The clinical and cost effectiveness of tight versus more relaxed glucose control around the time of birth in pregnancies complicated by gestational diabetes (GILD)

Final Version 1.1
12 June 2025

Short title: trial	Glucose control In Labour with Diabetes (GILD)
Acronym:	GILD
ISRCTN:	*if appropriate*
IRAS Project ID:	333765
Trial Sponsor:	University of Nottingham
Sponsor reference:	**25024**
Funding Source:	NIHR HTA funding 159223

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UPDATES TO THE PROTOCOL

Amendment number	Protocol version number	Type of amendment	Summary of amendment

SYNOPSIS

Title	The clinical and cost effectiveness of tight versus less tight glucose control around the time of birth in pregnancies complicated by gestational diabetes (GILD)
Acronym	GILD
Short title	Glucose control In Labour with Diabetes (GILD) trial
Chief Investigators	Chief Investigator (Clinical Lead): Professor Kate Walker Deputy Chief Investigator (Methodology Lead): Dr Eleanor Mitchell
Objectives	1. To establish whether 'more relaxed' blood glucose control is non inferior to tight control around the time of birth for women/birthing people with Gestational Diabetes Mellitus (GDM) for risk of neonatal hypoglycaemia and neonatal unit admission. 2. To investigate the benefits and harms of 'more relaxed' control compared to tight control in relation to maternal experience, other maternal outcomes (inc., admission to critical care, feeding and fluid intake during labour) and other neonatal outcomes (inc., neonatal death and breastfeeding) 3. To undertake an economic evaluation of 'more relaxed' control versus tight control 4. To conduct an internal pilot phase to evaluate key trial processes to inform progression from pilot to main trial 5. To assess the acceptability of a 'more relaxed' or tight blood glucose monitoring strategy, from the perspectives of women/birthing people and health professionals, by conducting a qualitative sub-study 6. To conduct a Study Within a Trial (SWAT) to evaluate the effectiveness of an 'inclusivity package', aimed at increasing participation of South Asian women/birthing people
Trial Configuration	Multi-centre, open-label, randomised, controlled, two-arm parallel group non-inferiority trial, with an internal pilot phase, and alongside economic and qualitative evaluation.
Setting	23 UK secondary care, consultant-led maternity units.
Sample size estimate	The sample size is based on the neonatal unit admission outcome with non-inferiority only concluded if non-inferiority is demonstrated on both primary outcomes. Assuming 10% of babies in both groups are admitted to the neonatal unit, an absolute non-inferiority margin of 5%, 90% power and 1-sided significance level of 0.025, a total sample size for analysis of 1594 is needed (using a continuity corrected Z test). Reported rates of neonatal hypoglycaemia in babies of women/birthing people with GDM are varied according to the definition used. Assuming that 7% of

	babies in both groups have neonatal hypoglycaemia (based on the GILD scoping study), a sample size of 1594 provides 97% power for an absolute non-inferiority margin of 5%. This means the overall power for the trial to conclude non-inferiority will be in excess of 87% (90x97). From our previous intrapartum clinical trials with pre-hospital discharge outcomes, we anticipate loss to follow-up will be minimal (2%), giving a target sample size for recruitment of 1630.
Number of participants	1630
Eligibility criteria	**Inclusion criteria:** 1) Women/birthing people with gestational diabetes mellitus 2) Aged 16 years or over (or <16 years if deemed Gillick competent) 3) Singleton pregnancy 4) Able to give informed consent 5) Planned birth ≥37 weeks gestation **Exclusion criteria:** 1) Known lethal fetal anomaly 2) At time of consent, known clinical indication to recommend birth <37 weeks
Description of interventions	Intervention: 'More relaxed' blood glucose control around the time of birth, i.e. blood glucose monitoring every 2-4 hours, target blood glucose level 4-10 mmol/L Comparator: 'Tight' blood glucose control around the time of birth, i.e. blood glucose monitoring every hour, target blood glucose level 4-7 mmol/L Maternal blood glucose monitoring (as per randomised allocation) will be from the point of admission in spontaneous labour, following artificial rupture of membranes or onset of regular contractions following induction of labour or admission for elective caesarean section, until birth with glucose testing by finger-prick testing.
Duration of study	Total duration: 40 months Individual women/birthing people: up to 10 weeks for the main trial, or up to 16 weeks for the main trial plus the qualitative study
Randomisation and blinding	Eligible women/birthing people will be individually randomised to more relaxed or tight control on a 1:1 ratio. Dynamic randomisation will use a probabilistic minimisation algorithm to balance across groups by recruitment site, antenatal treatment for GDM , treatment with beta-blockers during the third trimester and fetal growth restriction. These factors have been selected as they are risk factors for neonatal hypoglycaemia in the British Association of Perinatal Medicine (BAPM) guideline (1) The probabilistic element to allocation will make accurate prediction of the next allocation virtually impossible, minimising selection bias. Blinding of women/birthing people and health professionals is not possible, due to the nature of the intervention.

