that there was support for using CGM/sensors with all forms of diabetes in labour and that CSII (pump) was supported for T1DM only, with a VRIII being the treatment consensus for T2DM and GDM. The neonatal outcome that scored highest for being the primary neonatal outcome or to be included within a composite neonatal outcome was neonatal hypoglycaemia followed by neonatal unit admission. The highest scoring maternal outcome was mode of birth.

Trial design meetings were held by members of the co-applicant team to agree a trial design. A multicentre, non-inferiority master protocol design was considered the most appropriate for the RCT, which is discussed in detail in *Chapter 5*.

The proposed trial design was reviewed by HCPs and women to explore any barriers and possible facilitators to the conduct of the trial, discussions supported by an infographic produced by the study team. It was clear from interviews with women that they feel current guidance in terms of the frequency of glucose testing in labour is not being followed strictly, with many sharing experiences of infrequent or limited testing being carried out during their labour. They described being given confused and conflicting advice on testing at times and that raised values were not always actioned. Although this could have been influenced by women's memory, the finding agrees with the results of the women's survey conducted at the beginning of this project (work package 1c) and the service evaluation from 33 UK maternity units. Women with diabetes are used to testing their glucose and are aware of the antenatal target ranges as these are frequently and repeatedly reviewed and discussed in antenatal clinics and values above target are flagged in some monitoring apps (e.g. GDm-Health). Intrapartum glucose targets tend to be less often discussed in clinic and women may not be as clear as to the expectation of testing in the intrapartum period. At the point of approach to participate in any future trial, women need to be informed of what standard intrapartum glycaemic care would be and what the intervention would entail.

It will be important to ensure adherence to the randomised strategy is monitored closely, initially within the proposed internal pilot phase. Indeed, the conduct of such a trial might make staff on maternity units' question whether there is a need to maintain tight control, and they may accept higher glucose values in those who have been randomised to tight control. The study team have considered the issue of collecting information on glycaemic control in labour. One possible solution for testing adherence to the trial is to ask women to wear a CGM or sensor (e.g. Libre) for the labour, not for the purpose of glycaemic control, rather to assess time in target for the purpose of adherence to the randomised group in the trial.

Education around glycaemic control in labour is clearly lacking among some maternity staff, with some HCPs describing feeling uncomfortable and anxious caring for women with diabetes in labour. Their perception of what might happen to women if their glucose level is above an upper target range may be misconstrued. In addition to educating staff at participating sights on sliding scales, details on the reasoning for the trial and how to answer potential study-related questions would be important to limit conflicting information. The role of a study champion for the trial was also promoted by HCPs. One area where knowledge was not up to date was that both HCPs and women reported confusion in the target range for the standard care arm of the trial design (4–8 mmol/l); HCPs were unaware of the updated JBDS guidance.[1] Contradicting the women's survey results (work package 1c), participants during interviews (HCPs and women) suggested that a short video would be an appropriate method for education and informing them about the trial. Accessibility of study materials in different languages and information on pregnancy apps were also considered important to facilitate recruitment.

Participants reported variations in upper glucose targets set in varying trusts, albeit with a narrow span of 7–8 mmol/l. Some considered whether this would make the study more difficult to conduct. The study team considered the upper target range at length and judged that by the time any trial is undertaken, it is likely that many maternity units will have moved over to the JBDS[1] defined 'safer' target of 8 mmol/l rather than the 'strict' target of 7 mmol/l.

Neonatal hypoglycaemia and mothers' experiences of birth were two outcomes highly regarded by both women and HCPs and are in line with the planned trial design. One HCP suggested consideration for a longer-term follow-up than the 2 years proposed. While this may be an aspiration, it also raises many more challenges: more funding would be required and assessment of routine data at a non-routine time point would be difficult, with attrition potentially being amplified. However, women could be asked if they were willing to consent to future approach to ask if they wanted their child to participate in a longer-term follow-up, pending successful funding of such a study.

Women overall were positive about the trial stating it enabled them to contribute to improving future intrapartum care for women with diabetes. However, they wanted to feel that they had choice in participation, time to consider and ability to change their mind. Overall, they felt that the proposed trial achieved this. There was also the feeling among both HCPs and women that the time of approach optimally may differ between the groups. Women with pre-existing diabetes could be approached early in the third trimester. For women with GDM, however, the diagnosis is often made at 28 weeks, and there is a lot of information given to them at this point. Delay in approaching this group of women

until they had time to become accustomed to the diagnosis and the control of their glucose levels was considered the most suitable method.

While challenging to conduct, we consider that it is feasible and acceptable to conduct a clinical trial, comparing glucose-monitoring strategies for women with diabetes during labour. Using an umbrella trial design should enable efficiencies in conduct, while enabling women with all types of diabetes to be included. Further work with clinicians and women with diabetes is required to inform an acceptable non-inferiority margin in order to determine the sample size for such a trial. This should consider the proportion of women likely to have higher blood glucose values which would be managed differently using the permissive strategy as shown in *Chapter 4*. However, a trial with a smaller non-inferiority margin is likely to require a very large sample size, for example, a trial with a non-inferiority margin of 3% in women with pre-existing diabetes would require over 8000 women, potentially meaning such a trial is unviable. We consider that it will also be feasible to conduct a within-trial economic evaluation to estimate the incremental cost per neonatal hypoglycaemia prevented at birth. The trial design could be extended to explore the longer-term sequelae of GILD on neonatal hypoglycaemia, and to explore new modelling approaches to combine disparate outcomes for mothers and children in a single preference-based outcome measure. The trial could additionally provide an excellent vehicle to examine preference-based measures validated for use in infancy that permits the estimation of QALYs amenable to cost-effectiveness decision-making. It would be important to show that glucose-monitoring strategies can be delivered as allocated to avoid the potential of bias towards a conclusion of non-inferiority due to poor adherence to the allocated strategy. Given the challenges foreseen, we recommend a future randomised trial include an internal pilot phase, with clear progression criteria, focusing on recruitment, adherence to the randomised glucose-monitoring strategy and the ability to collect primary outcome data.

Comparison with published literature

National Institute for Health and Clinical Excellence guidelines recommend that capillary glucose should be checked every hour in the labour of women with diabetes and recommends that the glucose target should be 4–7 mmol/l.[2] It recommends that they are controlled in this target range by a VRIII. These guidelines were published in 2015 and the 2020 update made no changes to the intrapartum recommendations. The evidence that drives this recommendation is from eight observational studies, and not all describe the type of diabetes included. These studies found that there was an association between maternal hyperglycaemia and neonatal hypoglycaemia. However, association is not the same as causation and some of the studies fail to consider the influence of important confounders, such as antenatal glucose control, type of diabetes, prematurity and macrosomia. Studies may also fail to reflect current practice as their publication dates from 1985 to 2000, when technology and types of insulin available to care for women with diabetes were limited compared to current practice. The numbers of women included in these observational studies were small, ranging from 25 to 233, with half of studies involving < 100 women. Methods varied and included an audit of practice against historical controls,[52] retrospective case review,[53] prospective observational study[54] and an observational interventional study.[55] There were no published RCTs on intrapartum diabetes control. Studies included women who had elective and emergency caesarean section in addition to vaginal birth,[54] do not specify the target range of glucose[56] or use targets that are lower than current practice at 2.8–6.9 mmol/l[57] and < 5.6 mmol/l.[56] Definition of neonatal hypoglycaemia also differed from current practice in some studies at < 2.0 mmol/l[58] or < 1.7 mmol/l.[59]

The NICE guideline[2] states that their guideline development group placed greater emphasis on maintaining glucose between the range of 4 mmol/l and 7 mmol/l, without being prescriptive as to how this was achieved. It states that women using a CSIII could experience labour without using intravenous insulin regimens, although this is not clear unless the evidence within the full guideline rather than the summary version is read.

The JDBS originally published their guidance on intrapartum diabetes care in 2017 and updated this in April 2022, during the conduct of this study, making several changes to their recommendations.[1] A new pragmatic approach of aiming for a glycaemic target of 5–8 mmol/l is advocated, rather than the traditional approach and the one recommended by NICE. This is not based on new evidence, rather a lack of evidence as to what the optimal target should be, acknowledging that the study reported here was also being undertaken. The reason for this recommendation is that it would reduce the use of VRIII, allowing women more autonomy and mobility in labour, reduce the risk of

maternal hypoglycaemia and reduce the burden on maternity staff. They acknowledge that the recommendation has a limited evidence base and that women and staff may be fearful of an increased risk of neonatal hypoglycaemia. This fear, however, may be unfounded as recent evidence suggests that tight intrapartum control may not impact significantly on neonatal hypoglycaemia.[4,60] Rather, there is increasing evidence that prolonged maternal hyperglycaemia in the antenatal period, due to its link with fetal hyperinsulinaemia, is associated with neonatal hypoglycaemia, in addition to other complications such as macrosomia. Tight glycaemic control during labour may not reverse fetal hyperinsulinaemia and its consequences in women with poor antenatal control. Similarly, a short duration of slightly elevated blood glucose in the labouring mother is less likely to result in fetal hyperinsulinaemia and its consequence. Whether this recommendation is followed or whether maternity units continue to follow NICE guidance is yet to be established, and our service evaluation of intrapartum glycaemic control in UK maternity units, that pre-dated this change in the JDBS guidance, demonstrates that maternity units may develop their own guidance outside of those recommended nationally, particularly in women with GDM.

There is emerging but limited evidence that intrapartum care using both CGM and CSII can safely maintain blood glucose in labour. A retrospective case review of 65 pregnant women in 4 centres in Italy found that glycaemic control was similar in women who used CSII alone to those using a CSII with CGM/sensor, the latter achieving better intrapartum glycaemic control. No women required conversion to VRIII, and 11 babies (17%) developed transient hypoglycaemia.[61] Similarly, a retrospective cohort study of 161 pregnancies in T1DM, from 2000 to 2010, found that 19% continued on CSII therapy through labour, 16% converted from CSII to VRIII during labour, and the remaining 65% were on antenatal multiple daily injections of insulin and used VRIII for labour.[62] Women using CSII in labour demonstrated better glucose control than those changed to VRIII. The CONCEPTT trial of antenatal CGM versus capillary glucose monitoring reported neonatal hypoglycaemia rates of 15% in the former group compared to 28% in the latter arm.[16] Secondary analysis of women who used CGM in labour found no difference in maternal glucose levels of women whose babies had neonatal hypoglycaemia and those who did not, but the numbers were very small (n = 27).[63] A Danish RCT is in progress evaluating CSIII (pump) use with multiple daily injections throughout pregnancy (antenatal, intrapartum and post partum).[64]

Our service evaluation of intrapartum glycaemic control, women and HCP surveys and review of intrapartum diabetes guidelines demonstrates that there is increased use of CGM and CSII in labour in women with T1DM. JBDS acknowledge that women want to continue using CGM/sensor and CSII in labour and self-manage their diabetes and that some women, particularly with T1DM, are concerned about relinquishing glycaemic control in labour to staff with limited knowledge. The JBDS guideline recommends that women can monitor their glucose levels hourly using either capillary (finger prick) test or sensor (flash or CGM) but advocates capillary glucose values outside the target range should be used to adjust the VRIII or CSII rate. This is because CGM measures interstitial glucose levels, and changes may lag 5–10 minutes behind capillary glucose measurements. Such guidance has the potential to empower women to self-manage their diabetes and reduce burden on maternity staff. It is also in line with the highest priority in the James Lind Alliance priority setting partnership of diabetes in pregnancy (antenatal, intrapartum and post partum care) of how diabetes technology can be used to improve pregnancy and birth outcomes for the mother and baby.[65]

There is acknowledgement in the JDBS guidance that there may be a requirement for different intrapartum approaches for different diabetes types (T1DM, T2DM or GDM). This is reflected in current practice evidenced through our review of UK maternity unit guidelines, where 58% of units tested glucose 1 hourly in women with GDM.

The glucose concentration used in the definition of neonatal hypoglycaemia is controversial, has changed across time, with the most widely used value currently < 2.6 mmol/l supported by limited evidence.[66] The aim of defining neonatal hypoglycaemia is to identify a threshold value where brain function is compromised and where treatment would prevent brain injury. The issue is that this value is likely to be dependent on many factors including gestational age, comorbidities, metabolic demands and postnatal age. BAPM guidance was published in 2017 to give operational thresholds to guide interventions and suggested a value < 1.0 mmol/l at any time, a value < 2.5 mmol/l in the presence of abnormal clinical signs or an asymptomatic baby with two consecutive values < 2.0 mmol/l in babies with risk factors.[20] This contrasts with the earlier publication from NICE that recommends maintaining glucose values > 2.0 mmol/l.[2] The differences between these two national guidance may well account for the differences in thresholds for diagnosis of neonatal hypoglycaemia that were evident within our review of guidelines. This review confirms

the earlier findings of a survey of definition and monitoring of neonatal hypoglycaemia in neonatal units in England undertaken between April and August 2015, therefore shortly after the publication of the NICE diabetes in pregnancy guidance but before that of BAPM. Our audit summarises treatment recommendations, which was not included in the previously published survey. There is now a bimodal distribution of threshold values that trigger different interventions, which was not evident in the earlier survey, and this may reflect the differences in operational thresholds that was analysed in this study rather than simply a definition of neonatal hypoglycaemia. Indeed, using a threshold value of 2.6 mmol/l may lead to unnecessary interventions and undermining of mothers' confidence in their ability to breastfeed, and observational studies have shown that 12–14% healthy term babies have values below this in the first few days of life.[67] First-line treatment for asymptomatic neonatal hypoglycaemia is to encourage, if tolerated, an increase in maternal feeding of the baby. Milk is known to contain up to twice as many calories as a similar volume of 10% dextrose infusion.

It is well established that point-of-care testing of neonatal glucose is prone to inaccuracy when blood glucose levels are < 5.5 mmol/l, and especially so if the values range between 0 mmol/l and 2.0 mmol/l. It is recommended that a blood gas analyser should be used for the diagnosis of neonatal hypoglycaemia, as a compromise between speed of availability of the result and accuracy. Laboratory glucose takes longer to be analysed but is accurate but, in this study, < 10% of the UK guidelines recommended confirmation of neonatal hypoglycaemia in this way.

There is only one published RCT of glycaemic control in labour. It only included 76 women with GDM and compared tight control (defined as maternal glucose target range of 3.9–6 mmol/l with 1 hourly glucose checks) and liberalised control (defined as maternal glucose target range of 3.9–6.7 mmol/l). Both of these targets would be considered tight control in the UK and lower than both NICE and the JBDS target ranges. With an incidence of 24% in each group, it found no difference in neonatal hypoglycaemia (defined as glucose < 2.2 mmol/l in the first 24 hours of life).

We reviewed the literature of studies published in the last 10 years where the type of diabetes was specified and the incidence of neonatal hypoglycaemia in labour was reported. We excluded studies where the data they referred to in the study were historic (more than 10 years previously). We opted to restrict the study to the last decade as management, particularly of T1DM, has changed with the use of CGM and CSII. In addition to the one RCT, there were 16 other studies that we identified.

The incidence of neonatal hypoglycaemia in the UKRCOG service evaluation (defined as glucose < 2.6 mmol/l) occurred in 47%, 45% and 16% of babies born to mothers with T1DM, T2DM and GDM, respectively. These values are in the middle of the ranges in published literature, highlighted in *Table 38*, and higher than the ~ 30% for T1DM, ~ 20% in T2DM and ~ 5% in T1DM quoted in the JBDS guideline, referencing the 2018 Yamamoto systematic review[4] of intrapartum glycaemic control that included many older studies than in the table below. In any future trial, the data-monitoring committee should be asked to monitor the assumptions used in the sample size calculation, given the uncertainty in the incidence of neonatal hypoglycaemia.

In terms of the service evaluation conducted as part of this research it identified that although the majority of maternity units recommended 1 hourly glucose testing in labour, in practice it is highly questionable if this occurs. There is a lack of education and knowledge on diabetes in labour among many midwives and doctors, and this was further highlighted in our HCP survey. This may have led to 1 hourly glucose testing being deprioritised in the workload that maternity staff face. It may also be that glucose levels are tested in labour by women and the issue is that maternity staff fail to document these results in a systematic manner.

The development of core outcome sets to report trial outcomes has become increasingly popular over recent years, but there has been no such endeavour in intrapartum diabetes care. There are several Delphi surveys that have attempted to established core outcome sets in treatment of pre-existing diabetes or GDM throughout pregnancy. Egan *et al.*[84] identified 116 GDM outcomes through a systematic review and undertook a three-round, online Delphi survey. Of the 173 stakeholders (including women with current or history of GDM) who completed round 1 of the Delphi, 59% went on to complete the three rounds. A total of 30 potential treatment outcomes were discussed at a consensus meeting involving 23 participants, with 14 outcomes (6 maternal and 8 neonatal) included in the core outcome set. Of the outcomes that were relevant in intrapartum diabetes care were adherence to intervention, mode of birth, neonatal

TABLE 38 Publications where type of diabetes specified and incidence of neonatal hypoglycaemia reported – restricted to last 10 years.

Author	Year published (study conduct)	Country/ sample size	Study type	Diabetes type	NNH (definition: mmol/l)	Potential confounders
Crowther *et al.*[68]	2022 (2015–7)	New Zealand 1100	RCT tight vs. less tight AN control	GDM	27% (not specified)	Macrosomia (11%)
Harrison *et al.*[69]	2022 (2018–20)	Australia 2491	Retrospective cohort	GDM	8% (not specified)	Prematurity included (12%) Twins excluded
Corcillo *et al.*[70]	2022 (2012–7)	Switzerland 780	Prospective cohort	GDM	8% (< 2.6)	Prematurity included. Macrosomia 15%
Anwer *et al.*[71]	2021 (2017–9)	USA 853	Retrospective cohort	T1DM T2DM GDM-meds GDM-diet	64% (< 2.5) 54% 41% 27%	LGA (13%)
Riskin *et al.*[72]	2020 (2015–7)	Israel 479 GDM 47 (T1/T2)	Retrospective case control	GDM T1/T2DM	7% (< 2.2) 29%	Twins (9% vs. 13%) Prematurity (11% vs. 32%) Macrosomia (10% vs. 26%) Anomalies (4% vs. 13%)
Yamamoto *et al.*[60]	2020 (2007–4)	Canada 182 T1 350 T2 6208 GDM	Retrospective cohort	T1DM T2DM GDM	28% (Rx with i.v. dextrose) 18% 5%	Preterm (41/20/11%) Macrosomia (48/24/10%)
Hamel *et al.*[73]	2019 (2016–8)	USA 76	RCT intrapartum control	GDM-tight GDM-loose	9% (< 2.2) 9%	
Dalsgaard *et al.*[74]	2019 (2009–3)	Denmark 555 IC; 157 HC	Interventional cohort[a] and historical control	Control Intervention[a] (all diet GDM)	23% (< 2.5) 10%	Prematurity 4%
Bashir *et al.*[75]	2019 (2015–6)	Qatar 105	Retrospective cohort	T1DM	45%	Prematurity included. Macrosomia 7%
Voormolen *et al.*[76]	2018 (2015–8)	Netherlands 506 (22%-insulin)	Prospective cohort	GDM (insulin) GDM (diet) GDM (insulin) GDM (diet)	35% (< 2.6) 33% 21% (< 2.0) 20%	Macrosomia 17% (79% NNH in AGA) Exclusion: Prematurity, congenital anomalies
Al Nemri *et al.*[77]	2018 (2014–5)	Saudi Arabia 279 total (9 T1/36 T2/244 GDM)	Retrospective cohort	T1DM T2DM GDM	33% (< 2.6) 14% 11%	Prematurity (22/19/14%) LGA (16/11/10%) Congenital anomalies
Farrant *et al.*[78]	2017	New Zealand 733	Prospective cohort	GDM-I GDM-no I GDM-I GDM-no I	16% (< 2.6) 18% 8% (< 1.6) 5%	Prematurity (10%)
Joshi *et al.*[79]	2017 (2009–14)	Australia 261	Retrospective cohort	T1/ T2DM	47%	
Sargent *et al.*[80]	2015 (2007–14)	USA 95	Retrospective cohort	T1DM (CSIII) T1DM (MDI)	66% (< 2.6) 38%	Term
Maayan-Metzger *et al.*[81]	2014	Israel 576	Retrospective cohort	GDM	37% (< 2.6) 10% (< 2.2)	Term
Mitrovic *et al.*[82]	2014 (2006–10)	Serbia 156	Retrospective cohort	T1DM T2DM/GDM	52% (< 2.5) 17%	Macrosomia
Ramos *et al.*[83]	2012	USA 385	Retrospective cohort	T2DM and GDM on Rx GDM-diet	25% (< 2.5) 3%	Macrosomia

AGA, average for gestational age; i.v., intravenous; LGA, large for gestational age; NNH- neonatal hypoglycaemia.
a Breastfeeding and skin-to-skin contact within 2 hours of birth.

hypoglycaemia, neonatal death and stillbirth. Other intrapartum outcomes in this core outcome set such as birthweight, large or small for gestational age, gestation at birth are unlikely to be influenced by a trial of intrapartum diabetes care but require consideration as they may be potential confounders in a future trial. A further core outcome set was developed during a similar timeline by Bashir *et al.*[85] This study did not include women with lived experience of the condition in their stakeholder group and failed to present the data on number of rounds of a Delphi survey conducted (five were planned) and the number of individuals completing the rounds or participants in the stakeholder group. Outcomes relevant to the intrapartum period included maternal hypoglycaemia, neonatal unit admission and neonatal death. Kgosidialwa *et al.*[86] published an international core outcome set on treatment of pregnant women with pre-existing diabetes. Of the 205 stakeholders, who included women with T1DM/T2DM completing the first round, 80% completed the third round. There were 26 voting stakeholders in the consensus meeting. Of the 131 initial outcomes, 19 included within their final core outcome set and those relevant to intrapartum care not previously stated were maternal death and shoulder dystocia, the latter being more a reflection of antenatal care than intrapartum glycaemic control. All of the relevant intrapartum outcomes highlighted in this study were included within our Delphi study. We had slightly fewer people (n = 133) completing the first round of our Delphi study, but our consensus meeting included a few more participants (n = 30), but attrition was significantly higher with only 17% of those who completed round 1 going on to complete round 3.

Interviews with women on a future trial suggested that altruism was an important consideration, in enabling them to contribute to improving future intrapartum care for women with diabetes. It is often-quoted in reasoning behind participation in research studies. Some systematic reviews, however, suggest that the desire of helping others/contributing to science does not lead a volunteer to participate in a study, unless a personal benefit is also perceived.[87] A scoping review of studies involving antenatal breast milk expression (including in women with diabetes) highlighted that the themes for participation in studies included (1) confidence of familiarity with the process/intervention; (2) perceived impact of the intervention; (3) learning and resources around the subject; (4) altruism; (5) challenges of the intervention and (6) physical symptoms related to the intervention.[88] A future trial therefore needs to try and ensure that women have access to information around these themes to maximise recruitment rates. The timing of this information is also crucial, and this study suggested optimal timing of some of this information.

Strengths of the study

There is no doubt that developing a trial to examine intrapartum glycaemic care in women with all forms of diabetes is a challenge. There are many complex issues to consider, not limited to the significant difference in incidence of the different types of diabetes, equipoise among women and the different HCPs involved in intrapartum diabetes care, the variation in current UK practice and the variability of technologies that are offered to inform glycaemic control in the different types of diabetes. By funding this scoping exercise, the National Institute for Health and Care Research (NIHR)-Health Technology Assessment (HTA) has offered us the opportunity to explore these different aspects to aid the design of a trial that is most likely to be feasible to perform. We have also had the opportunity to question both HCPs and women with lived experience of diabetes in pregnancy and labour on their views of this trial design in terms of acceptability, barriers and facilitators to conducting the research.

Survey results highlight the strength and weaknesses UK midwife respondents felt in confidence and training in various theoretical and practical components of glycaemic control in labour and advocate the development of a training package to be delivered alongside site initiation visits for trial compliance and conduct. Evidence from this study shows that despite maternity unit guidelines recommending 1 hourly glucose levels are performed during established labour, this is either poorly adhered or poorly documented within maternity notes. It has also led us to consider if a possible solution to issues regarding adherence to the randomised arm would be to establish this by retrospectively calculating time in target using a CGM device, even in those women who are not using these in the clinical setting to monitor their glycaemic control.

Gestational Diabetes UK has a very active social media presence of women currently pregnant with GDM or recently had their baby. The support they afforded in publicising the various aspects of this study that required participation of women with lived experience of the condition was invaluable in including women from wide geographical areas, diverse

ethnicities and levels of experience. We also included an active PPI advisory group of women of diverse backgrounds that guided the research team as they ran the project ensuring that participant perspectives were central to this project.

Weaknesses of the study

We had aimed to collect clinical guidelines from 60% of consultant-led Delivery Suites in the UK. The proportion that we achieved was below this target, but we consider that they are representative of practice across the UK and guidelines were received that covered England, Scotland and Wales. They included large and small maternity units and district general and teaching hospitals. We explored several avenues to collect as many guidelines as we were able as the response rate from asking the labour ward leads of the BICS was poor. We supplemented this by asking contacts within the Clinical Research Networks and personal contacts of the co-applicants to boost the number of guidelines that we were able to gather.

Diabetes UK had agreed to support publicity for relevant aspects of the study to their following. Unfortunately, they were unable to support the women's' survey in the required timeline and 95% of responses were from women with GDM. We did consider running another survey at the end of the project to gather more views from women with T1DM and T2DM but in discussion with the study steering committee elected to purposively sample more women with T1DM and T2DM in the qualitative study as this was likely to give richer information than a survey.

The service evaluation undertaken by UKRCOG was large, including 594 cases. However, the glycaemic-testing frequency information recorded in this study was less frequent than expected in most cases so it was not possible to ascertain who had intensive control and who had more relaxed control. Overall, only 8% of women had a documented glucose measurement within 1 hour of admission to Labour Suite or 11% within 2 hours. We had planned to compare maternal and fetal outcomes, and in particular neonatal hypoglycaemia, in mothers who had intensive glycaemic control in labour and mothers who maintained a more relaxed control, and this was not possible due to being unable to determine the glycaemic control groups. Similarly, we had then planned to determine if the presence of other risk factors such as size of the baby (macrosomia/growth restriction), presence of infection/sepsis, hypothermia, third-trimester control were potential confounders and again this was not possible.

The Delphi survey that was conducted included both HCPs and women with diabetes as they are often experts in their condition and are a key part to delivery of a RCT. The numbers of participants in the Delphi survey are in line with other published Delphi studies on diabetes in pregnancy.[84–86] However, the attrition rate between rounds in our Delphi survey was greater than previously published and the numbers that completed round 3 were limited in this Delphi. There is no clear reason that we see for this, but postulate that it could either be as the rounds were quite close to each other to ensure that the study as a whole remained on target or whether the impact of COVID meant that participants had less mental capacity to deal with repeated completion of such a survey.

Limitations of the study

This study was conducted between December 2020 and November 2022. This was after the first COVID-19 lockdown of March 2020 but coincided with two UK national COVID-19 lockdowns starting in November 2020 and January 2021, COVID vaccination commencing in December 2020 and restrictions being lifted in July 2021. As a result of the COVID pandemic, the study methodology had to be adapted to allow for social distancing and suspension of in-person meetings. We had planned our PPI advisory group attend and disseminate the women's survey at their local groups (e.g. mother and baby) and support women to complete the questionnaires, targeting women from ethnic minority and under-served groups. It was not possible to do this, but the survey remains diverse in terms of ethnicity.

For the surveys, which asked participants to provide subjective views on intrapartum glycaemic control and neonatal hypoglycaemia, we had targeted 300 and 200 responses in the HCP and women's survey and the 174 and 159 responses in the HCP and women's surveys, respectively, came close to this target. We are unable to ascertain if there were multiple responses from one maternity unit, but the wide geographical representation of responses from across

the country makes the surveys likely to be representative. The HCP survey was responded to mainly by midwives (69%) and obstetricians (29.9%), with only 1.1% of responses from endocrinologists and diabetes specialist nurses. Endocrinologists were likely to be on a medical on call rota and therefore frontline workers in dealing with the COVID-19 pandemic. This may have affected their capacity to be able to respond, with staff commonly describing exhaustion due to increased workload, fear, fatigue, and resulting in increased levels of stress, anxiety and lack of sleep at this time.[89] However, although endocrinologists and diabetes specialist nurses are vital in the provision of care of women with diabetes in pregnancy, they are significantly less likely to be directly involved in the intrapartum glucose control of women; therefore, many aspects of the questionnaire were designed for completion by midwives and obstetricians. Also, the wording at the beginning of the questionnaire asking participants to confirm if they were happy to complete the survey and involved in intrapartum care of women with diabetes in the UK may have put endocrinologists and diabetes specialist nurses off completing the survey perceiving that they had no direct role. Views of endocrinologists were considered in the National Diabetes in Pregnancy conference in November 2021, where 675 delegates attended virtually and were involved in a debate on 'Stricter or safer intrapartum glucose targets', prior to the publication of the updated JBDS guideline. The view from the conference was that there was need to provide safer care and adjust the JBDS guidance and that this should go ahead without a research trial. A RCT was perceived by diabetologists as being challenging and would require too large a sample size. This perception is very different from those of obstetricians, who have equipoise to conduct very large clinical trials (e.g. GBS3: ISRCTN49639731) and in challenging circumstances e.g. post partum haemorrhage (WOMAN trial: ISRCTN76912190) and preterm birth (Cord pilot trial: ISRCTN21456601). Our women's survey also positively highlights that women would be willing to participate in a potential trial of glycaemic control in labour, with 66% willing to participate, 23% unsure and only 11% declining. These figures are likely to be higher than those who would agree to participate if an actual trial was offered to them, but it does demonstrate that this is an important research question that women want to find the answer for.

For women participating in the qualitative interviews, recruitment was restricted to women who spoke adequate English to participate. We tried to purposively sample women of different ethnicity and the study characteristics of 74% White British, 15% ethnic minority and 11% other White ethnicity are in keeping with the UK population. We have included women from ethnic minority backgrounds within the PPI advisory group to try to ensure that the results of this study are relevant to a diverse population. This is discussed further in the following section.

Chapter 7 Equality, diversity and inclusion

Throughout the conduct of this study, we have attempted to include representation of the views of a diverse population of women and HCPs to ensure that the design of a future RCT represents the thoughts of all relevant women and stakeholders within its design. We have considered aspects relating to equality, diversity and inclusion and the differences between impact and knowledge of diabetes in the different types of diabetes (T1DM, T2DM and GDM). Fundamental to this study was the inclusion of a parent and patient advisory group comprised of five women with personal experience of diabetes during pregnancy and birth (one with T1DM, one with T2DM and three with GDM). Three members were White British, one Black British and one Asian British, and they lived across England (North, North West, Yorkshire and the Humber, Midlands, South East). The group included Maternity Voices Partnership lay members, peer supporters and a NICE expert patient.

Participant representation

This study was co-designed from the outset with a PPI co-applicant and collaborators who influenced and guided the development of this project into its final submission. Our PPI co-applicant Plachcinski led a PPI advisory group throughout the study to advise the study team on study conduct, documentation and interpretation. Additionally, four meetings of approximately 90 minutes were held on Zoom with the Chief Investigator and the PPI advisory group.

The inclusion of a PPI advisory group for this study we deemed important for a number of reasons. First, we were conscious that diabetes, and particularly GDM, was common in women from ethnic minority groups. Second, we were aware that engagement in research and clinical care in women from ethnic minority groups is more challenging. Indeed, the 'Better Births' national maternity review of 2016 has suggested that care is tailored for this group, with increased engagement and extra time required to gauge understanding and recognise cultural differences.[90] We therefore wanted to ensure that our PPI advisory group would be able to provide a voice for women from ethnic minority groups and advise us on how best to engage with women from these groups and facilitate wording of documentation that facilitated this. We therefore proactively recruited diverse members into the PPI advisory group. The group highlighted issues such as low literacy in some minority groups, and communities where women were expected to follow traditional dietary advice during pregnancy. The PPI advisory group was closely involved in discussions about the primary outcome (maternal or fetal focus), and all members emphasised the importance of minimal mother and baby separation after birth as an outcome measure.

Diabetes in pregnancy encompasses three distinct groups: T1DM, T2DM and GDM. The incidence of the conditions in pregnancy is skewed significantly so that approximately 87.5% of the population has GDM, with 7.5% of the population having T1DM and 5% T2DM.[2] The numbers of women with GDM and T2DM in pregnancy are increasing due to increased maternal age and body mass index at conception. We therefore wanted the views of all forms of diabetes to be included in the PPI advisory group and ensured that we had representation covering all three types when the group was formed. The different experiences of our members gave us an excellent insight into the wide range of patient expertise in managing diabetes, especially those with GDM. There was acknowledgement that there is huge variation in the knowledge of women on how to manage their diabetes. Some women would be confident in managing their own diabetes and would find it stressful to hand over control of their diabetes care to staff in labour, when they have been managing it themselves through the antenatal period. The counter was also highlighted – that some women (particularly those with GDM in their first pregnancy) who had other priorities in labour or were feeling unwell may not feel it appropriate to control their own blood glucose in labour. One woman described the thought as 'stressful to think about managing birth and then doing A-level maths (diabetes control) straight after'. The PPI advisory group felt that it would be important to develop educational resources for women, that is a preparation for labour guidance. They also felt that education would be necessary to explain why tight control in labour may be more hazardous than loose control as women are repeatedly told that tight control is essential in the antenatal period.

Considering participation of women of diverse backgrounds, the PPI advisory group recommended that women required more support in terms of discussing the study and the time needed for this. The suggestion was that information given to women was made very simple, as many highly deprived areas have low literacy levels in their population. Innovative suggestions also included the use of Facebook stickers and profile frames.

In addition to our PPI advisory group, we used social media to engage a wider audience of parents in our work. This included conducting a virtual meeting with members of the Bump2Baby parents' voices Facebook group run by Nottingham Clinical Trials Unit and supplying study updates and posts to the Gestational Diabetes UK Facebook group, as well as advertising the elements of the study that required participant involvement on different social media networks. In terms of the women's survey (work package 1a), we recruited women from diverse ethnicities, with 23% of respondents from non-White British ethnicity, which is significantly more diverse than the UK population (87% White).[91] The survey was predominantly completed by women with GDM through publicity afforded us by our collaboration with Jo Paterson from Gestational Diabetes UK. Unfortunately, although we had made similar contact with Diabetes UK to support publicity to women with T1DM and T2DM, they were unable to do this in the required timescale for completion of the survey. We attempted to publicise the study through other social media channels but are aware that the survey results do not effectively record the views of women with T1DM and T2DM. We therefore decided to ensure that when it came to the qualitative interviews, we would purposively attempt to record the views of more women with T1DM and T2DM.

We did not collect the ethnicity of those competing the HCP survey, rather here we were more interested in diversity in job roles (profession), level of experience, teaching hospital or district general background, size of the maternity unit, geographical location and whether those who responded had a special interest in intrapartum diabetes care or not. We interpreted the results of these demographics in having achieved the desired diversity of responses with the exception of the number of responses received from endocrinologists and diabetes specialist nurses. We tried to engage and publicise the study to the profession, utilising the ABCD, Twitter and personal contacts. We are also aware that the survey was conducted during the height of the COVID-19 pandemic, when endocrinologists are especially likely to have been working on a general medicine on call rota and under extreme pressure and not have time to prioritise such a survey.

In terms of the Delphi survey and the consensus meeting, we felt that the most important aspect of this study was to be diverse in terms of the job professions that participated in these discussions, and we feel that all the relevant stakeholders were included within these aspects of the study. It is well known that there is a significant attrition in the number of individuals who complete the first part of a Delphi survey and those who complete the third round. We attempted to ensure that those who signed up were aware that participation in all three rounds was important. Sadly, the attrition rate in this study was much larger than some previous published studies. It is difficult to account for why this may be, or whether the COVID-19 pandemic had any influence. We do, however, think that the views of those who responded to round 3 are representative of wider views.

The qualitative interviews of women were diverse in that 25% of the participants were non-White British and there was 21% representation from women with pre-existing diabetes.

We have ensured that any participant-facing documentation, including surveys and information for the qualitative interviews, is distributed to the PPI advisory group to ensure that the wording of this documentation is inclusive. We feel that this is an example of good practice and would encourage such action in future research. The cost of an alongside PPI advisory group, that meets to support the research staff in developing inclusive documentation and facilitate participation from under-served groups, is a small cost consideration in comparison to the overall costs of running a clinical trial and would be a rewarding investment.

Our PPI advisory group has also expressed an interest in further involvement in a future trial and made several suggestions regarding dissemination of elements of this project to lay audiences. Members felt that the surveys of clinical practice and women's experiences would be of particular interest to maternity voice partnerships and other coproduction groups in maternity and pointed out the importance of producing materials that could be used by peer support projects during pregnancy.

Experienced team members were able to support and guide those with less experience through the project. The research team for this project is diverse in terms of job roles, experience and expertise, which has allowed us to develop the best possible RCT design for a study on glycaemic care of women with diabetes in labour. We have also ensured that we have significant diversity within the wider team with the inclusion of a PPI advisory group as a core part of the team. We hope that this will enable any future RCT to be representative of the population with diabetes as a whole and diverse in its participation/recruitment.

Chapter 8 Conclusions

Through a series of work packages, this scoping study has determined substantial differences in current practice in the care of women with diabetes during labour, but despite this, there appears to be an appetite from women with lived experience of diabetes during labour and HCPs that conducting a randomised clinical trial would be acceptable based on their assumption of risks to mother and baby. Data from all work packages have been used to determine the most appropriate design for a future trial. An umbrella trial design will enable women with any type of diabetes to be included, which was considered important by all stakeholders, while a master protocol will enable the study to be conducted efficiently, to minimise burden at participating sites. The trial we have designed was considered necessary, acceptable and feasible by the women and HCPs who took part in qualitative interviews, though some important considerations were raised which would need to be accounted for in a future trial. In particular, it would be important to be very clear about the exact timing of approach to ensure informed consent and randomisation into the trial. Additionally, consideration should be given to not overburden clinical teams by data collection and utilising routinely recorded data where possible, and to ensure a multidisciplinary team approach to conducting the trial at sites, with HCP 'champions', ensuring effective leadership at trial sites.

We therefore recommend that a clinical trial comparing glucose-monitoring strategies in labour, for women with diabetes, is conducted, which includes an internal pilot phase to test key aspects of trial conduct, given the challenges we have identified during this scoping study.

Additional information

Contributions of authors

Nia Wyn Jones (https://orcid.org/0000-0003-0793-0967): (Clinical Associate Professor of Obstetrics and Gynaecology) was the Chief Investigator. She led on the original grant application and design of the study. She oversaw the management of the study and assisted with interpretation of the study findings and wrote the main study report.

Eleanor J Mitchell (https://orcid.org/0000-0002-6998-4533): (Associate Professor of Clinical Trials) cowrote the original grant application, co-designed the study and led from a clinical trials perspective in the study team. She assisted with interpretation of the study findings and contributed to codrafting of the study report.

Kate F Walker (https://orcid.org/0000-0001-5794-7324): (Clinical Professor in Obstetrics) was a coinvestigator. She cowrote the original grant application, codesigned the study, led on the Delphi component of the study and giving a clinical trials and obstetric perspective, she contributed to the drafting of the study report.

Susan Ayers (https://orcid.org/0000-0002-6153-2460): (Professor of Maternal and Child Health) was a coinvestigator. She cowrote the original grant application and led on the qualitative aspects of the study. She was responsible for developing the interview schedule and oversaw the interviews and their thematic analysis. She contributed to codrafting of the study report.

Lucy Bradshaw (https://orcid.org/0000-0001-8382-6040): (Medical Statistician) was a coinvestigator. She cowrote the original grant application, co-designed the study (including plans for analysis for each work package), contributed to the design of the future trial and assisted with drafting of the study report.

Georgina Constantinou (https://orcid.org/0000-0002-2389-7901): (Research Psychologist) was a research assistant who delivered the interventions for the qualitative interviews, contributing to data collection, analysis and drafting of the report.

Tasso Gazis (https://orcid.org/0000-0003-3883-2761): (Consultant Endocrinologist) was a coinvestigator. He was part of the original study team and led from a clinical endocrine perspective assisting with interpretation of the study findings and drafting of the report.

Shalini Ojha (https://orcid.org/0000-0001-5668-4227): (Professor of Neonatal Medicine) was a coinvestigator. She cowrote the original grant application, co-designed the study and led from a neonatal perspective and giving a clinical trials perspective, assisted with interpretation of the study findings and drafting of the report.

Phoebe Pallotti (https://orcid.org/0000-0002-7545-0415): (Associate Professor of Midwifery) was a coinvestigator. She was part of the original study team and led from a midwifery perspective, assisting with interpretation of the study findings and drafting of the report.

Stavros Petrou (https://orcid.org/0000-0003-3121-6050): (Professor of Health Economics) was a coinvestigator. He led on the health economics section of the study and assisted with interpretation of the health economic study findings and drafting of the report.

Rachel Plachcinski (https://orcid.org/0000-0001-9908-0773): (Independent parent and public involvement consultant) was a coinvestigator. She cowrote the original grant application, co-designed the study and led from a PPI perspective. She chaired the PPI advisory group and assisted with interpretation of the study findings and drafting of the report.

Michael Rimmer (https://orcid.org/0000-0002-3295-8753): (MRC Clinical Research Fellow in Obstetrics and Gynaecology) was a coinvestigator. He was part of the original study team and led from the UKRCOG perspective, assisting with the design and interpretation of the UKRCOG service evaluation and drafting of the report.

Liz Schroeder (https://orcid.org/0000-0003-0236-2833): (Senior Researcher in Health Economics) was a research fellow who delivered the interventions for the health economic evaluation, contributing to data collection, analysis and drafting of the report.

Jim G Thornton (https://orcid.org/0000-0001-9764-6876): (Professor of Obstetrics and Gynaecology) was a coinvestigator. He was part of the original study team and led from a clinical trials and obstetric perspective, assisting with interpretation of the study findings and drafting of the report.

Natalie Wakefield (https://orcid.org/0000-0001-5474-3115): (Study Co-ordinator) was the study manager. She was responsible for maintaining study documentation, co-ordinating meetings, surveys and audit responses, liaised with potential participants. She assisted with the drafting of the report.

Acknowledgements

The Study Steering Committee

Katie Morris, Reader of Clinical Trials, University of Birmingham (Chair); Helen Murphy, Professor of Medicine, University of East Anglia; Annette Briley, Professor of Women's Health and Midwifery, Flinders University (Australia); Ed Wilson, Senior Lecturer in Health Economics, University of East Anglia; Andy Vail, Professor of Clinical Biostatistics, University of Manchester; Sophie Pidgeon, PPI member; Abigail Mainwaring, PPI member.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to data may be granted following a review of data-sharing applications. Any data shared will be pseudo-anonymised which may impact on the reproducibility of published analyses. The protocol is freely available on the NIHR Journals Library website.

Ethics statement

Ethical approval for the entire study was provided by the University of Nottingham Faculty of Medicine & Health Sciences Research Ethics Committee on 23 August 2021 (ref: 304-0621). All participants involved in the work package 4 provided written informed consent.

Information governance statement

The University of Nottingham is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679.

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/KHGD2761.

Primary conflicts of interest: Jim G Thornton was a member of the NIHR HTA and EME Editorial Boards from 2016 to 2022.

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Appendix 1 Healthcare professional's survey questions (work package 1b)

GILD study – work package 1b: Midwife and healthcare professional's survey.

Final version 1.0, 20 July 2021.

Introduction

We are conducting a survey to gather the views and opinions of midwives and HCPs who have experience of caring for women with diabetes in pregnancy and specifically in labour. We need to find out:

- What you currently do to control blood sugars in labour?
- The level of training you have or would need for a future clinical trial which would be testing ways to monitor blood sugars in labour.

We will use this information to design a research study to compare different approaches to blood sugar-monitoring in labour.

Currently, in the UK, 5% of all pregnant women are affected by diabetes in their pregnancy. Women with diabetes in pregnancy (type 1, type 2 or gestational) have their blood sugar levels monitored during labour to reduce the effects of high sugar on their baby after birth. High blood sugar in the mother can cause low blood sugar in the baby, which the baby can sometimes struggle to cope with and can lead to admission to the neonatal unit.

Blood sugar monitoring during labour can be intrusive to women and expensive. We do not have any research evidence about the best way of monitoring blood sugar levels in women with diabetes in pregnancy, while they are in labour.

This study has been commissioned and funded by the National Institute of Health Research, which is the research part of the NHS.

We anticipate it will take you approximately 10 minutes to complete the survey. The responses you give will be anonymous and will not be linked back to you personally. We will use data from the survey, including anonymous quotes, to help us plan a study in the future.

You have the option of being entered into a prize draw to win a £80 shopping voucher. We will also ask you if you would like to receive the results at the end of the study or take part in a further survey later in this project. If you agree to any of these options, you will be asked to provide your name and e-mail address at the end of the survey. Your contact details will not be used for any other purpose and will be held securely at the University of Nottingham. Information about the University of Nottingham's privacy policy, in line with the GDPR, can be accessed here: www.nottingham.ac.uk/utilities/privacy.aspx.

Thank you for taking time to read this information and completing the survey. Your help will ensure that the future study will take into consideration the views and experience of HCPs who care for women with diabetes in pregnancy. Please remember that this survey focuses on blood sugar monitoring during labour, rather than throughout pregnancy.

If you have any questions, please contact: gild@nottingham.ac.uk

Section 1: consent and screening questions

Q No.	Question/statement	Responses
1	I have read the information provided and am willing to complete the survey	Yes – continue to Q2 No – continue to statement Thank you for your time and interest in this study. However, we would only like to receive responses from healthcare professionals who have read the information provided and provided their consent
2	Are you currently employed as a midwife, obstetrician or endocrinologist, delivering care to women with diabetes in pregnancy in the NHS?	Yes – continue to Q3 No – continue to statement Thank you for your time and interest in this study. However, we would only like to receive responses from midwives, obstetricians or endocrinologists currently delivering care to women with diabetes in pregnancy in the NHS

Section 2: questions about your current practice

Q No.	Question/statement	Responses
3	Do you look after women with diabetes during labour?	Yes No
4	Roughly, how many women have you looked after in the last month with diabetes during active labour?	Whole number
5	How often do you test blood glucose levels in women with pre-existing diabetes (type 1 or type 2) in active labour?	1 hour 2 hours 4 hours With meals Other (please specify)
6	How often do you test blood sugars in women with GDM in active labour?	1 hour 2 hours 4 hours With meals Other (please specify)
7	What technology do you use to test blood glucose level? (tick all that apply)	Finger prick Glucose sensor patch (e.g. Libre or Dexcom) Other (please specify)
8	At what level of blood glucose (rounded) (mmol/l) would you start insulin in women with pre-existing diabetes (type 1 or type 2)?	3 4 5 6 7 8 9 10 11 12 13 14
8a	Is this based on one reading or more than one reading?	One reading Two readings Other (please specify)

Q No.	Question/statement	Responses
9	At what level of blood glucose (rounded) (mmol/l) would you start insulin in women with GDM?	3 4 5 6 7 8 9 10 11 12 13 14
9a	Is this based on one reading or more than one reading?	One reading Two readings Other (please specify)
10	How would you administer insulin?	Insulin infusion or sliding scale (VRIII) Patient's insulin pump SC insulin Other (please specify)

Section 3: questions about your experience

Q No.	Question/statement	Responses
11	How confident are you in looking after a woman with type 1 diabetes in labour?	Not confident Slightly confident Somewhat confident Fairly confident Extremely confident
12	How confident are you in looking after a woman with type 2 diabetes in labour?	Not confident Slightly confident Somewhat confident Fairly confident Extremely confident
13	How confident are you in looking after a woman with GDM in labour?	Not confident Slightly confident Somewhat confident Fairly confident Extremely confident
14	How helpful do you find the hospital guidelines on diabetes in pregnancy when managing women with this condition in labour?	Not helpful Slightly helpful Somewhat helpful Fairly helpful Extremely helpful
15	What other information would be helpful for you?	*Free text*
16	Have you had any training in looking after diabetes control in women with diabetes in labour?	Yes – *go to Q17* No – *go to Q18*
17	What type of training have you received? (Tick all that apply)	Theoretical: Intrapartum care of women with diabetes VRIII use Patient's own insulin pumps Glucose sensor patch, for example, Libre, Dexcom Treatment of hypoglycaemia Practical: Finger-prick testing Glucose sensor patch, for example, Libre, Dexcom VRIII use Patient's own insulin pumps Other (please specify)

18	If we were to research the management of glucose control in labour for women with diabetes, would you feel that any additional training would be needed? (Specify one)	Necessary Helpful but not mandatory Unnecessary
19	How important would training be for each of the following aspects prior to a research study? Theoretical: Intrapartum care of women with diabetes VRIII use Patient's own insulin pumps Glucose sensor patch, for example, Libre, Dexcom Treatment of hypoglycaemia Practical: Finger-prick testing Glucose sensor patch, for example, Libre, Dexcom VRIII use Patient's own insulin pumps	Not important Slightly important Somewhat important Fairly important Extremely important
20	How confident are you in in dealing with maternal hypoglycaemia in labour?	Not confident Slightly confident Somewhat confident Fairly confident Extremely confident Not confident
21	How confident are you in diagnosis of hypoglycaemia in a term newborn baby whose mother has diabetes?	Slightly confident Somewhat confident Fairly confident Extremely confident
22	How confident are you in treatment of hypoglycaemia in a newborn baby whose mother has diabetes?	Not confident Slightly confident Somewhat confident Fairly confident Extremely confident
23	How important would any training in management of baby with low blood sugar be prior to performing a research study?	Not important Slightly important Somewhat important Fairly important Extremely important

Section 4: questions about your unit

Q No.	Question/statement	Responses
24	How many deliveries are conducted in your unit annually? (Approximately)	≤ 1000 1001–2000 2001–5000 5001–10,000 > 10,000
25	Does your hospital have a diabetes specialist midwife to support care of women? (Tick all that apply)	No Yes for antenatal care Yes for intrapartum care
26	Does your hospital have a diabetes specialist nurse to support care of women? (Tick all that apply)	No Yes for antenatal care Yes for intrapartum care

27	What type of hospital do you work in?	District general as one option and Teaching a second
28	What region of the UK do you work in?	East Midlands Eastern Greater Manchester Kent, Surrey and Sussex North East and North Cumbria North Thames North West Coast North West London Northern Ireland Scotland South London South West Peninsula Thames Valley and South Midlands Wales West Midlands West of England Wessex Yorkshire and Humber

Section 5: questions about you

Q No.	Question/statement	Responses
29	What is your profession?	Diabetes nurse Endocrinologist Midwife Neonatologist Obstetrician
30	How many years of experience do you have in this profession?	0–5 5–10 10–15 15–20 > 20
31	How many years of experience do you have working in the labour ward?	0–5 5–10 10–15 15–20 > 20
32	Do you have a specialist interest in diabetes?	No Yes (please specify)
30	Would you like to receive the results of this study at the end (anticipated Autumn 2022/Spring 2023)	• Yes • No
31	Would you like to participate in a Delphi survey on glycaemic control in labour later in the project?	• Yes • No
32	Would you wish to receive further information and potentially participate in one-to-one interviews on the feasibility of conducting a trial comparing permissive to intensive glycaemic control for women with diabetes later in the project?	• Yes • No
33	If you have answered yes to any of the previous three questions, please provide your contact details: *Your personal details will not be linked to your survey responses in any way*	• Name • e-mail address

Appendix 2 Women's survey questions (work package 1c)

GILD study – work package 1c: Women's survey

Final version 1.0, 20 July 2021

Introduction

We are conducting a survey to gather the views and opinions of women who have personal experience of diabetes in pregnancy and specifically in labour. We need to find out:

- What pregnant women do to control their blood sugars?
- Your views on how diabetes is monitored in labour (we are not focusing on the rest of the pregnancy or those women who had an elective caesarean section).
- Your priorities for the health of women and their babies following a pregnancy in a woman with diabetes.

We will use this information to design a research study to compare different approaches to blood sugar monitoring in labour.

Currently, in the UK, 5% of all pregnant women are affected by diabetes in their pregnancy. Women with diabetes in pregnancy (type 1, type 2 or gestational) have their blood sugar levels monitored during labour to reduce the effects of high sugar on their baby after birth. High blood sugar in the mother can cause low blood sugar in the baby, which the baby can sometimes struggle to cope with and can lead to admission to the neonatal unit.

Blood sugar monitoring during labour can be intrusive to women and expensive. We do not have any research evidence about the best way of monitoring blood sugar levels in women with diabetes in pregnancy, while they are in labour.

This study has been commissioned and funded by the National Institute of Health Research, which is the research part of the NHS.

We anticipate it will take you approximately 10 minutes to complete the survey. The responses you give will be anonymous and will not be linked back to you personally. We will use data from the survey, including anonymous quotes, to help us plan a study in the future.

You have the option of being entered into a prize draw to win a £80 shopping voucher. We will also ask you if you would like to receive the results at the end of the study or take part in a further survey later in this project. If you agree to any of these options, you will be asked to provide your name and e-mail address at the end of the survey. Your contact details will not be used for any other purpose and will be held securely at the University of Nottingham. Information about the University of Nottingham's privacy policy, in line with the GDPR, can be accessed here: www.nottingham.ac.uk/utilities/privacy.aspx.

Thank you for taking time to read this information and completing the survey. Your help will ensure that the future study will have the views of women with diabetes in pregnancy at its core. Please remember this survey focuses on blood sugar monitoring during labour, rather than throughout pregnancy.

If you have any questions, please contact: gild@nottingham.ac.uk

Section 1: consent and screening questions

Q No.	Question/statement	Responses
1	I have read the information provided and am willing to complete the survey	Yes – continue to Q2 No – continue to statement
		Thank you for your time and interest in this study. However, we would only like to receive responses from women who have or have had diabetes in pregnancy in the last 3 years, have read the information provided and provided their consent.
2	Do you currently have, or have had in the last 3 years, diabetes in pregnancy?	Yes – continue to Q3 No – continue to statement
		Thank you for your time and interest in this study. However, we would only like to receive responses from women who have or have had diabetes in pregnancy in the last 3 years and are aged 16 and over
3	Are you aged 16 or over?	Yes – continue to question 4 No – continue to statement in Q2

Section 2: questions about you

Q No.	Question/statement	Responses
4	How old are you?	16–19 20–24 25–29 30–34 35–39 40–45 Over 45
5	Which statement most accurately describes you?	• This is my first pregnancy with diabetes – go to Q6 • I am currently pregnant with diabetes and had diabetes in a previous pregnancy – go to Q6 • I am not currently pregnant, but have given birth in the last 3 years and had diabetes during the pregnancy – go to Q7 • Other; please give details: go to Q7
6	How many weeks pregnant are you?	• 1–12 weeks (first trimester) • 13–27 weeks (second trimester) • 28–42 weeks (third trimester)
7	What type of diabetes in pregnancy do/did you have?	• Type 1 diabetes • Type 2 diabetes • GDM • Other; please give details

Q No.	Question/statement	Responses
8	What is your ethnicity?	WHITE • British • Irish • Any other White background MIXED • White and Black Caribbean • White and Asian • Any other Mixed background ASIAN OR ASIAN BRITISH • Indian • Pakistani • Bangladeshi • Any other Asian background BLACK OR BLACK BRITISH • Caribbean • African • Any other Black background CHINESE OR OTHER ETHNIC GROUP • Chinese • Any other ethnic group
9	Which area of the UK are you located?	• East Midlands • Eastern • Greater Manchester • Kent, Surrey and Sussex • North East and North Cumbria • North Thames • North West Coast • North West London • Northern Ireland • Scotland • South London • South West Peninsula • Thames Valley and South Midlands • Wales • West Midlands • West of England • Wessex • Yorkshire and Humber

Section 3: questions if you have given birth previously

Question not available to women who have selected 'This is my first pregnancy with diabetes' to question 5 in *Section 2*.

Q No.	Question/statement	Responses
10	During your previous pregnancy, how often were your blood sugars tested during labour?	• Every hour • Every 2 hours • Every 4 hours • When I ate a meal • I do not remember • Not tested – go to Q13 • Other; give details
11	How did you find the frequency of your blood sugar monitoring during labour?	• Too often • Not enough • About right • Other; give details

Q No.	Question/statement	Responses
12	How were your blood sugars tested during labour?	• Finger-prick test • Patch • I do not remember • Not tested • Other; give details
13	What was your main concern with respect to your blood sugar levels during your labour?	• I had no concerns • Unstable blood glucose levels resulting in requiring an insulin drip (sliding scale or VRIII) • Not being able to eat or eat the right foods during labour in order to control blood glucose levels • Unstable blood glucose levels leading to lack of strength, tiredness and feeling unwell during labour • Unstable blood glucose levels leading to complications for the baby once born, that is low blood glucose • Other (please specify)
14	Did you receive any treatment for your sugars in labour and what was this? (Tick all that apply)	• Asked not to eat • Given tablets • Given insulin injections • Given insulin via a drip • Asked to eat a suitable snack • Asked to drink a sugary drink • Given glucose via a drip • I do not remember • Nothing recommended • Other; give details
15	Did you have sliding scale insulin via a drip (VRIII) for labour?	• Yes • No • Do not remember • Other; give details
16	Why was this started?	• Routinely recommended for labour • My sugar levels were high • My sugar levels were low • I was on insulin in pregnancy • I do not remember • Other; give details
17	Were you allowed to eat in labour?	• Yes • No • Do not remember • Other; give details

Section 4: questions if you have not given birth previously

Question only available to women who have selected 'This is my first pregnancy with diabetes' to question 5 in *Section 2*.

Q No.	Question/statement	Responses
18	Have you been given information (written, verbal or other) about what to expect during labour, with respect to blood sugar control and monitoring?	• Yes • No • Unsure

Q No.	Question/statement	Responses
19	Has the information you have been given been helpful?	• Yes – go to Q • No – go to Q • Unsure – go to Q
20	If it has not been helpful, why not?	Free text
21	What is your main concern about your blood sugar control and monitoring during your labour?	• I have no concerns • Unstable blood glucose levels resulting in requiring an insulin drip (sliding scale or VRIII) • Not being able to eat or eat the right foods during labour in order to control blood glucose levels • Unstable blood glucose levels leading to lack of strength, tiredness and feeling unwell during labour • Unstable blood glucose levels leading to complications for the baby once born, that is low blood glucose

Section 5: questions about participating in a research study

Q No.	Question/statement	Responses
22	If you were being approached to ask if you would like to participate in a research study, comparing methods of monitoring blood glucose levels in labour, at what time point would you first like to receive information about the study?	• During antenatal appointments • When attending hospital for scans • At the start of labour • Other (please specify)
23	How would you like to receive this information? (Please tick all that apply)	• A paper information sheet • A short information sheet, followed by a longer information sheet which gives full information • A short video • A verbal explanation • Other (please specify)
24	We would like you to imagine a scenario: you are invited to take part in a study comparing different blood sugar monitoring methods during labour. You are provided with all the information to make an informed choice. The information will provide you with benefits and risks of the different strategies that would be compared in the study. In order for the study to be a fair test, you are not able to choose how you will be monitored, one of the methods being studied will be chosen by a computer. The reason for doing this is because doctors and researchers do not currently know the best way to monitor blood sugar levels during pregnancy Would you consider participating in the study?	• Yes • No • Unsure
25	If you answered 'no' or 'unsure' to the previous question, why not?	• I would not like to take part in a research study • I would not like the decision being made a computer • I would prefer my doctor to decide how best to monitor my blood sugar levels • I would prefer to decide how best to monitor my own blood sugar levels • Other, please state:
26	If we are to design a big research study comparing different strategies to monitor blood sugar levels during labour, what do you think are the most important outcome measures to include for the mother and baby? *An outcome measure is a way measuring how effective something has been; in this case, how effective the strategy to test blood sugar monitoring during labour*	• Low blood sugar in mother during or shortly after labour • Blood sugar control impacting on ability of mother to breastfeed after birth • Low blood glucose in my baby • Low blood glucose that made my baby unwell • Low blood glucose levels so that my baby needed a sugar solution or milk other than my own

Q No.	Question/statement	Responses
		• Admission of my baby to the neonatal unit • My baby needing glucose solution into their vein • How my baby is fed when I go home • How long my baby and I have to stay in hospital • How I feed my baby when they are 6 weeks old • How my baby is doing when they are 2 years old • Other (please specify)

Section 5: optional questions

Thank you for taking the time to complete this survey – your help in designing the bigger study is much appreciated.

Q No.	Question/statement	Responses
27	Would you like to be entered into a free prize draw to win a £80 shopping voucher?	• Yes • No
28	Would you like to receive the results of this study at the end (anticipated Autumn 2022/Spring 2023)	• Yes • No
29	Would you like to participate in further related surveys later in the project?	• Yes • No
30	If you have answered yes to any of the previous three questions, please provide your contact details: *Your personal details will not be linked to your survey responses in any way.*	• Name • e-mail address

Thank you for your time. There are no further questions. You have now reached the end of this survey. You can close this browser. If you have any questions for the study team, please contact gild@nottingham.ac.uk.

Appendix 3 UKRCOG national service evaluation questions (work package 1d)

GILD study – work package 1d:

National audit of adherence to clinical guidelines via UKARCOG

Final version 1.0 16 June 2021

Inclusion: Any woman with any form of diabetes (T1DM, T2DM, GDM, other) who laboured at term (37 + 0 weeks or later) on labour ward.

Exclusion:

- any woman delivered by elective lower segment caesarean section (LSCS) (emergency LSCS in labour are eligible)
- any woman who delivered or laboured to full dilatation before admission to labour ward.

Demographics

Study ID	
Hospital	
Maternal age at delivery	
Ethnicity	WHITE • British • Irish • Any other White background MIXED • White and Black Caribbean • White and Black African • White and Asian • Any other Mixed background ASIAN OR ASIAN BRITISH • Indian • Pakistani • Bangladeshi • Any other Asian background BLACK OR BLACK BRITISH • Caribbean • African • Any other Black background CHINESE OR OTHER ETHNIC GROUP • Chinese • African
Parity	
Number of previous vaginal births	
Number of previous LSCS	
Height at booking (cm)	

Study ID	
Weight at booking (kg)	
Last documented weight (kg)	
at what gestation	
Estimated due date	
Type of DM	T1DM T2DM GDM Other: specify
If T1DM or T2DM	
Pre-pregnancy treatment	Diet Metformin Insulin
HbA1c at booking	Value: mmol/mol Gestation: weeks + days
Diabetes complications prior to pregnancy	Retinopathy Nephropathy Neuropathy Hypertension Vascular disease (ischemic heart disease, cerebral vascular accident, peripheral vascular disease)
If GDM	
Date of diagnosis	
Gestation of diagnosis	
Test used and result/value	
GTT (fasting and 2 hour)	
HbA1c	
Random glucose	
Fasting glucose	
Treatment prior to labour	Diet Metformin Insulin subcutaneous injections Insulin subcutaneous pump
Last HbA1c in pregnancy	Value: mmol/mol Gestation: weeks + days
Antenatal complications	Pre-eclampsia Macrosomia (AC or EFW > 90th centile) Small for gestational age (EFW < 10th centile) Congenital anomaly; specify Polyhydramnios (AFI 25 cm or max pool depth 8 cm)
Diabetes complications in pregnancy	Retinopathy Nephropathy Neuropathy Hypertension Other, please specify
Last scan	
Date	
Gestation of scan	
Amniotic fluid index	

Study ID
Head circumference
Abdominal circumference
Femur length
Estimated fetal weight

Intrapartum care

Onset of labour	Spontaneous Induced Augmented (SROM)
If induction: Glucose-monitoring plan for prostaglandin/balloon (tick all that apply)	Pre-meals Post meals Hourly Not tested Other: specify
If on subcutaneous insulin pump in the antenatal period was this continued in labour	Yes No Not on subcutaneous insulin pump in antenatal period
If no	Stopped as Unit guideline to change to intravenous insulin infusion Stopped as patient unwell/unable to manage DM control in labour
Is there a documented plan for oral intake in labour?	Yes No
Is the oral intake documented, for example, on a fluid balance chart?	Yes No
Date and time of admission to labour ward	
Date and time of onset of first stage or syntocinon infusion if induction	
Date and time of onset of second stage (if applicable)	
Date and time of birth of baby	
Date and time of delivery of placenta	
Clear plan documented for postnatal diabetes treatment	Yes No Not applicable
Date and time insulin stopped or changed to postnatal treatment	*Give option for*: Not applicable Not documented
Mode of delivery	Normal Forceps Rotation: Yes or no Ventouse Rotation: Yes or no Caesarean section Vaginal breech
Place of birth	Room Theatre
Estimated blood loss	
Complications to mother	Shoulder dystocia third-/fourth-degree tear Post partum haemorrhage requiring blood transfusion

Onset of labour	Spontaneous Induced Augmented (SROM)
Feeding planned at birth	Breast Artificial Mixed

Maternal glucose control in labour

Date	Time	Glucose level	Treatment
		If outside unit protocol Any explanation for deviation	Not applicable
			No Oral glucose (or sugary drink) Food consumed: Intravenous glucose 5% Intravenous glucose 20% Hypostop Metformin Insulin: subcutaneous injection Insulin: intravenous infusion Insulin: subcutaneous pump Other: specify

Baby outcomes

Birthweight	
Gestation at birth	
Sex	
5-minute Apgar score	
Cord arterial pH at birth	
Cord venous pH at birth	
Cord arterial base deficit	
Complications to baby	Hypothermia Shoulder dystocia Fracture; specify hypoxic ischemic encephalopathy; specify grade Active therapeutic hypothermia (cooling) required Seizure Respiratory distress requiring ventilation Respiratory distress requiring surfactant Respiratory distress requiring admission to the neonatal unit Jaundice requiring phototherapy or other treatment Congenital anomaly Early-onset neonatal sepsis (systemic infection where infection screen performed) Local infection
Neonatal unit admission	Yes No
Indication for admission to neonatal unit	
Date and time of admission to neonatal unit	
Date and time of discharge from to neonatal unit	
Date and time of discharge from transitional care	
Date and time of discharge from to postnatal ward	

Did the baby have hypoglycaemia?	No Yes, asymptomatic Yes, symptomatic
If yes, symptomatic Please specify symptoms present during episode of hypoglycaemia	Jitteriness Irritability Lethargy Abnormal feeding Hypotonia/floppy High-pitched cry Tachypnoea/respiratory distress Tachycardia/bradycardia Seizures Apnoea Hypothermia Altered level of consciousness

Glucose levels in baby +/– immediate treatment

Date and time	Glucose level	How tested	Treatment	Is this within guideline or deviates from GL
		Glucometer point-of-care test	None	Yes
			Increased feeding with mother's own milk	No
		Blood gas Analyser		
		Laboratory Sample	Increased feeding with human donor milk	
			Increased feeding with infant formula	
			Oral glucose supplement	
			Nasogastric feeding	
			Intravenous glucose	
			Other (including drugs, specify)	

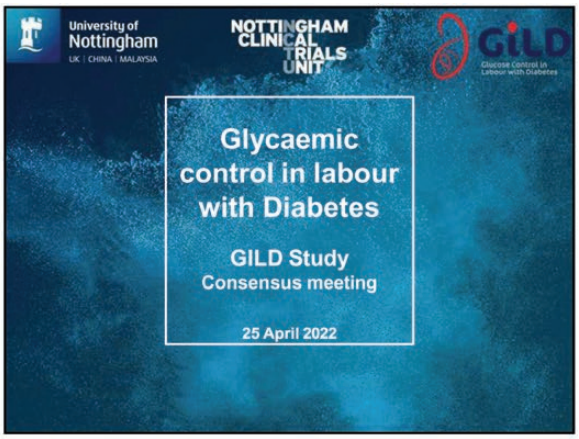
Subsequent management	
Feeding method on discharge	Breastfeeding Bottle feeding Mixed
Did the hypoglycaemia result in cessation of breastfeeding?	Yes No Not applicable
Did the baby require any postnatal imaging as a result of the hypoglycaemia?	Not applicable MRI for other indication: No Yes, MRI (specify number of MRI) Yes, Cranial USS (specify number of cranial USS)
Were there further investigations in terms of extended hypoglycaemia screen done on the baby? Was the baby transferred to another neonatal unit post birth?	Yes No Not applicable (did not have hypoglycaemia) Yes No

Unit-specific questions (please complete once for your unit)

T1DM	
Unit guideline for glucose in labour: target range	
Upper limit	
Action required if above	
Lower limit	
Action required if below	
Technology used for testing in antenatal period (please tick all that apply)	Finger-prick Sensor (e.g. Libre) Other: specify
Technology used for testing in labour (please tick all that apply)	Finger-prick Sensor (e.g. Libre) Other: specify: Not tested
Treatment used in antenatal period (please tick all that apply)	Diet Metformin Insulin subcutaneous injections Insulin subcutaneous pump Other: specify
Treatment used in labour (please tick all that apply)	Metformin Insulin: subcutaneous injection Insulin: intravenous infusion Insulin: subcutaneous pump Other: specify
T2DM	
Unit guideline for glucose in labour: target range	
Upper limit	
Action required if above	
Lower limit	
Action required if below	
Technology used for testing in antenatal period (please tick all that apply)	Finger-prick Sensor (e.g. Libre) Other: specify
Technology used for testing in labour (please tick all that apply)	Finger-prick Sensor (e.g. Libre) Other: specify: Not tested
Treatment used in antenatal period (please tick all that apply)	Diet Metformin Insulin subcutaneous injections Insulin subcutaneous pump Other: specify
Treatment used in labour (please tick all that apply)	Metformin Insulin: subcutaneous injection Insulin: intravenous infusion Insulin: subcutaneous pump Other: specify

GDM	
Unit guideline for glucose in labour: target range	
Upper limit	
Action required if above	
Lower limit	
Action required if below	
Technology used for testing in antenatal period (please tick all that apply)	Finger-prick Sensor (e.g. Libre) Other: specify
Technology used for testing in labour (please tick all that apply)	Finger-prick Sensor (e.g. Libre) Other: specify: Not tested
Treatment used in antenatal period (please tick all that apply)	Diet Metformin Insulin subcutaneous injections Insulin subcutaneous pump Other: specify
Treatment used in labour (please tick all that apply)	Metformin Insulin: subcutaneous injection Insulin: intravenous infusion Insulin: subcutaneous pump Other: specify
Does your unit have a transitional care for neonates?	Yes No

Appendix 4 GILD consensus meeting slides: summary of results of work packages 1a–1d and Delphi survey (work package 2)



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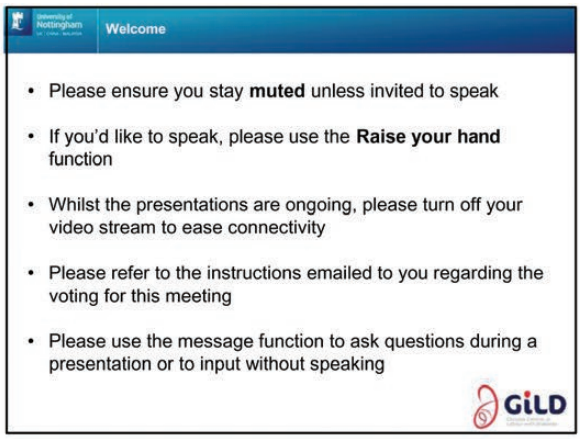

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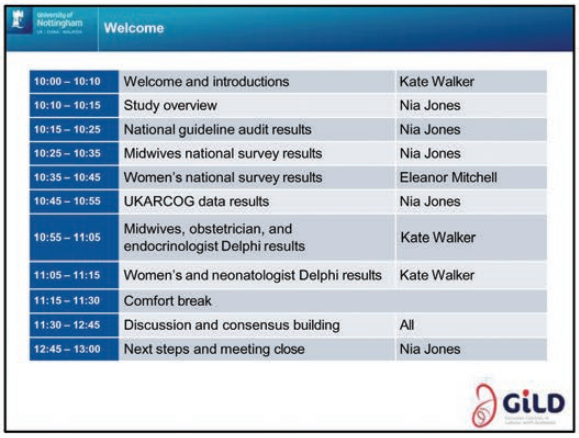

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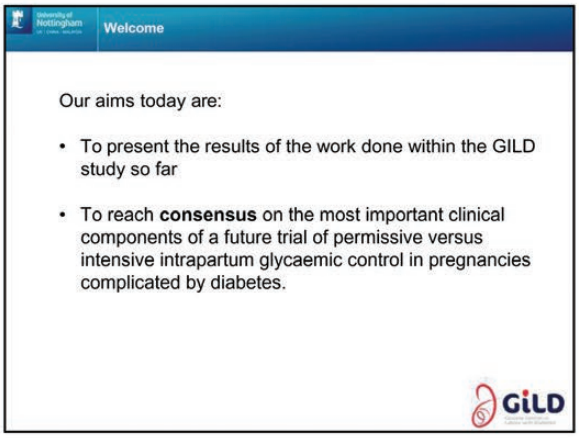

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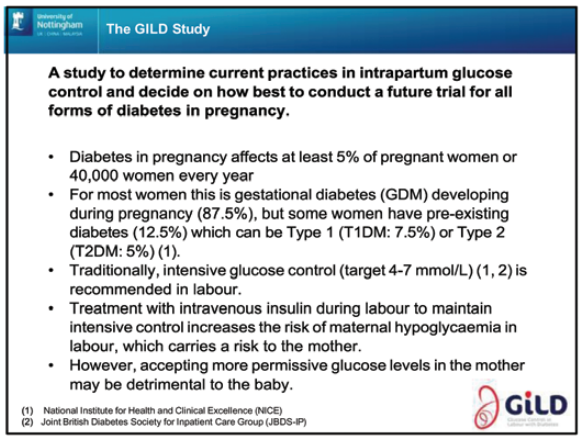
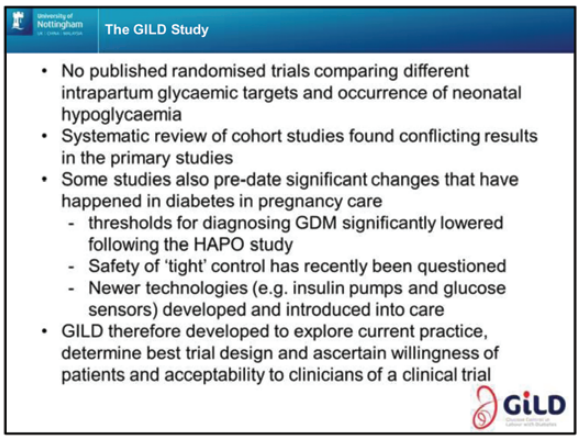
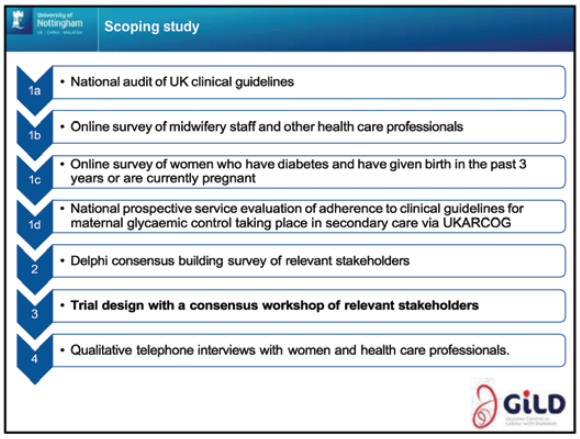

The GILD Study
A study to determine current practices in intrapartum glucose control and decide on how best to conduct a future trial for all forms of diabetes in pregnancy.
• Diabetes in pregnancy affects at least 5% of pregnant women or 40,000 women every year
• For most women this is gestational diabetes (GDM) developing during pregnancy (87.5%), but some women have pre-existing diabetes (12.5%) which can be Type 1 (T1DM: 7.5%) or Type 2 (T2DM: 5%) (1).
• Traditionally, intensive glucose control (target 4-7 mmol/L) (1, 2) is recommended in labour.
• Treatment with intravenous insulin during labour to maintain intensive control increases the risk of maternal hypoglycaemia in labour, which carries a risk to the mother.
• However, accepting more permissive glucose levels in the mother may be detrimental to the baby.
(1) National Institute for Health and Clinical Excellence (NICE)
(2) Joint British Diabetes Society for Inpatient Care Group (JBDS-IP)
GILD

7


The GILD Study
• No published randomised trials comparing different intrapartum glycaemic targets and occurrence of neonatal hypoglycaemia
• Systematic review of cohort studies found conflicting results in the primary studies
• Some studies also pre-date significant changes that have happened in diabetes in pregnancy care
- thresholds for diagnosing GDM significantly lowered following the HAPO study
- Safety of 'tight' control has recently been questioned
- Newer technologies (e.g. insulin pumps and glucose sensors) developed and introduced into care
• GILD therefore developed to explore current practice, determine best trial design and ascertain willingness of patients and acceptability to clinicians of a clinical trial
GILD

8


Scoping study
1a • National audit of UK clinical guidelines
1b • Online survey of midwifery staff and other health care professionals
1c • Online survey of women who have diabetes and have given birth in the past 3 years or are currently pregnant
1d • National prospective service evaluation of adherence to clinical guidelines for maternal glycaemic control taking place in secondary care via UKARCOG
2 • Delphi consensus building survey of relevant stakeholders
3 • Trial design with a consensus workshop of relevant stakeholders
4 • Qualitative telephone interviews with women and health care professionals.
GILD

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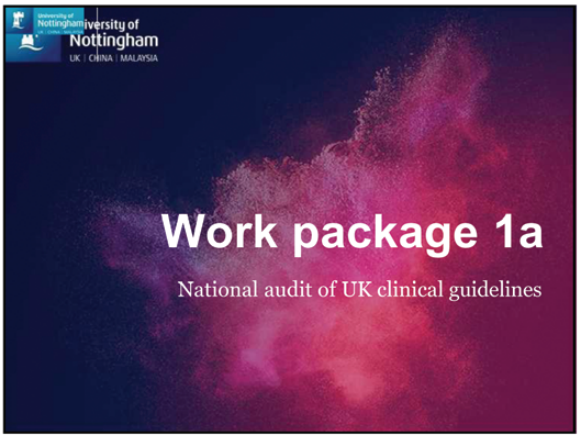
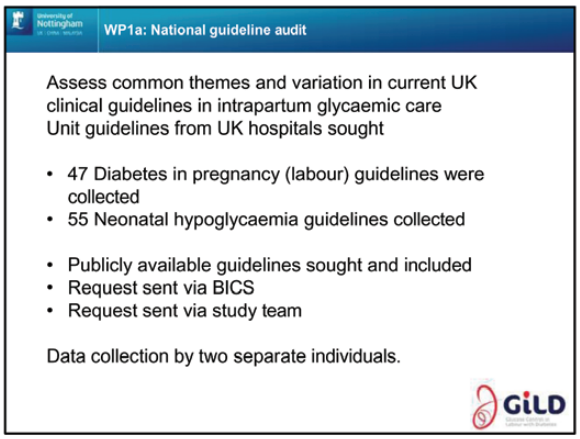
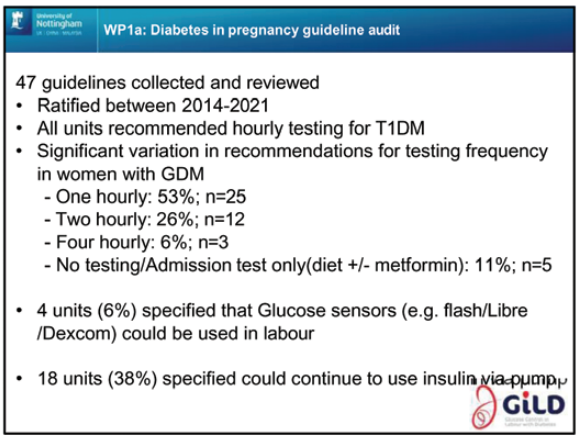

University of Nottingham
UK | CHINA | MALAYSIA
Work package 1a
National audit of UK clinical guidelines

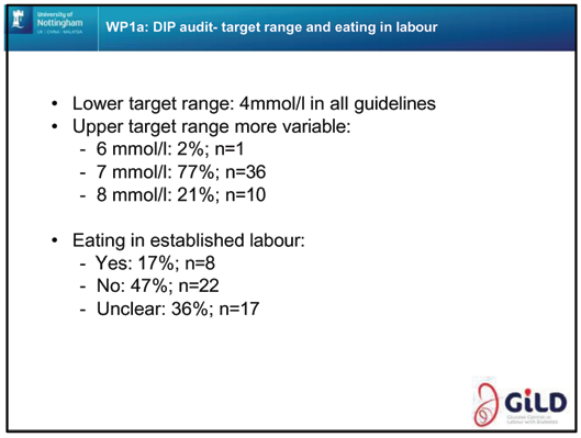
10


WP1a: National guideline audit
Assess common themes and variation in current UK clinical guidelines in intrapartum glycaemic care
Unit guidelines from UK hospitals sought
• 47 Diabetes in pregnancy (labour) guidelines were collected
• 55 Neonatal hypoglycaemia guidelines collected
• Publicly available guidelines sought and included
• Request sent via BICS
• Request sent via study team
Data collection by two separate individuals.
GILD

11


WP1a: Diabetes in pregnancy guideline audit
47 guidelines collected and reviewed
• Ratified between 2014-2021
• All units recommended hourly testing for T1DM
• Significant variation in recommendations for testing frequency in women with GDM
- One hourly: 53%; n=25
- Two hourly: 26%; n=12
- Four hourly: 6%; n=3
- No testing/Admission test only(diet +/- metformin): 11%; n=5
• 4 units (6%) specified that Glucose sensors (e.g. flash/Libre /Dexcom) could be used in labour
• 18 units (38%) specified could continue to use insulin via pump
GILD

12



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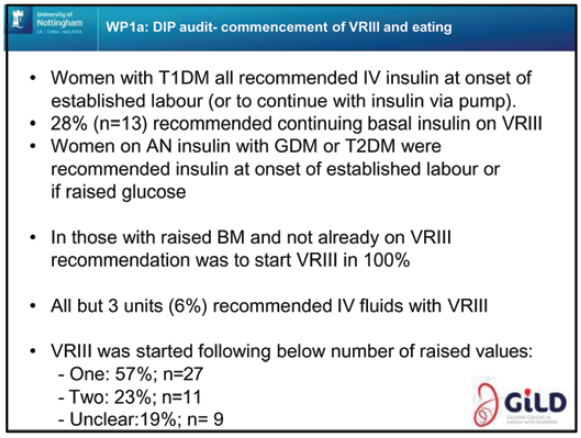

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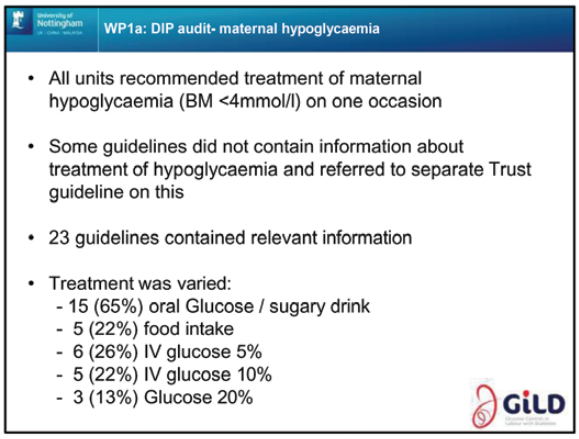

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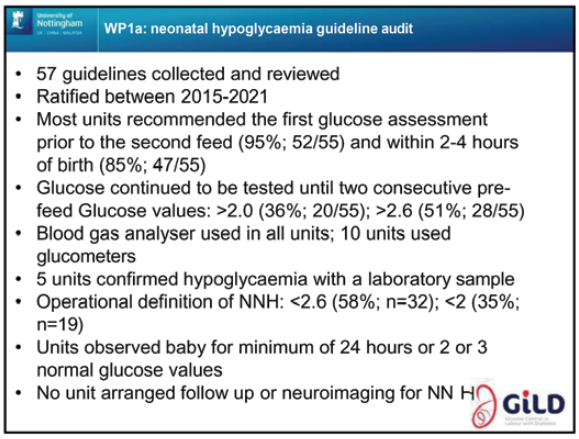

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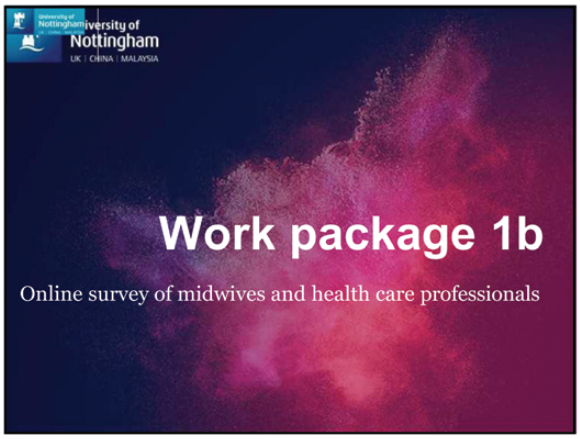

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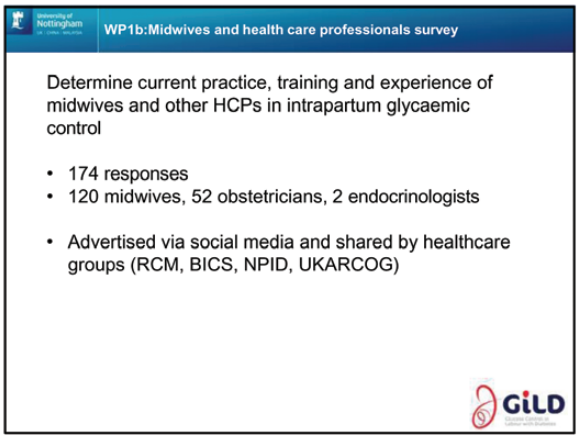

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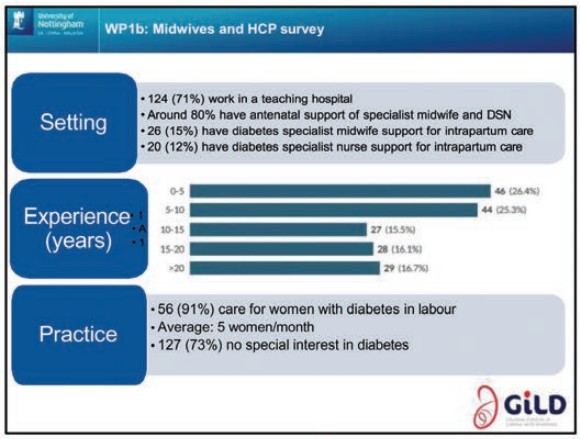

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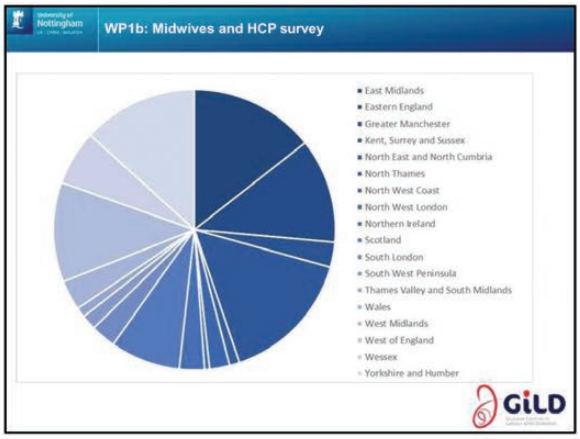

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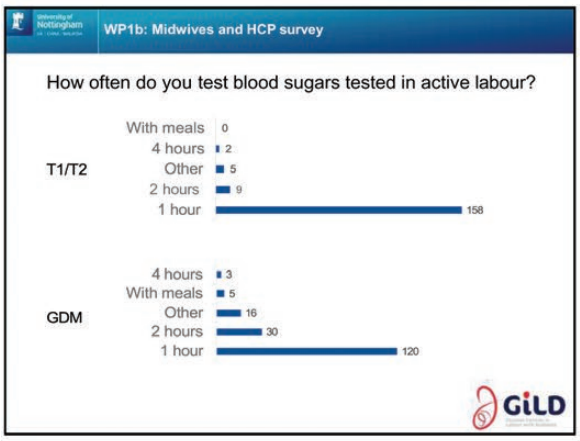

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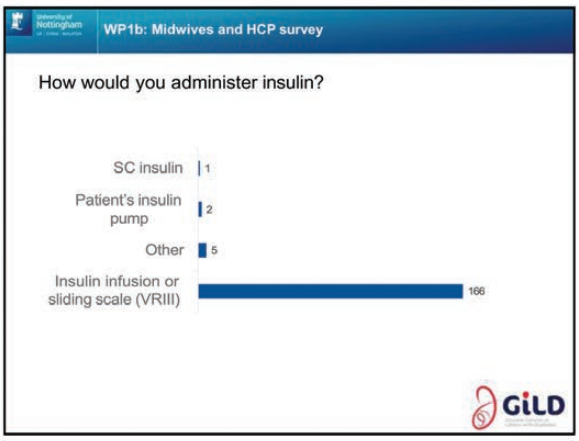

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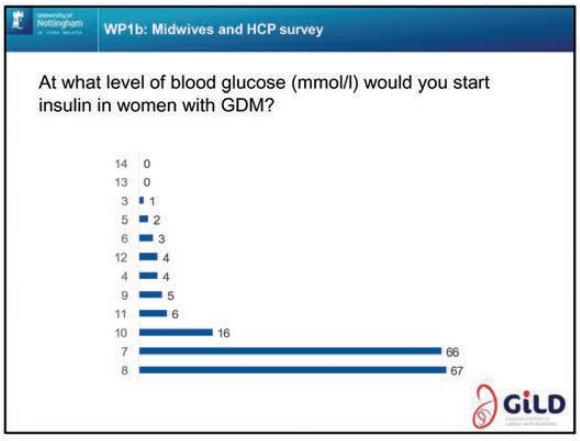

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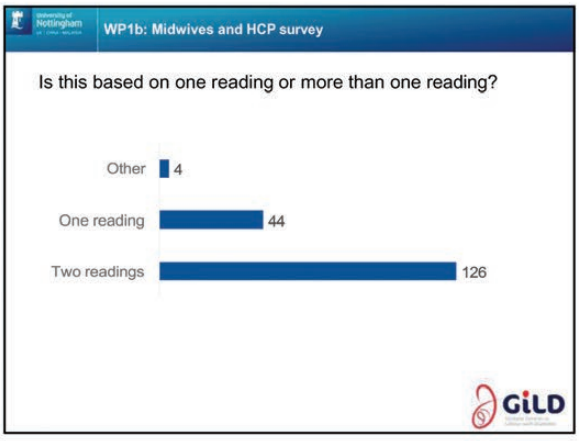

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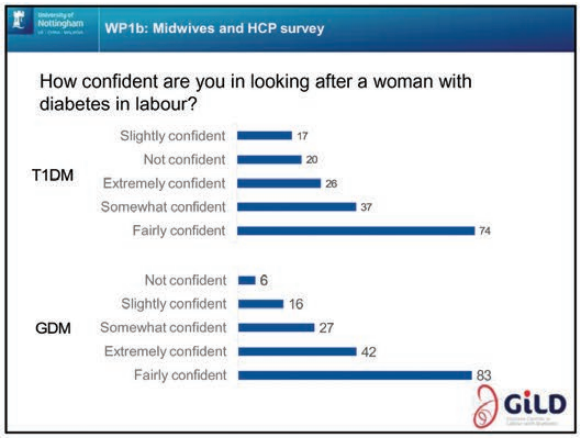

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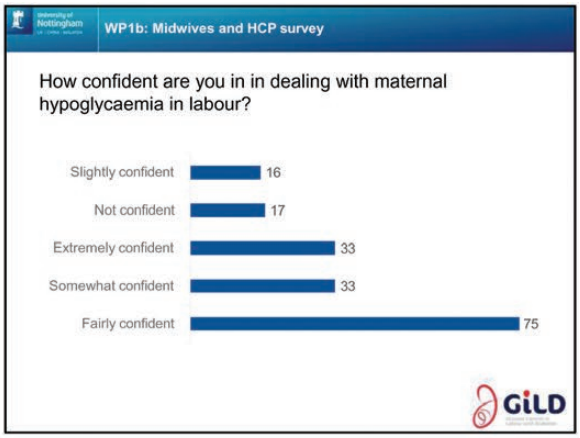

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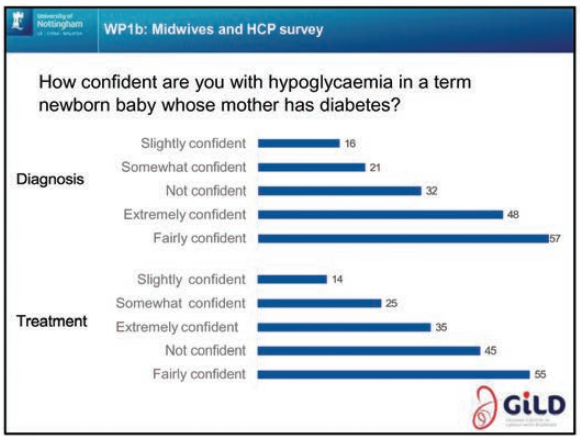

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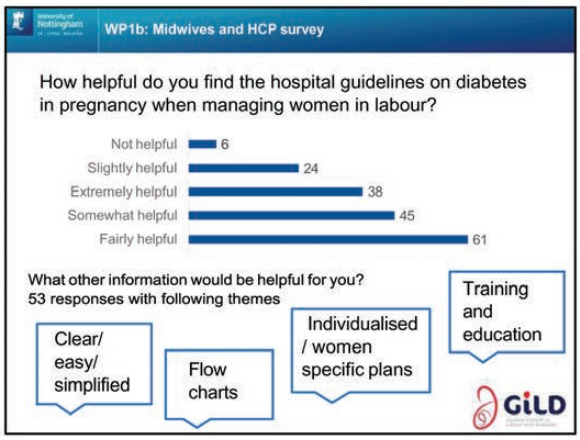

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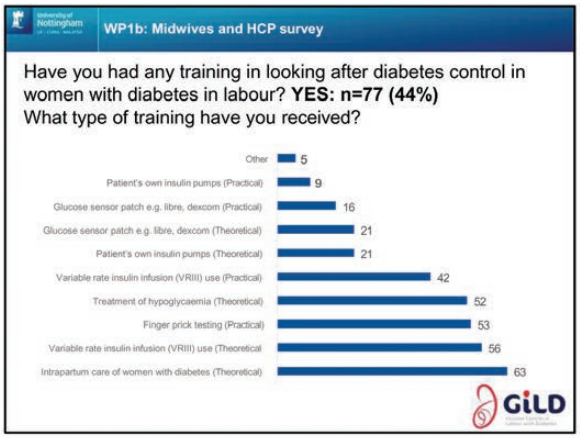

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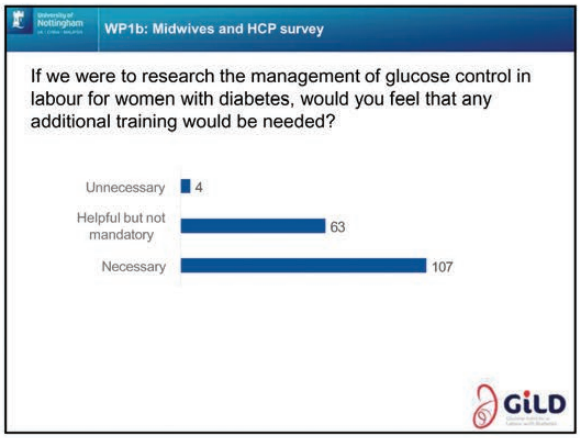

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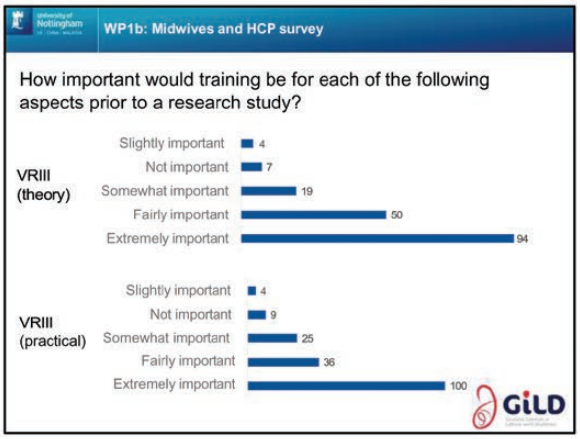

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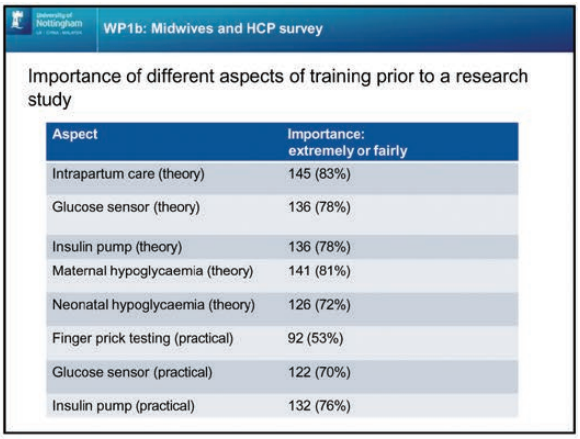

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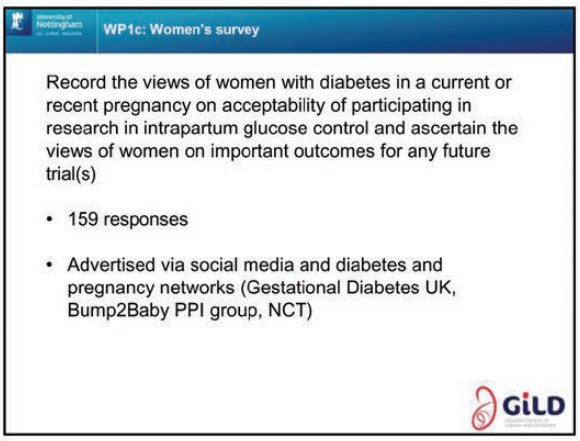

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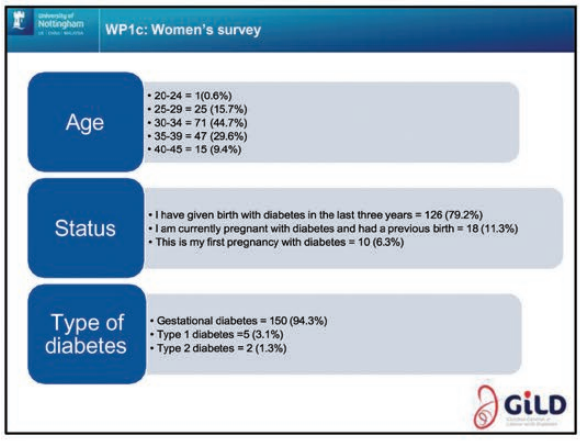

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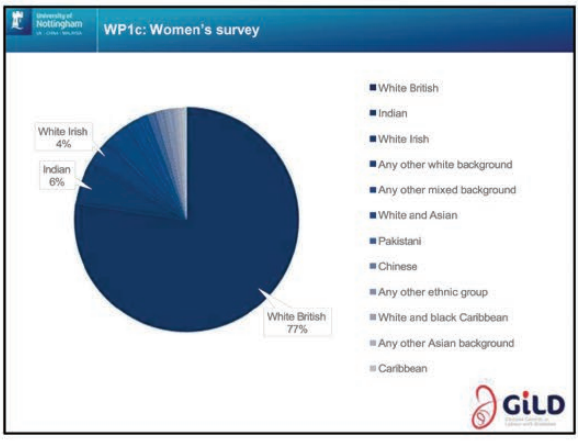

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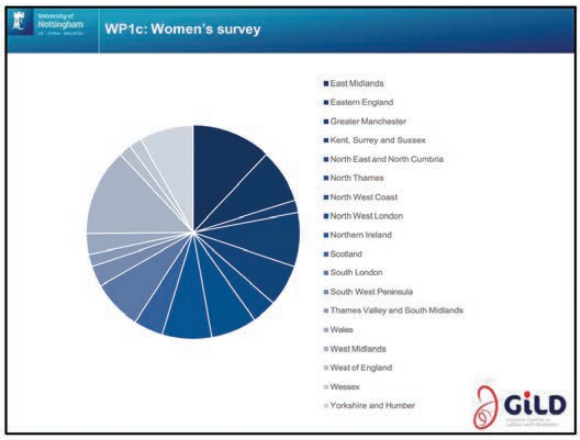

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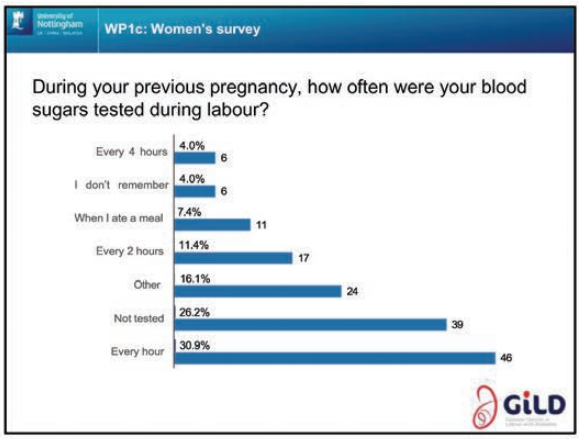

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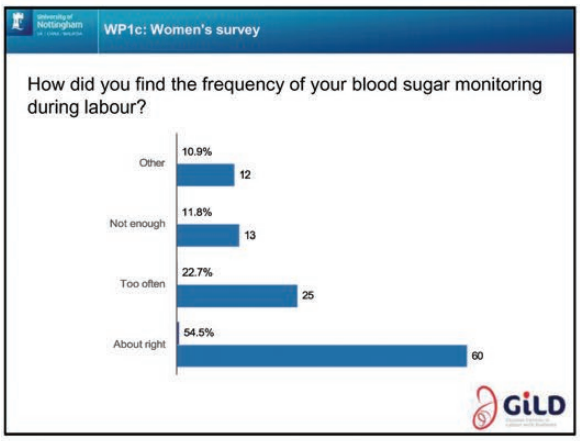

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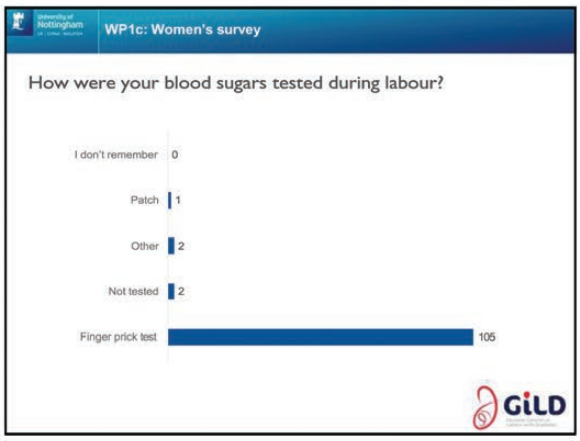

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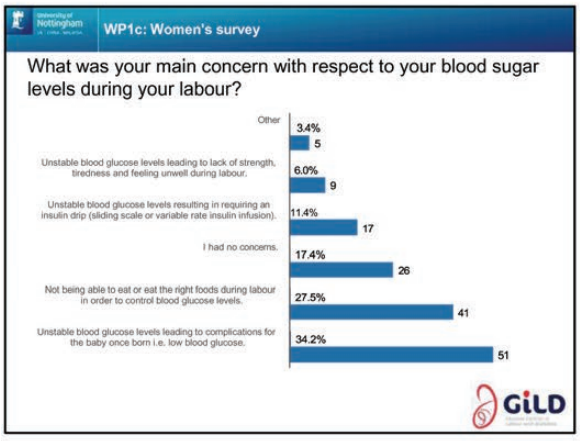

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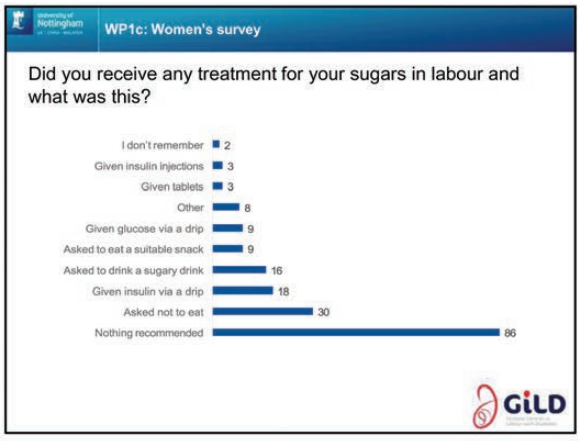

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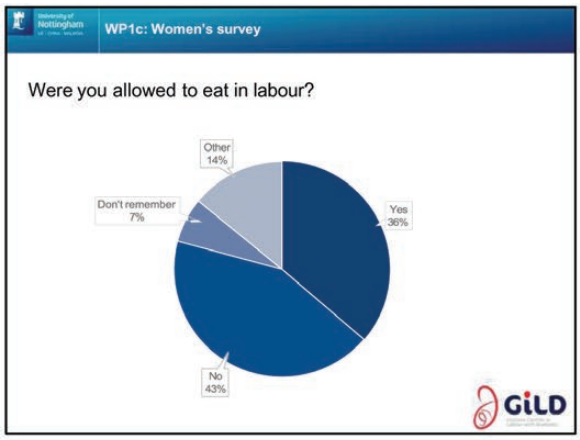

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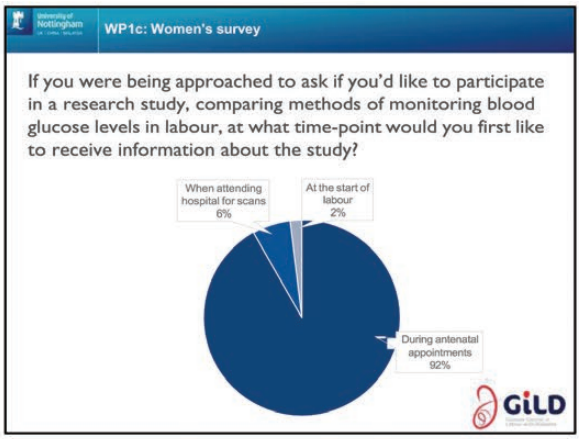

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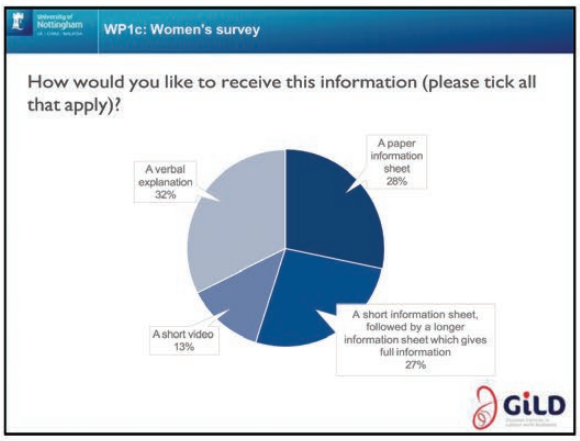

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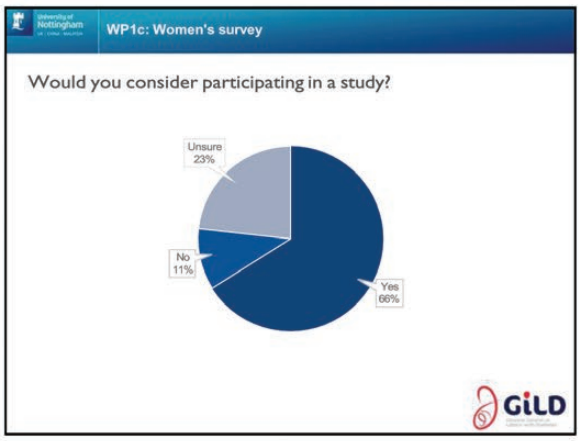

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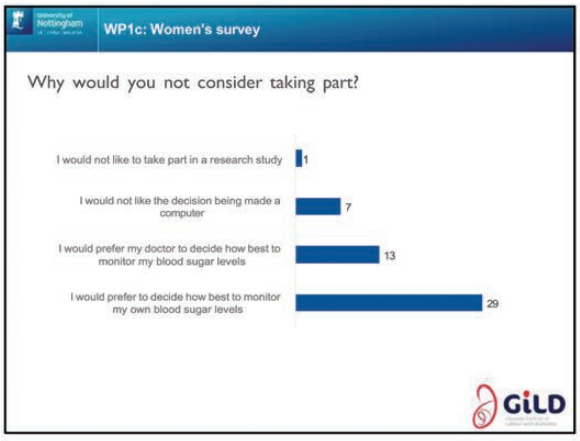

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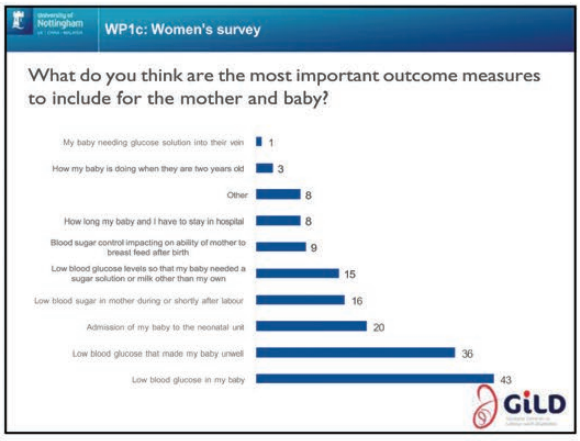

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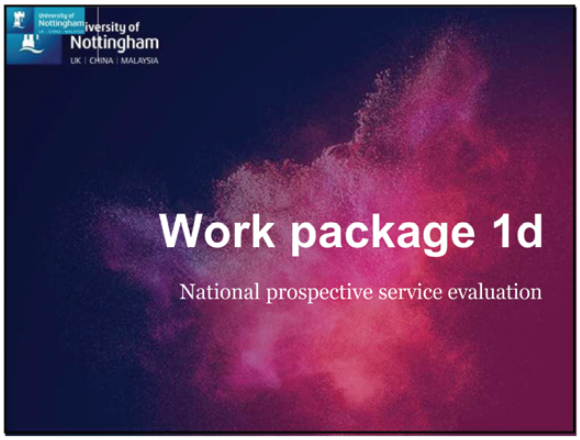

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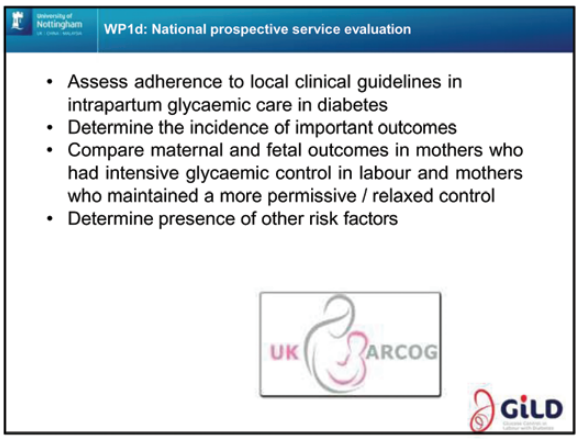

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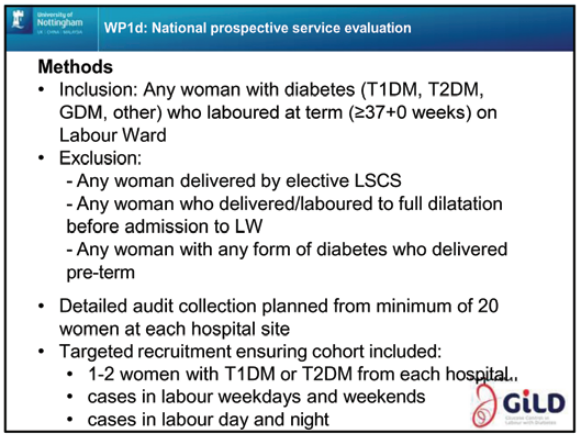

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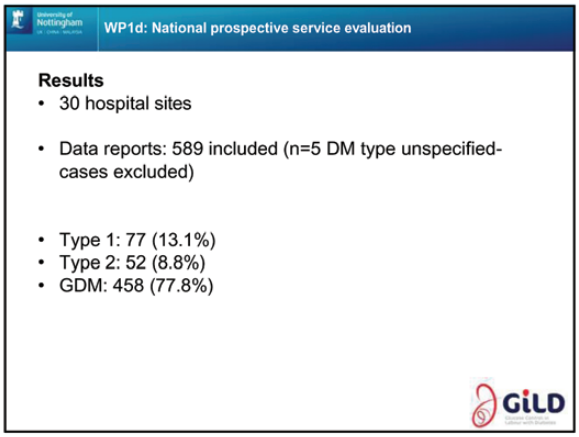

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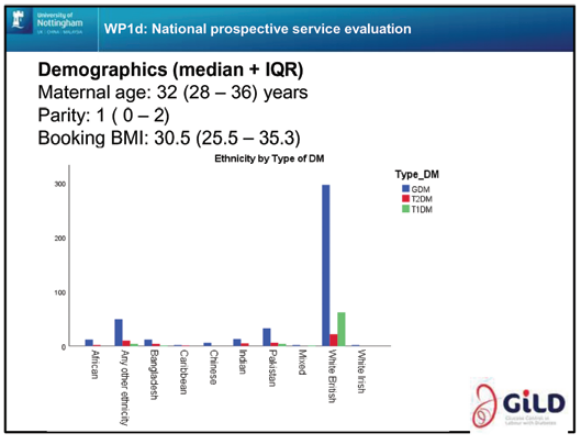

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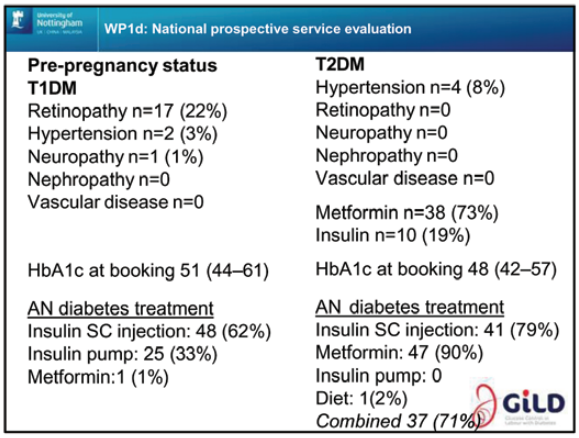

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WP1d: National prospective service evaluation

GDM diagnosis and treatment

		GTT_fasting	GTT_2Hour	HbA1c	Random_Glc	Fasting_Glc
N	Valid	294	248	297	221	265
Minimum		3.7	3.5	27	3.1	2.5
Maximum		9.6	15.6	80	12.5	10.3
Percentiles	25	4.6	7.8	33	4.9	4.8
	50	5.1	8.3	36	6.0	5.4
	75	5.7	9.3	40	7.7	5.9

		Preg Metformin No	Preg Metformin Yes	Total
Preg Insulin injection	No	187* (41%)	158 (34%)	345
	Yes	51 (11%)	62 (14%)	113
Total		238	220	458

*diet

55

WP1d: National prospective service evaluation

Antenatal obstetric complications

	T1DM	T2DM	GDM
Pre-eclampsia	4 (5%)	5 (10%)	13 (3%)
Suspected Macrosomia	28 (36%)	15 (29%)	101 (22%)
Suspected SGA	4 (5%)	1 (2%)	20 (4%)
Congenital anomaly	2 (3%)	1 (2%)	5 (1%)
Polyhydramnios	6 (6%)	4 (8%)	29 (6%)
Total	77	52	458

Macrosomia statistically significant p=0.04 (Chi squared test)

Diabetes complications in pregnancy

	T1DM	T2DM	GDM
Retinopathy	11 (14%)	1 (2%)	0
Nephropathy	1	0	1
Neuropathy	1	0	1
Hypertension	4 (5%)	5 (10%)	22 (5%)
Total	77	52	458

Retinopathy statistically significant p<0.001 (Chi squared test)

56

WP1d: National prospective service evaluation

Intrapartum care: Onset of labour

	T1DM	T2DM	GDM
Spontaneous	5 (7%)	5 (10%)	120 (26%)
Induced	59 (77%)	42 (81%)	296 (65%)
Augmented (PROM)	3 (3%)	2 (4%)	18 (4%)
Not reported	11 (14%)	3 (6%)	24 (5%)

Onset of labour statistically significant between DM types p=0.003 (Chi squared test)

	T1DM	T2DM	GDM
Planned oral intake	22 (29%)	15 (29%)	136 (36%)

Pre- and post- meal glucose most frequent monitoring option before established labour

25 women had AN insulin pump: 18 (72%) continued in labour

7 (28%) were stopped - 3 patient unwell

- 4 Unit Guideline

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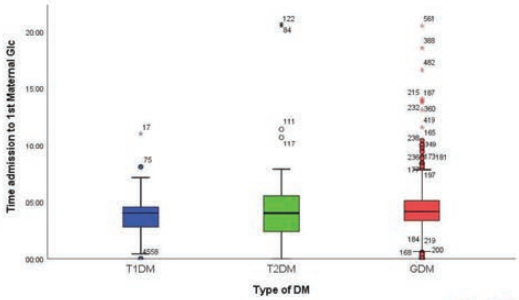
WP1d: National prospective service evaluation

Intrapartum care: Maternal Glucose control in labour



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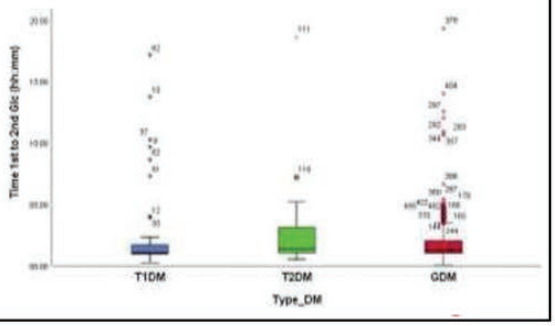
WP1d: National prospective service evaluation

Intrapartum care: Maternal Glucose control in labour



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WP1d: National prospective service evaluation

Intrapartum care: Maternal glucose control in labour * statistically significant

	T1DM	T2DM	GDM
Time Admission to first Glucose	04:00 (02:45 – 04.35)	04:00 (02:17 – 05.46)	04:07 (03:19 – 05.08)
Median first glucose	6.2 (5.4 – 7.6)* Missing data:20	5.9 (5.0 – 6.9)* Missing data: 17	5.3 (4.6 – 6.2)* Missing data 175
Number with Glucose <4.0 mmol/l	7 (1%)	1 (2%)	20 (7%)
Number with Glucose >7.0 mmol/l	18 (32%)	8 (23%)	24 (8%)
Number with Glucose >8.0 mmol/l	13 (23%)	6 (17%)	9 (3%)
Time between 1st and second Glucose	01:00 (00:54 – 01:47)	01:20 (01:01 – 03:33)	01:15 (01:00 – 02:00)
Median 2nd Glucose	6.2 (5.1 – 8.0) * n=51	5.7 (4.8 – 7.0) * n=31	5.3 (4.7 – 6.3) * n=213

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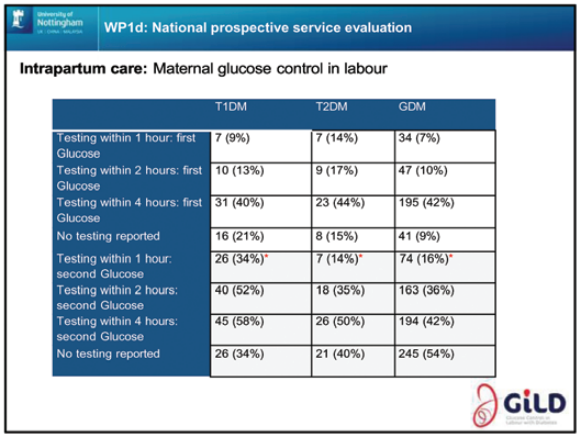

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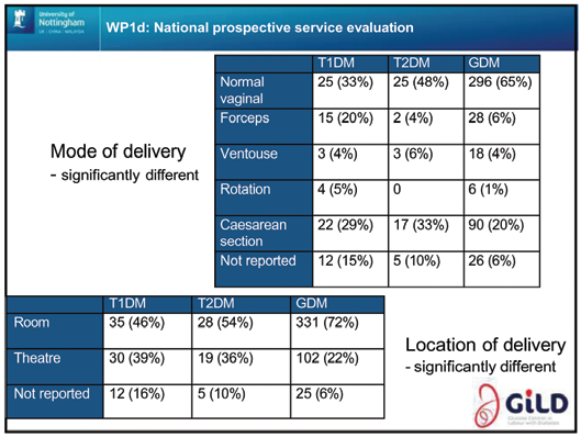

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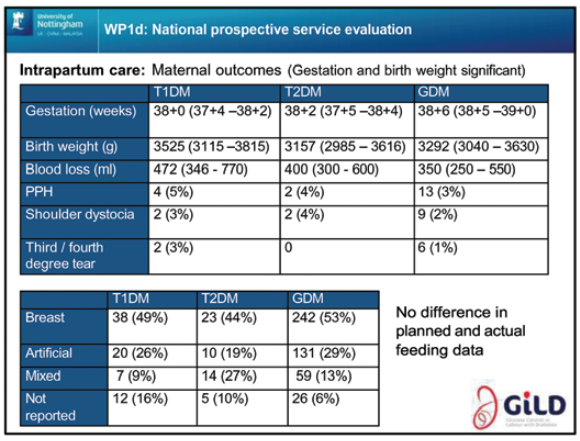

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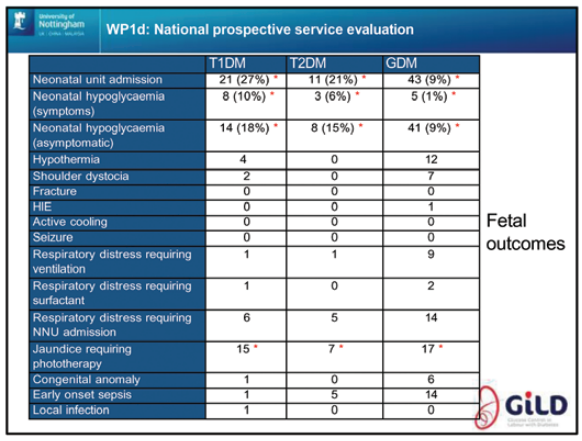

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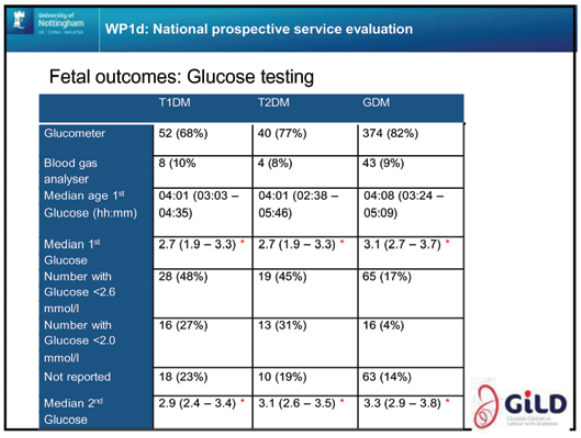

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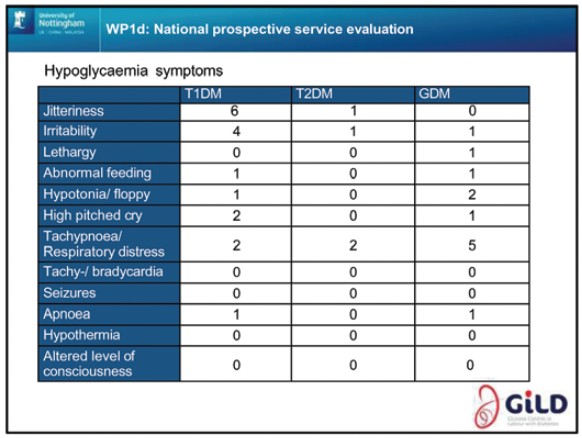

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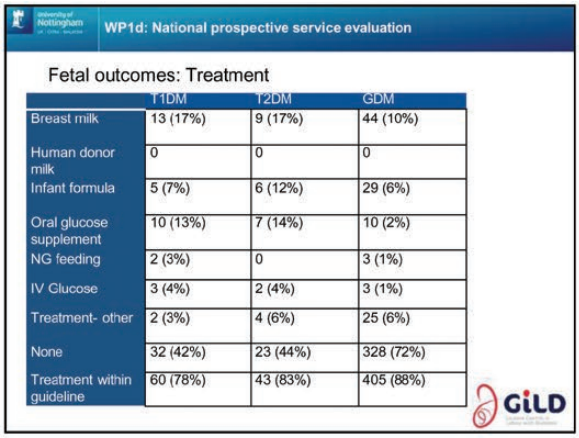

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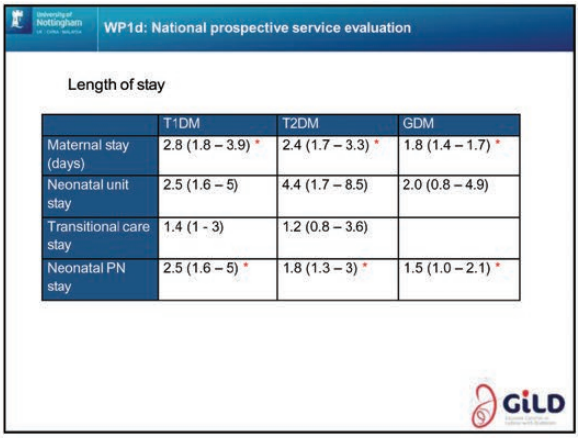

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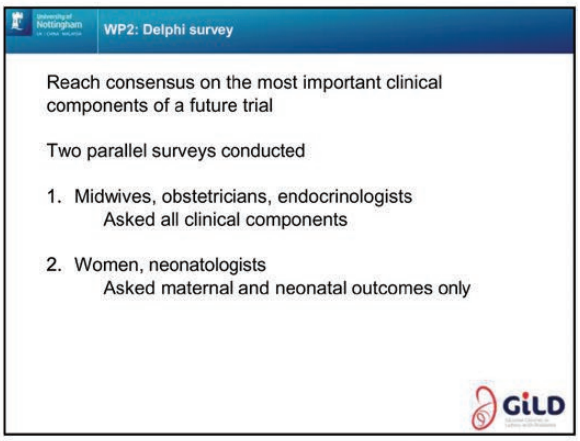

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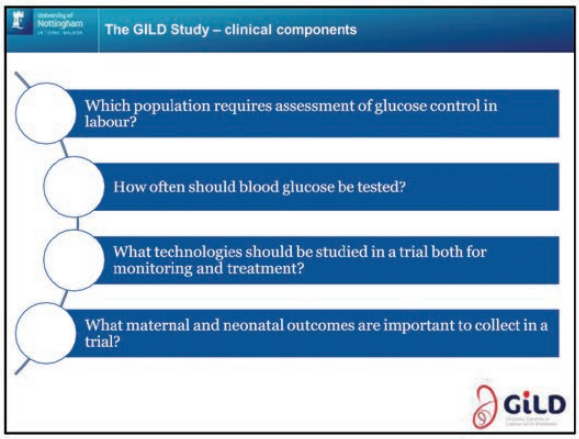

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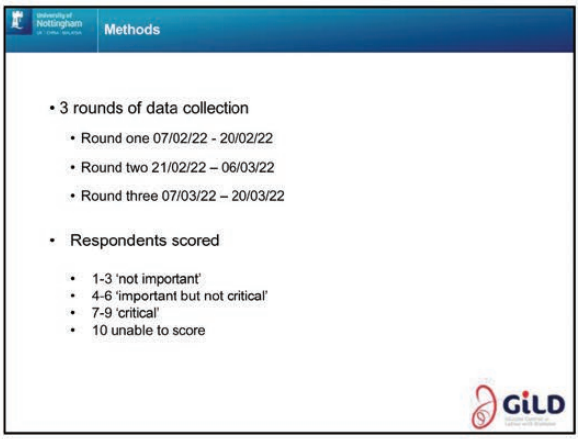

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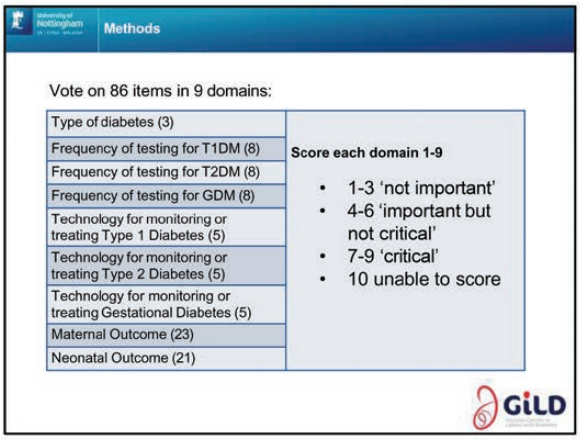

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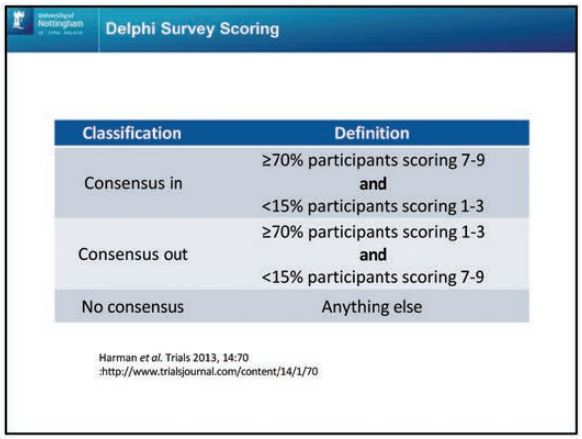

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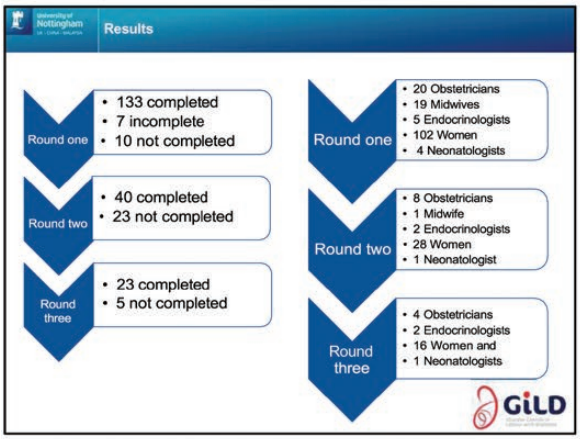

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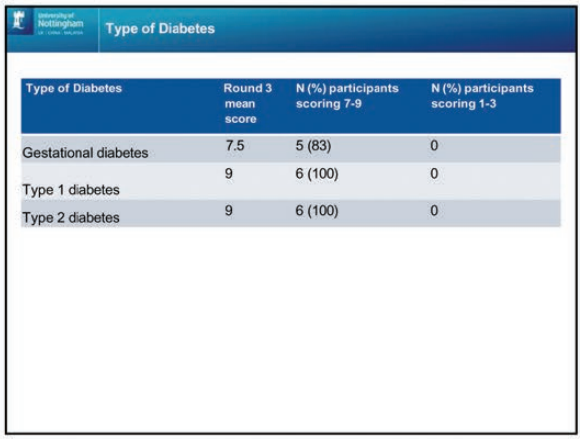
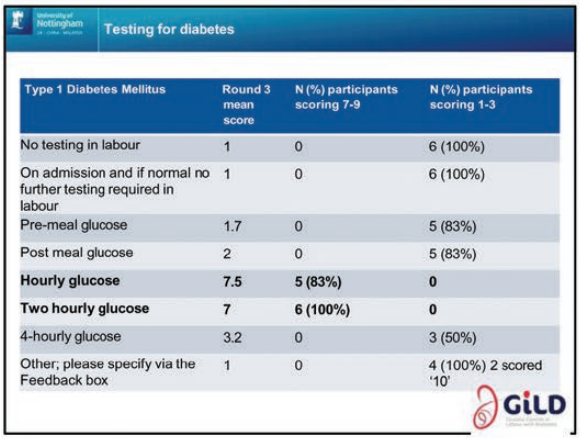


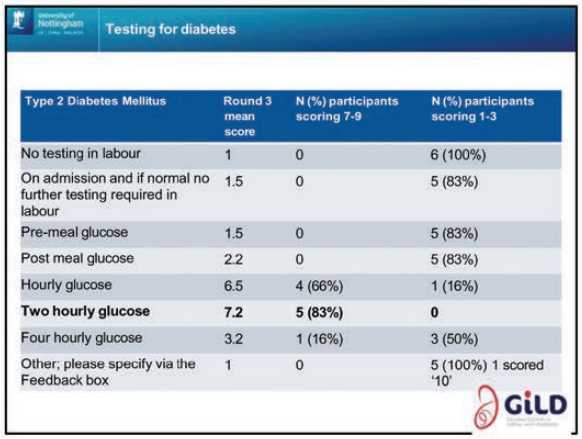
Type of Diabetes	Round 3 mean score	N (%) participants scoring 7-9	N (%) participants scoring 1-3
Gestational diabetes	7.5	5 (83)	0
Type 1 diabetes	9	6 (100)	0
Type 2 diabetes	9	6 (100)	0

76



Type 1 Diabetes Mellitus	Round 3 mean score	N (%) participants scoring 7-9	N (%) participants scoring 1-3
No testing in labour	1	0	6 (100%)
On admission and if normal no further testing required in labour	1	0	6 (100%)
Pre-meal glucose	1.7	0	5 (83%)
Post meal glucose	2	0	5 (83%)
Hourly glucose	**7.5**	**5 (83%)**	**0**
Two hourly glucose	**7**	**6 (100%)**	**0**
4-hourly glucose	3.2	0	3 (50%)
Other; please specify via the Feedback box	1	0	4 (100%) 2 scored '10'

77



Type 2 Diabetes Mellitus	Round 3 mean score	N (%) participants scoring 7-9	N (%) participants scoring 1-3
No testing in labour	1	0	6 (100%)
On admission and if normal no further testing required in labour	1.5	0	5 (83%)
Pre-meal glucose	1.5	0	5 (83%)
Post meal glucose	2.2	0	5 (83%)
Hourly glucose	6.5	4 (66%)	1 (16%)
Two hourly glucose	**7.2**	**5 (83%)**	**0**
Four hourly glucose	3.2	1 (16%)	3 (50%)
Other; please specify via the Feedback box	1	0	5 (100%) 1 scored '10'

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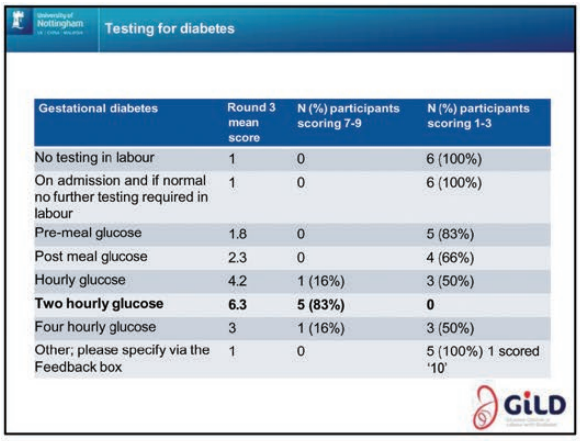

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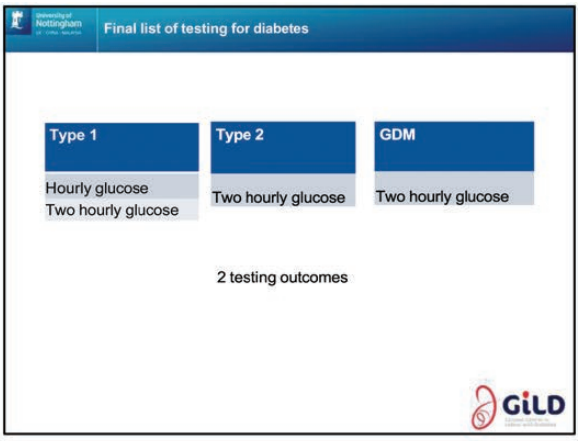

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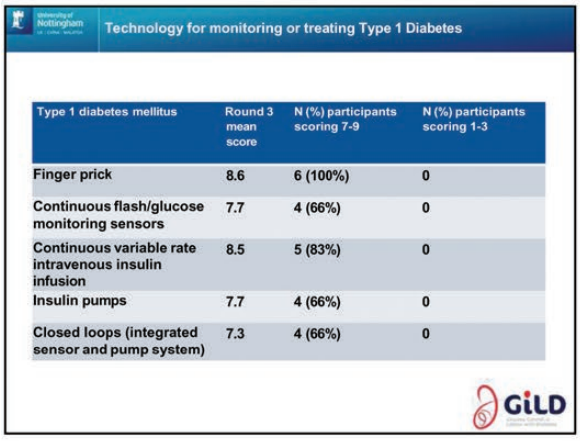

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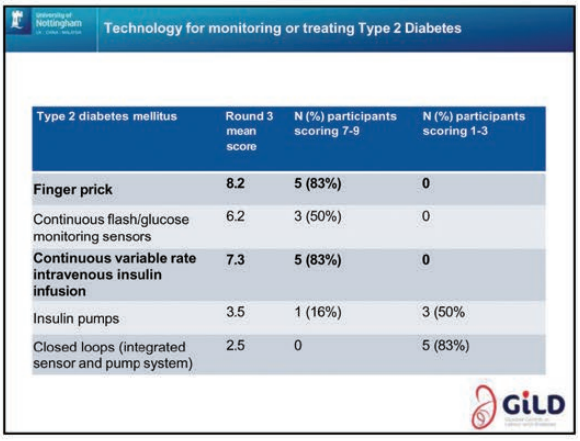

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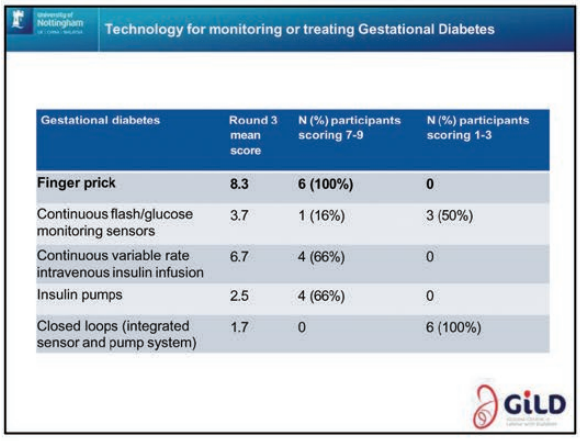

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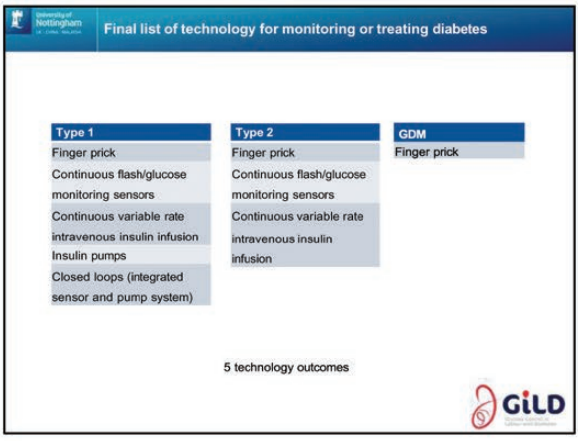

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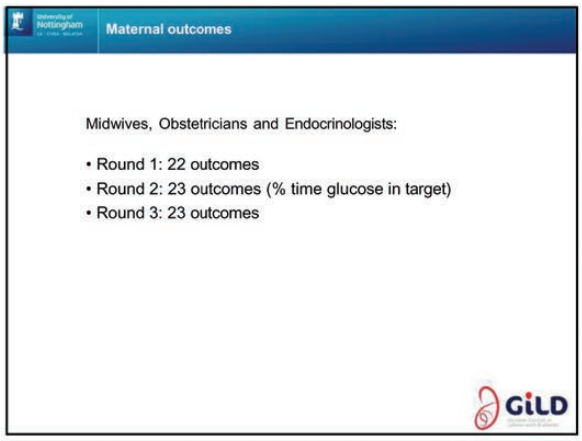

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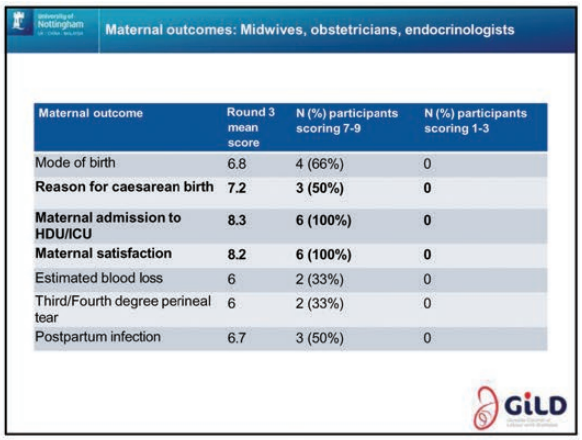

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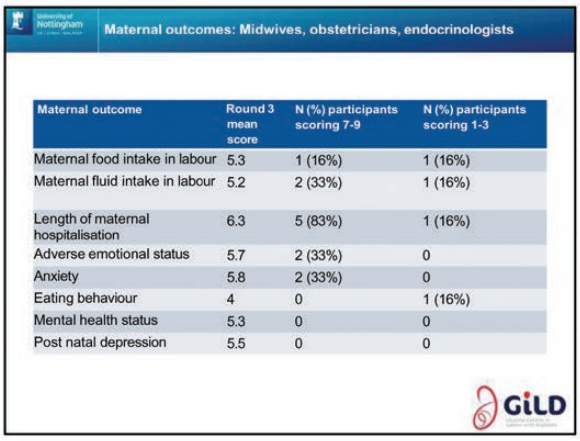

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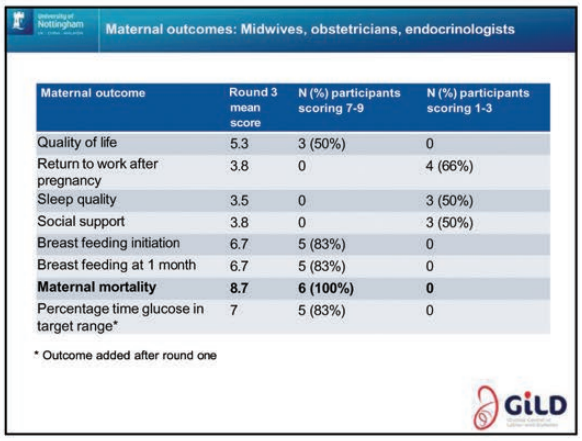

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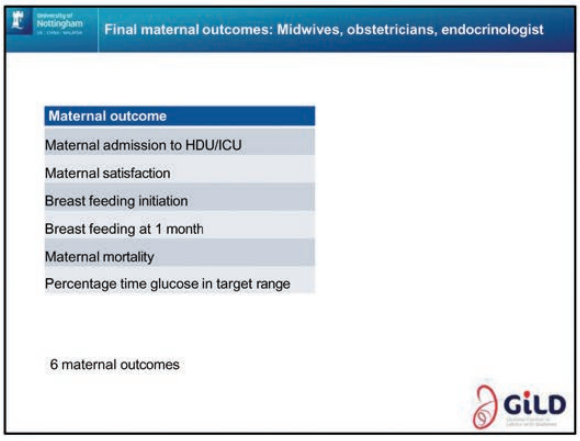

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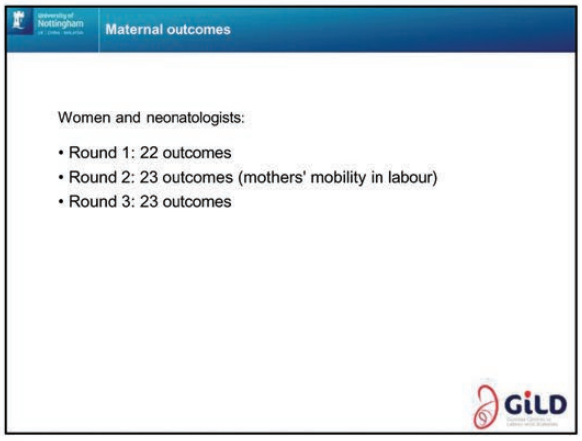

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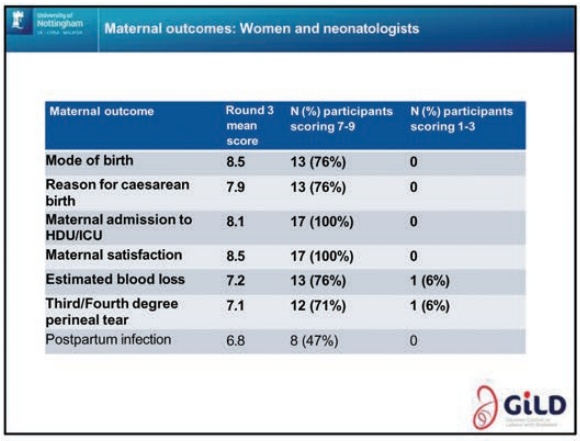

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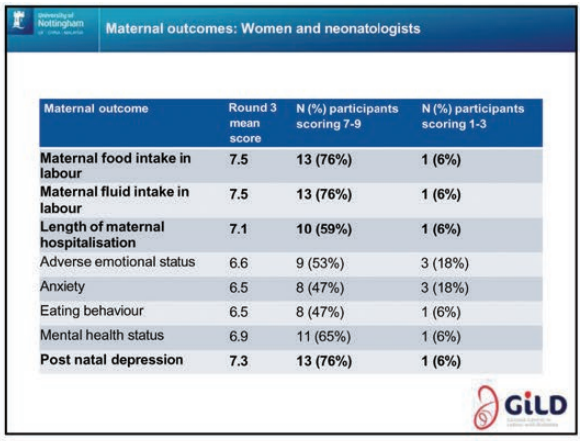

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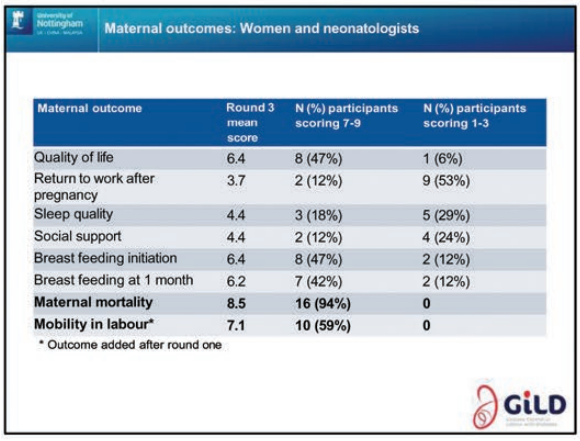

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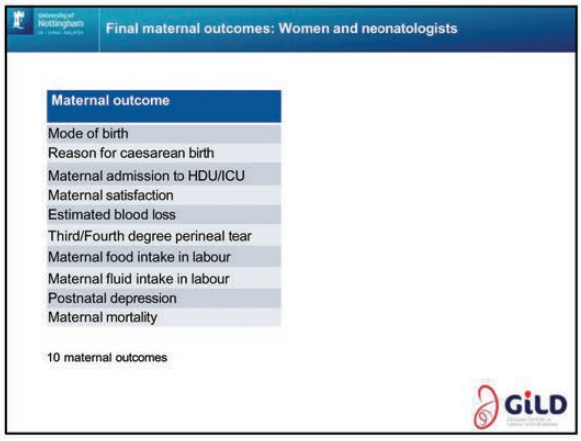

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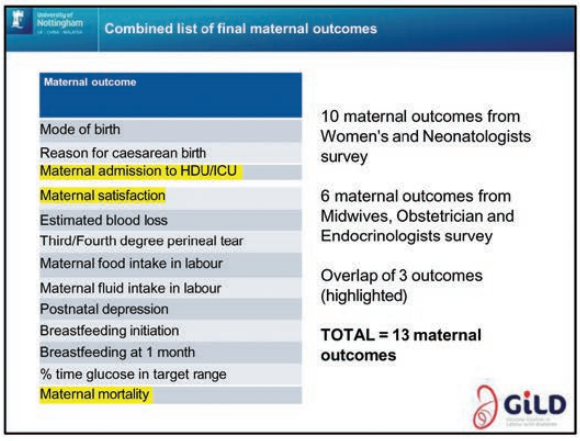

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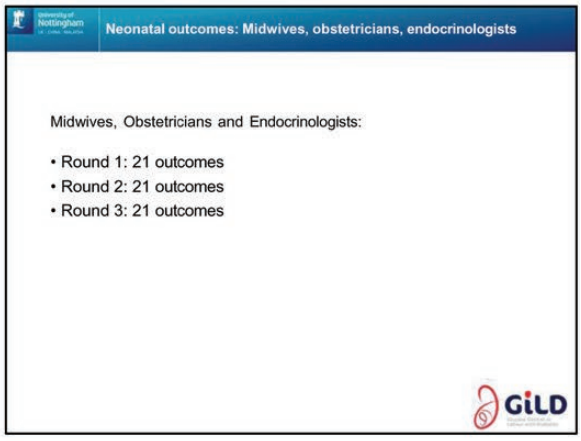

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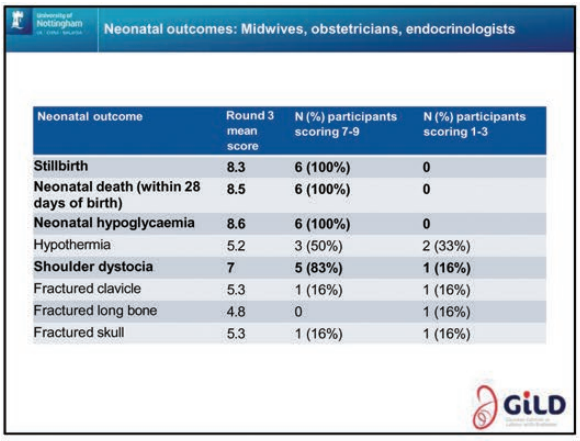

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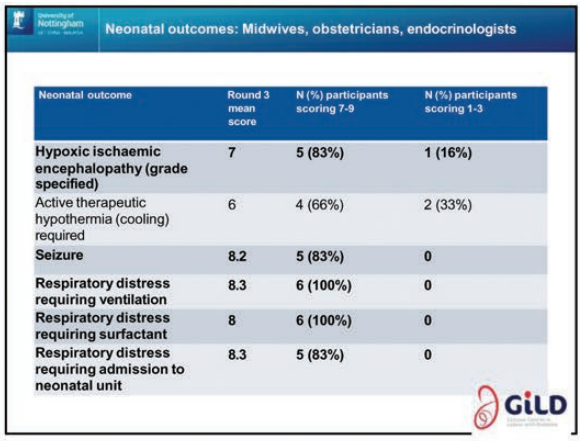

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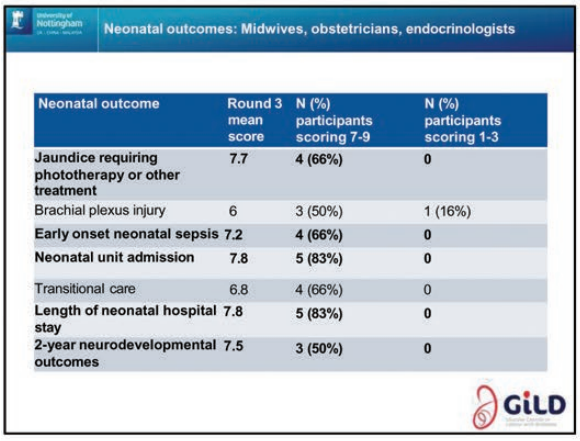

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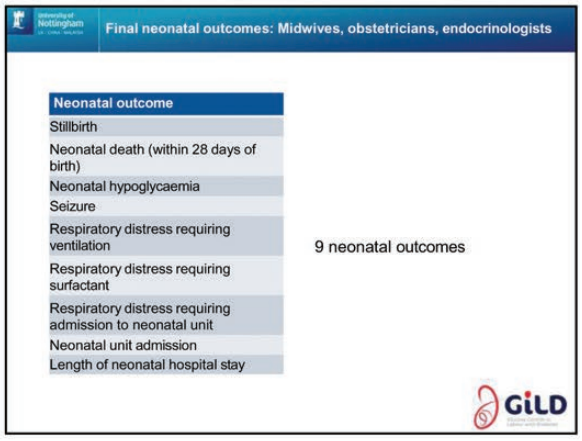

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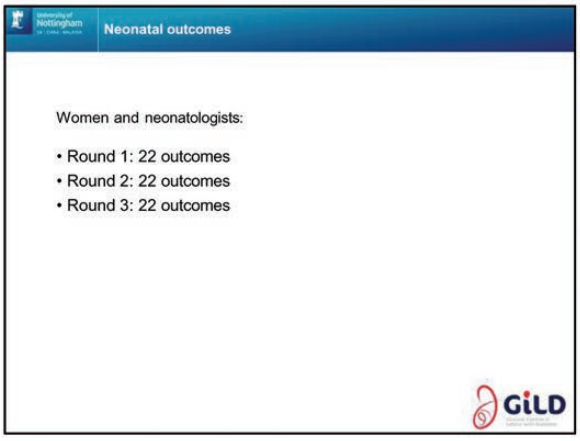

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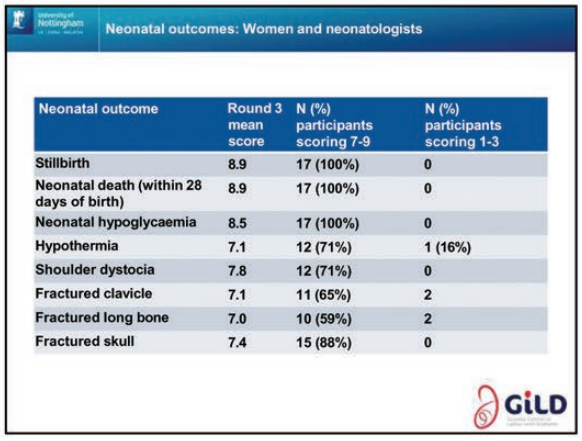

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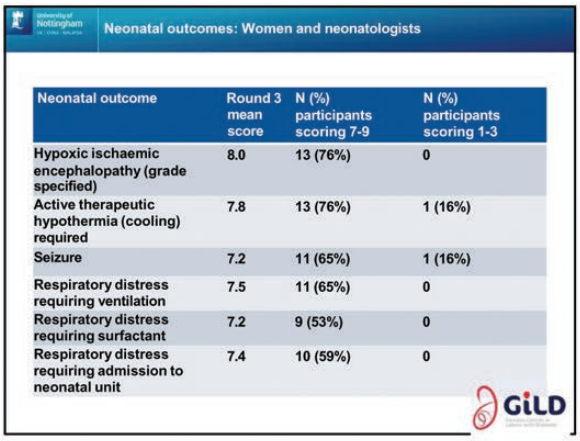

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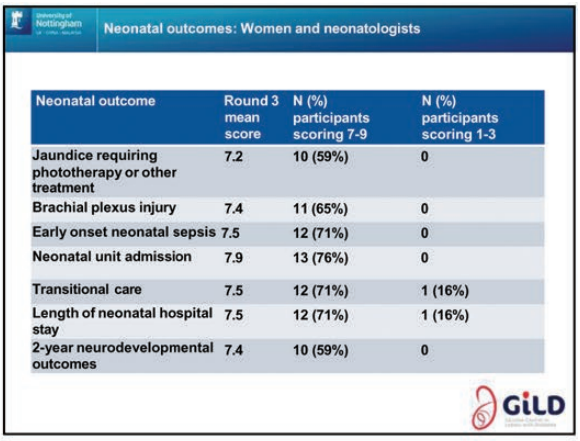

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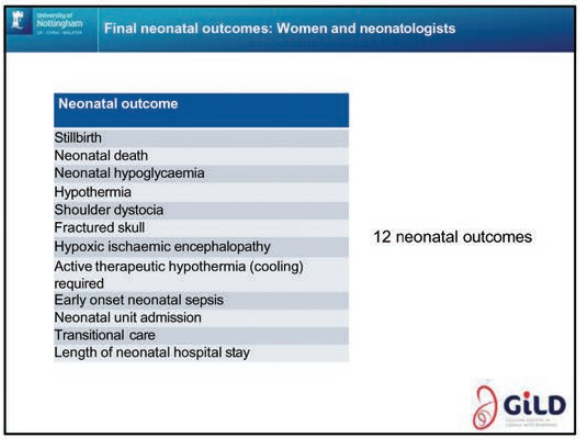

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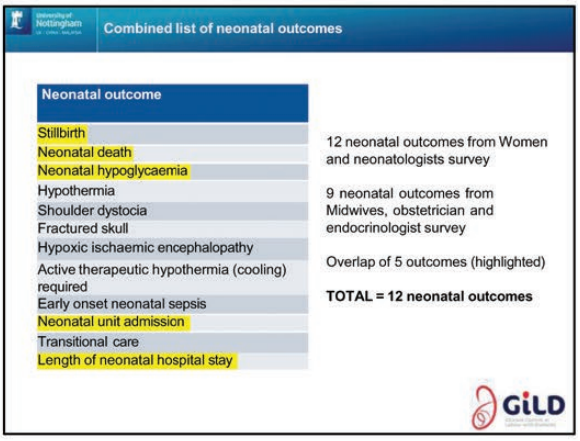

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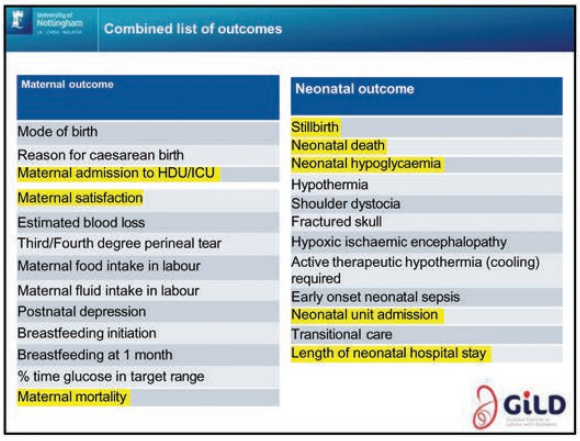

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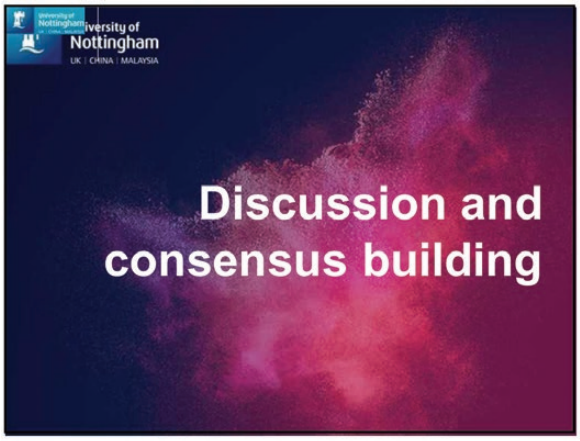

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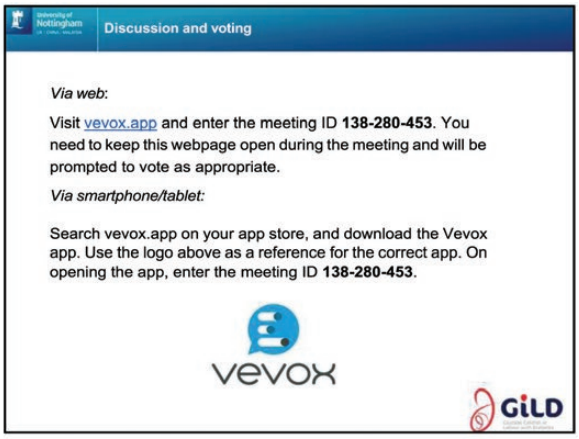

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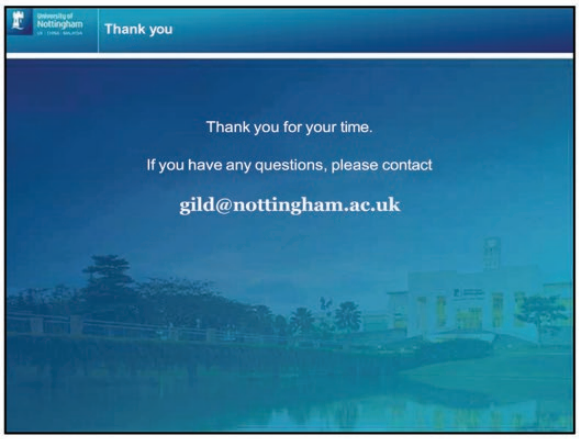

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Appendix 5 Healthcare professional qualitative interview guide (work package 4)

GILD study qualitative interview guide (clinical staff)

Title of study: glycaemic control in labour with diabetes

Principal Investigator: Dr Susan Ayers, Professor of Maternal and Child Health, City, University of London.

Research Fellow: Georgina Constantinou, Research Assistant, City, University of London.

Name of Chief Investigators (GILD): Dr Nia Wyn Jones, Associate Professor, Division of Child Health, Obstetrics and Gynaecology, University of Nottingham.

Aim of interviews

To conduct individual telephone or video interviews with obstetricians, endocrinologists or midwives to determine the acceptability and feasibility of the planned RCT comparing permissive to tight glycaemic control for women with diabetes.

Structure

1. Introductions
2. Confidentiality and consent
3. Interview
4. Information about additional support if needed after the session.

Introductions

We are interested in your views of the acceptability and feasibility of the planned RCT comparing permissive to tight glycaemic control for women with diabetes in labour.

Women with diabetes in pregnancy have their blood sugar levels closely monitored during labour in order to minimise the effects of high sugar on their baby after birth. High blood sugar in the mother can cause low blood sugar in the baby, which can be a problem and lead to babies being admitted to the neonatal unit. However, this monitoring can be intrusive to women during labour and is expensive. Also having tight control risks the women having low blood sugar in labour which may be harmful to them. New evidence suggests that it may not be as important for preventing problems in the baby as previously thought and that antenatal control is much more important than the control in labour in the risks to baby. This first study is being carried out to design a larger, second research study comparing blood sugar-monitoring strategies in labour. We are interested in the views of HCPs about whether this kind of study would be acceptable and of interest to them, and therefore possible to do in the future.

This is an important issue as diabetes in pregnancy is increasing in the UK. It currently affects 5% of all pregnant women. Most have GDM, which develops during pregnancy and goes away after birth, with the rest having diabetes before they get pregnant.

Confidentiality and consent

- Please can you confirm that you have read and understood the information sheet for this study?
- As you will know from the information sheet, your participation is voluntary and that you are free to withdraw at any time, without giving any reason. The interview will be recorded and the transcript will be anonymised to maintain your confidentiality.
- Re-confirm consent (verbally): Are you still happy to give your consent to be interviewed?

Interview

Different types of techniques

Outline the different techniques the research looked at (permissive or tight control):

1. What are your views on managing glycaemic control for women with diabetes in labour?
2. Can you share any relevant experiences of managing glycaemic control for women with diabetes in labour from your clinical work?
3. What strategy would you usually use when faced with this scenario?

Probes: Why this strategy? Pros and cons? Have you always used this strategy?

4. What would be the most important outcome(s) for you in terms of which type of glycaemic control approach is most effective in labour?

Acceptability of a trial

1. Thinking about a RCT of managing glycaemic control for women with diabetes in labour, what are your views on how acceptable it is to conduct research like this?

Probes: Would you be willing to randomise women into the trial? Do you anticipate any challenges with randomising women to the type of control?

2. Would you be prepared to take part in a trial testing the effectiveness of different strategies to manage glycaemic control for women in labour with diabetes?

Probes: Yes, why? No, why? Not sure, why?

3. What factors are important to you in deciding whether to take part?

Probes: types of strategies trialled, resources, training, timing.

4. Do you think the primary outcome of neonatal hypoglycaemia is appropriate? If not, why?
5. Do you have any concerns about the glycaemic target ranges included in this trial?
6. What advice, if any, would you give the research team about how to make the trial more acceptable to HCPs?

Probe: Do you think this may have any impact on the trial or outcome?

Feasibility of a trial

The trial we are proposing to do will compare (permissive) with (tight) control techniques in labour (not the antenatal period).

7. How feasible do you think it would be to run this trial in your Trust?

8. Do you think you or your colleagues would require any training in order to conduct the trial? Probe: what kind of training?
9. What do you think would be the main barriers or challenges in your Trust to running this trial?
10. What could be done to facilitate the trial running at your Trust?
11. What advice would you give the research team about how to make the trial more feasible to implement in different Trusts?
12. Is there anything else you would like to add?

Sociodemographic Information

1. What is your health profession or discipline? For example, obstetrician, endocrinologist or midwife, etc.
2 .What is your grade of qualification?
3. How many years have you been practising since qualification?
4. How would you rate your exposure to glycaemic control for women with diabetes in labour in your role?

For example, approximately how many women a month do you care for with diabetes in labour?

Information about additional support if needed

See Resource Sheet Version 1

Appendix 6 Women's qualitative interview guide (work package 4)

GILD study qualitative interview guide (women)

Title of study: glycaemic control in labour with diabetes

Principal Investigator: Dr Susan Ayers, Professor of Maternal and Child Health, City, University of London.

Research Fellow: Georgina Constantinou, Research Assistant, City, University of London.

Name of Chief Investigators (GBS3): Dr Nia Wyn Jones, Associate Professor, Division of Child Health, Obstetrics and Gynaecology, University of Nottingham.

Aim of interviews

To conduct individual telephone or video interviews with women to determine the acceptability and feasibility of the planned RCT comparing loose to tight glycaemic control for women with diabetes.

Structure

1. Introductions
2. Confidentiality and consent
3. Interview
4. Information about additional support if needed after the session.

Introductions

We are interested in women's views of the acceptability and feasibility of different ways to manage glycaemic control for women with diabetes in labour. We are interested in the views of women with diabetes who have given birth or are currently pregnant about whether this kind of study would be acceptable and of interest to them, and therefore possible to do in the future.

Women with diabetes in pregnancy have their blood sugar levels closely monitored during labour in order to minimise the effects of high sugar on their baby after birth. High blood sugar in the mother can cause low blood sugar in the baby, which can be a problem and lead to babies being admitted to the neonatal unit. However, this monitoring can be intrusive to women during labour and is expensive. Also having tight control risks the women having low blood sugar in labour which may be harmful to them. New evidence suggests that it may not be as important for preventing problems in the baby as previously thought and that antenatal control is much more important than the control in labour in the risks to baby. This first study is being carried out to design a larger, second research study comparing blood sugar-monitoring strategies in labour.

This is an important issue as diabetes in pregnancy is increasing in the UK. It currently affects 5% of all pregnant women. Most have GDM, which develops during pregnancy and goes away after birth, with the rest having diabetes before they get pregnant.

Confidentiality and consent

- Please can you confirm that you have read and understood the information sheet for this study?

- As you will know from the information sheet, your participation is voluntary and that you are free to withdraw at any time, without giving any reason. The interview will be recorded and the transcript will be anonymised to maintain your confidentiality.
- Re-confirm consent (verbally): Are you still happy to give your consent to be interviewed?

Interview

Experiences of management of diabetes in labour

1. Please could you tell me about your experience of diabetes in labour?
   a. What type of diabetes T1DM/T2DM or GDM do you have experience of?
2. What was the management of your diabetes like during your baby's birth?

Prompts: How often were your blood sugars tested? How did that impact your experience in labour? (Prompt away from talking about antenatal control – only want experiences of control in labour).

Different types of techniques

Show women the different strategies to monitor blood glucose that the research will compare (loose or tight control).

3. What are your views on the different strategies for managing glycaemic control for women with diabetes in labour?
   a. What are your views on being randomised to different frequencies of monitoring blood sugar levels in labour? (e.g. loose or tight control).
   b. What are your views on having hourly/2–4 hourly blood sugar testing during labour (depending on type of DM)? Does the frequency seem reasonable to you?

4. If you had a choice of how your blood sugars were monitored in labour, which strategy would you prefer to be used with you and your baby?

Probes: Why do you prefer this option? If no preference, why?

a. What would you see as the advantages of the strategy you prefer?
b. What would you see as the disadvantages?

5. What would be the most important outcome(s) for you in terms of which strategy is best to use?

Probes: How do you think this would affect you during your labour? How do you think this would affect your baby? Would these things be important outcomes for you?

6. In general, do you think there is a strategy that would be more acceptable in labour to parents?
7. Similarly, do you think there is a strategy that would not be acceptable to parents?

Willingness to be involved in a trial

Explain what a RCT is. To test the effectiveness of these strategies, we would need to randomly allocate women to have one particular strategy used on them and their baby if they needed glycaemic control for their diabetes in labour and compare this to another strategy. The purpose of a trial in this area is to see if loose control is just as effective for mother and baby, without involving such a burden for testing and monitoring during labour.

8. What are your views of how acceptable it would be to do this research with women during their labour?
9. If asked to, would you be prepared to take part in a trial looking at the most effective strategy to manage glycaemic control for diabetes in labour?

Probes: Yes, please can you explain why? No or not sure, please can you elaborate on why?

10. What factors are most important to you in deciding whether to take part?
    a. What would encourage you to take part in the trial?
    b. What would put you off taking part in the trial?
    c. What could the research team or clinicians do to change this?

11. In terms of being invited to take part in the trial:
    a. When would be the best time to be approached and asked to take part? Probes: Trial design approaches women between 28 and 36 weeks, is this suitable in your opinion?
    b. How would you like to be approached?

Probes: Who? How? (e.g. in person, writing)

c. What would you like to know when being invited to take part?

Probes: Would a video explaining the trial help you to decide whether to take part or would written information be enough?

d. What are your views on the best way to obtain consent from women to take part?

Probes: Timing, who, how?

12. What advice would you give a team of clinicians and researchers about how to carry out this research trial in a way that is most acceptable to women and their babies?
13. What outcomes do you think research should look at when considering how effective the different strategies are?

Probe: What would be the most important outcome for you, and what would be the most important outcome for baby?

14. We are proposing to take a blood sample from the baby which would help us check how effective monitoring the mother during labour has been for the baby. Would this influence your views on the trial?
15. Is there anything else you would like to add?

Sociodemographic Information (optional)

1. What is your date of birth?
2. What is your ethnicity?
3. When was your most recent birth?
4. How many children do you have?
5. Can you confirm your relationship status? (single, married, divorced, etc.).
6. What is your highest level of education? [GCSE, A-Level, Diploma, Graduate (BA, BSc), Post Graduate (MSc, PhD, etc.)].
7. What is your occupation?

Information about additional support if needed

See Resource Sheet Version 1.

Appendix 7 Gestational diabetes trial design infographic (work package 4)

Glycaemic control in labour with gestational diabetes

What is the purpose of the study?

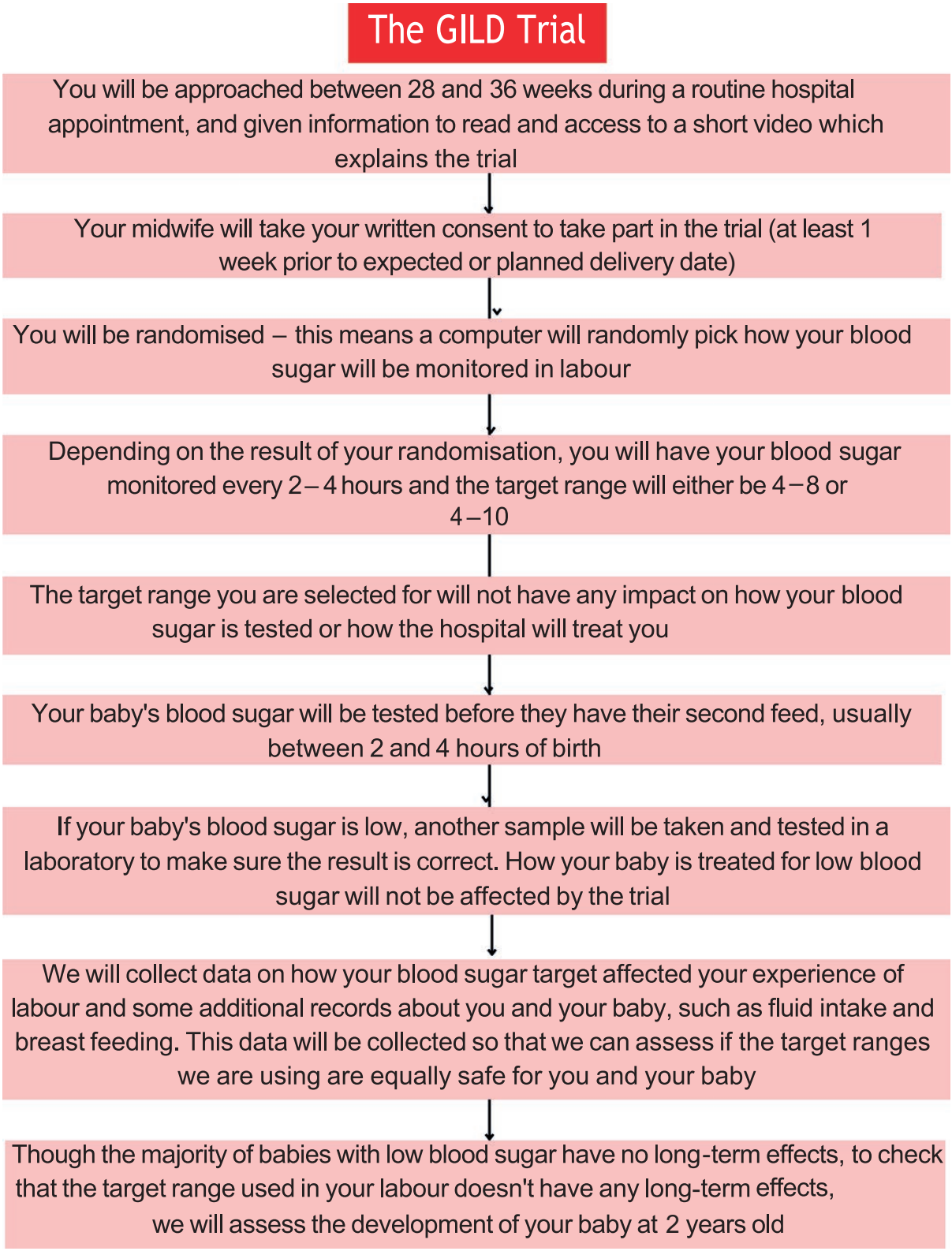
There is evidence that controlling your blood sugars tightly when pregnant could reduce the risk of complications for you and your baby during and after birth. This is because high blood sugars in the mum results in extra sugar passing across the placenta, and the baby makes up for this by producing extra insulin. Insulin stimulates growth in the baby and can result in a big baby. After the baby is born, the extra insulin can cause baby to have low blood sugars.

Some research now suggests that 'tight' control during labour might not be necessary, because there may not be such a close link between mother and baby sugar levels. Maternal care after the birth of the baby routinely advises 'loose' control of blood sugars.

Previous research has shown that different maternity units look after women with similar forms of diabetes differently, in terms of testing sugars during labour. Traditionally 'tight' glucose control (target 4–7 mmol/l) is recommended in labour. Treatment with insulin through a vein (i.e. intravenous) may be needed during labour to maintain 'tight' control; however, this increases the risk of low sugars for the mother during labour, which carries a risk to the mother, if untreated low blood sugars in the mother can result in fits or the mother becoming unconscious. Hourly blood sugar testing during labour can be intrusive for women and time consuming for healthcare practitioners. However, accepting 'less strict' or looser glucose levels in the mother may be harmful to the baby and result in more babies having low blood sugar levels.

We are running a research study looking at whether loose control of blood sugar (4–10 mmol/l) during labour is as safe for the baby as the more traditional tight control. We are inviting women, like you, who have any type of diabetes during their pregnancy.

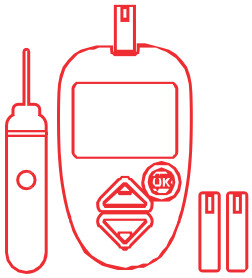
Taking these pros and cons into account, would you be happy to have LOOSE control during your labour if:



The GILD Trial

Here is some information about the advantages and disadvantages of tight and loose control. We'd like you to look through these and consider the question at the bottom of the page

'Tight' control: target 4–8 mmol/L	'Loose' control: target 4–10 mmol/L
Hourly testing of maternal glucose	Less frequency of testing
More likely to need insulin infusion in labour	Less likely to need insulin infusion in labour
Increased risk of maternal hypoglycaemia	No risk of maternal hypoglycaemia (low blood sugar)
May be combined with restriction in oral intake	More flexibility for oral intake
Intrusive and time consuming	Less intrusive for mother
Around 20 in 100 babies have low blood sugar after birth 	**We do not know the exact difference in rate of low blood sugar in the baby – this is why we are doing the study**



Taking these pros and cons into account, would you be happy to have LOOSE control during your labour if:

22 out of 100 babies had low blood sugar

Yes or No?

25 out of 100 babies had low blood sugar

Yes or No?

30 out of 100 babies had low blood sugar

Yes or No?

Appendix 8 Type 1 diabetes mellitus/type 2 diabetes mellitus trial design infographic (work package 4)

Glycaemic control in labour with pre-existing diabetes

What is the purpose of the study?

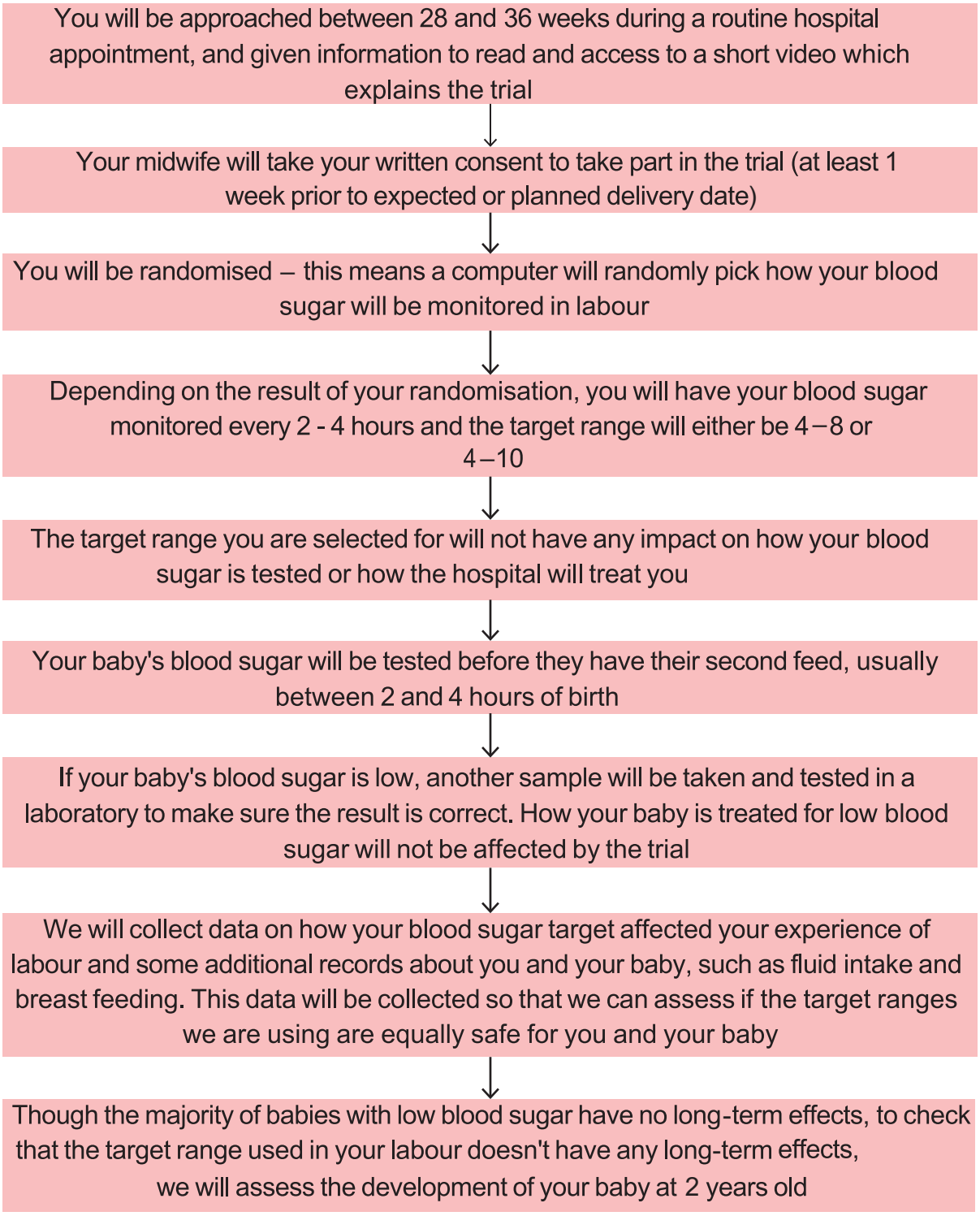
There is evidence that controlling your blood sugars tightly when pregnant could reduce the risk of complications for you and your baby during and after birth. This is because high blood sugars in the mum results in extra sugar passing across the placenta, and the baby makes up for this by producing extra insulin. Insulin stimulates growth in the baby and can result in a big baby. After the baby is born, the extra insulin can cause baby to have low blood sugars.

Some research now suggests that 'tight' control during labour might not be necessary, because there may not be such a close link between mother and baby sugar levels. Maternal care after the birth of the baby routinely advises 'loose' control of blood sugars.

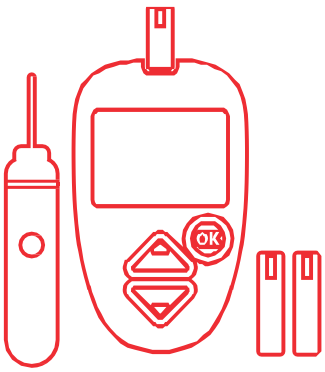
Previous research has shown that different maternity units look after women with similar forms of diabetes differently, in terms of testing sugars during labour. Traditionally 'tight' glucose control (target 4–7 mmol/l) is recommended in labour. Treatment with insulin through a vein (i.e. intravenous) may be needed during labour to maintain 'tight' control; however, this increases the risk of low sugars for the mother during labour, which carries a risk to the mother, if untreated low blood sugars in the mother can result in fits or the mother becoming unconscious. Hourly blood sugar testing during labour can be intrusive for women and time consuming for healthcare practitioners. However, accepting 'less strict' or looser glucose levels in the mother may be harmful to the baby and result in more babies having low blood sugar levels.

We are running a research study looking at whether loose control of blood sugar (4–10 mmol/l) during labour is as safe for the baby as the more traditional tight control. We are inviting women, like you, who have any type of diabetes during their pregnancy.

Taking these pros and cons into account, would you be happy to have LOOSE control during your labour if: 55 out of 100 babies had low blood sugar.


You will be approached between 28 and 36 weeks during a routine hospital appointment, and given information to read and access to a short video which explains the trial
Your midwife will take your written consent to take part in the trial (at least 1 week prior to expected or planned delivery date)
You will be randomised – this means a computer will randomly pick how your blood sugar will be monitored in labour
Depending on the result of your randomisation, you will have your blood sugar monitored every 2 - 4 hours and the target range will either be 4–8 or 4–10
The target range you are selected for will not have any impact on how your blood sugar is tested or how the hospital will treat you
Your baby's blood sugar will be tested before they have their second feed, usually between 2 and 4 hours of birth
If your baby's blood sugar is low, another sample will be taken and tested in a laboratory to make sure the result is correct. How your baby is treated for low blood sugar will not be affected by the trial
We will collect data on how your blood sugar target affected your experience of labour and some additional records about you and your baby, such as fluid intake and breast feeding. This data will be collected so that we can assess if the target ranges we are using are equally safe for you and your baby
Though the majority of babies with low blood sugar have no long-term effects, to check that the target range used in your labour doesn't have any long-term effects, we will assess the development of your baby at 2 years old

Here is some information about the advantages and disadvantages of tight and loose control. We'd like you to look through these and consider the question at the bottom of the page

'Tight' control: target 4–8 mmol/L		'Loose' control: target 4–10 mmol/L
Increased risk of maternal hypoglycaemia		Less risk of maternal hypoglycaemia (low blood sugar)
May be combined with restriction in oral intake		More flexibility for oral intake
Lower maternal satisfaction		Maternal satisfaction enhanced
Antenatal control may be more important for risk of low blood sugar in baby after birth than control in labour		Testing and treatment technology not stipulated
Around 50% of babies have low blood sugar after birth 		**We do not know the exact difference in rate of low blood sugar in the baby – this is why we are doing the study** ?

Taking these pros and cons into account, would you be happy to have LOOSE control during your labour if:

55 out of 100 babies had low blood sugar

Yes or No?

60 out of 100 babies had low blood sugar

Yes or No?

65 out of 100 babies had low blood sugar

Yes or No?

Appendix 9 Healthcare professional trial design infographic (work package 4)

Glycaemic control in labour with diabetes

What is the purpose of the study?

There is evidence that 'tight' glucose control in the antenatal period of pregnancy reduces the risk of adverse outcomes (e.g. big baby) for the mother and the baby. This is because maternal hyperglycaemia results in excess transfer of glucose across the placenta, and the baby increases insulin production to compensate. Insulin stimulates growth in the baby.

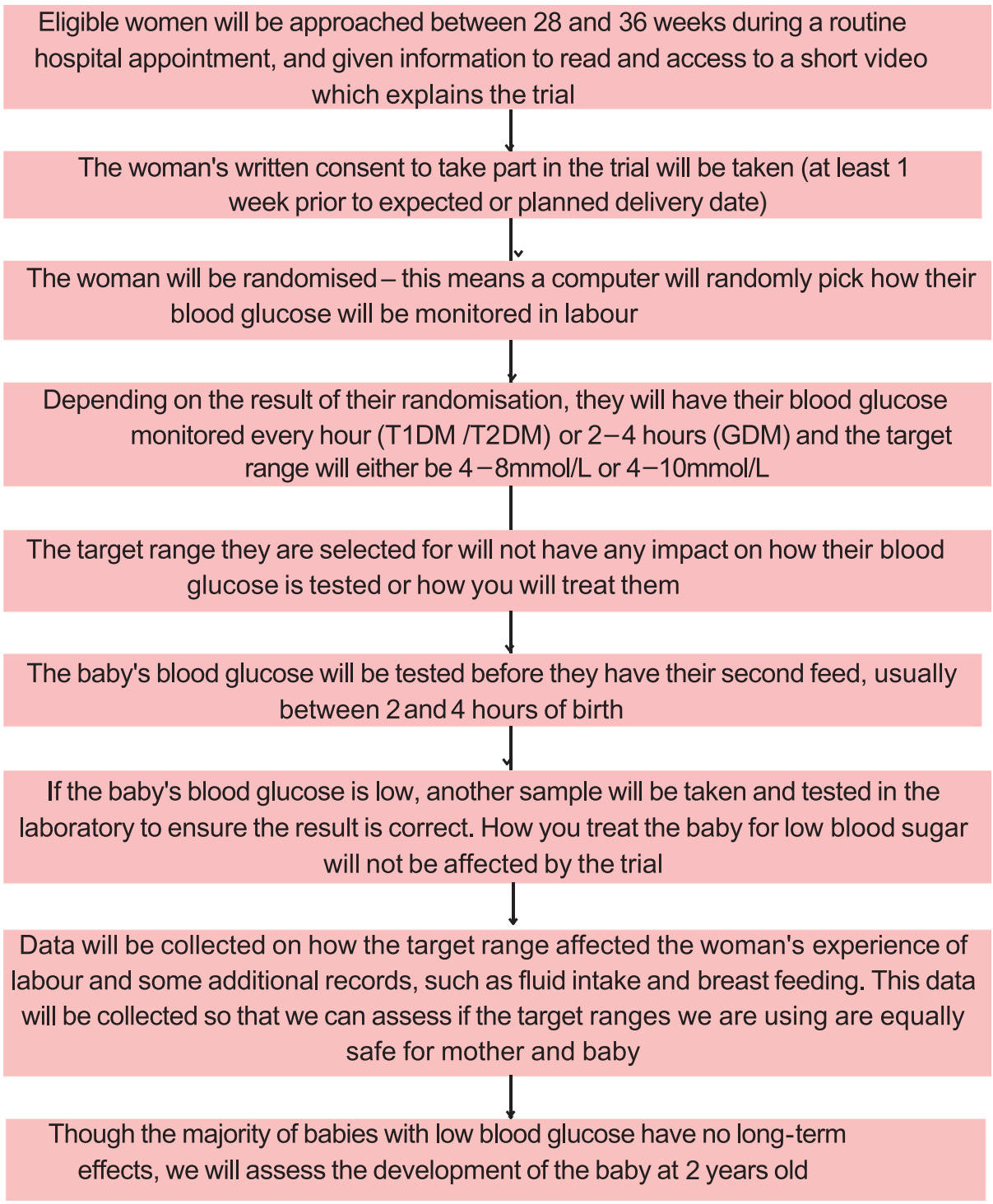
There is a body of evidence that now suggests that 'tight' control may not be as closely linked as previously thought to the risk of low blood glucose in the baby after birth and may be unnecessary for the duration of labour. Maternal care after the birth of the baby routinely advises more permissive or 'loose' control.

Our previous studies have shown that different maternity units manage women with similar forms of diabetes diversely in labour in terms of glucose testing. Traditionally 'tight' glucose control (target 4–7 mmol/l) is recommended in labour. Treatment with intravenous insulin may be needed during labour to maintain 'tight' control; however, this increases the risk of maternal hypoglycaemia in labour, which carries a risk to the mother. Hourly intrapartum testing is also intrusive for women and time consuming for healthcare practitioners. Conversely, accepting more permissive glucose levels in the mother may be detrimental to the baby.

We are running a randomised trial looking at whether loose control of glucose (4–10 mmol/l) in active labour is as safe for the baby as the more traditional tight control. In women with GDM, we will also randomise women to less frequent testing if on diet or oral medication antenatally. The main outcome of this study is to test our hypothesis that there will be no difference in the rates of low blood glucose in the baby in the two arms of the study.

What will the trial mean for my caring for women in labour?

This is a pragmatic trial with the hypothesis that more permissive glycaemic control in labour will not lead to increased risk of neonatal hypoglycaemia in the baby than tight control. Those randomised to permissive arm of trial will have target glucose level of 4–10 mmol/l.



The National Institute for Health and Clinical Excellence recommends that all women with diabetes have their capillary glucose tested every hour in labour with a target glucose of 4–7 mmol/l; the newer JBDS guideline recommends a target of 5–8 mmol/l. Those randomised to tight control will follow the usual care pathway for their hospital, which is usually in line with NICE or JBDS. Some hospitals currently do not follow national guidelines and do not test women with GDM on diet as often as is recommended nationally. Therefore, some women with GDM in the tight control group will have increased frequency of testing to outside the trial, whereas in other units this will be reduced. Only around 10–20% of women with GDM in labour will require insulin infusion in labour.

If glucose levels are higher or lower than the targeted range, then usual hospital pathways should be followed to facilitate return of glucose to target. In those women with GDM who require an insulin infusion to be commenced in labour, the frequency of testing may need to be altered to be in line with their unit policy for insulin infusion, which will usually be hourly. These women will stay within the trial and will need to have their randomised target range maintained.

The trial does not dictate how to test glucose in labour: sensors or finger-prick testing will be permitted. The trial does not dictate how insulin is given in T1DM – VRIII or continuous pump insulin are both permitted within the trial protocol – hospital pathways should be followed.

If a baby has a low blood glucose level on testing with a glucometer, a capillary sample should be undertaken and sent to the laboratory to confirm the value. Treatment can start before the laboratory glucose result is available.

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