Outcome measures	Safety outcomes are indicated with a * **Co-primary outcomes:** • **Neonatal hypoglycaemia***, as defined by a blood glucose level of <2 mmol/l at any time and/or a single value of <2.5 mmol/l in a baby with abnormal clinical signs. • **Neonatal unit admission*** (any level; 1-3) **Secondary outcomes** *Clinical effectiveness and safety parameters* ***Neonatal*** • Outcome of birth (live/stillbirth)* • Symptomatic neonatal hypoglycaemia, measured on a 'symptoms' checklist* • Treatment for neonatal hypoglycaemia (e.g. buccal glucose, peripheral or central line IV dextrose)* • Duration of Neonatal unit admission* • Neonatal hypothermia (any episode <36.5°C)* • Hypoxic ischaemic encephalopathy (HIE) requiring active therapeutic hypothermia* • Neonatal death (death ≤ 28 days)*. • Breastfeeding (any maternal breast milk prior to maternal hospital discharge, breastfeeding initiation defined as initiated breastfeeding within 1 hour of birth, breastfeeding at maternal hospital discharge, breastfeeding at 6 weeks) ***Maternal*** • Maternal hypoglycaemia*. • Maternal admission to critical care, around the time of birth* • Postnatal depression. Measured by the Edinburgh Postnatal Questionnaires (validated questionnaire completed by the woman/birthing person) 6 weeks after birth ***Treatment acceptability and adherence*** • Maternal satisfaction with childbirth experience. Measured by Birth Satisfaction Scale Revised (BSS, validated questionnaire completed by the woman/birthing person) and selected questions from the Childbirth Experience Questionnaire Version 2 (where not covered by the BSS). 6 weeks postnatal; • Maternal satisfaction with blood glucose monitoring strategy. Measured by a study-specific questionnaire. • Woman/birthing person able to eat/drink what they want (food/volume) around the time of birth.

	Cost-effectiveness • Maternal health-related quality of life collected using EQ-5D-5L at baseline/maternal hospital discharge/6 weeks. ***Resource use.*** The main resources to be monitored include: • The costs associated with glucose monitoring in labour for both more relaxed control and tight control groups • Time and resource use incurred in NHS secondary care due to maternal or neonatal hypoglycaemia, admission of mothers or babies to neonatal care (any level, 1-3) or to treat any other adverse events • Duration of hospital stay for the woman/birthing person • Duration of hospital stay for the baby • Maternal or neonatal re-admissions to secondary care or attendances at primary care or unscheduled postnatal outpatient contacts due to complications attributable to GDM ***Process outcomes for the woman/birthing person:*** Adherence with the allocated strategy including: • Frequency of blood glucose monitoring • Number of blood glucose tests conducted • Use of intravenous insulin Obtained from continuous glucose monitor • Percentage of time blood glucose is in target according to randomised allocation from point of commencement of capillary blood monitoring (see 4.2 BLOOD GLUCOSE MONITORING) to birth • Percentage of time blood glucose is 7-10mmol/l • Percentage of time blood glucose is >10mmol/l • Percentage of time blood glucose is < 4mmol/l ***Process outcomes for the baby*** (all are usual care for neonatal hypoglycaemia, as per BAPM guidelines) • Mother and baby received support for early feeding within the first hour of birth including o Dry and place the baby skin-to-skin care in draught free room o Encourage and support early breastfeeding within the first hour after birth o For women/birthing people who choose to formula feed, feed within first hour of birth and give a volume appropriate for 40-60 ml/kg/day • Verbal and written information was given to parents to explain how to prevent hypoglycaemia, need for baby's

	glucose monitoring, listing signs that may indicate hypoglycaemia, and advice to inform a member of the healthcare team if they are concerned about the baby's well being • Baby's pre-feed glucose was measured before second feed (within 2-4 hours after birth) • Baby's pre-feed glucose monitoring was continued until two consecutive values ≥2mmol/L on regular feeding was obtained
Statistical methods	There will be two analyses of the co-primary outcomes to allow assessment of the robustness of the results – an intention to treat (ITT – according to randomised allocation regardless of adherence with allocated blood glucose monitoring strategy) and a per protocol (PP) analysis. Analysis of the co-primary outcomes will be performed using a mixed effects model for binary outcomes adjusting for site as a random effect and other minimisation variables as fixed effects to estimate a risk difference for each outcome. Secondary outcomes will be considered as supportive of the co-primary outcomes. Between-group comparisons will use appropriate regression models (depending on the outcome data type), using a generalised linear mixed model framework, adjusting for the minimisation variables as described for the primary outcomes.
Health Economics	The economic evaluation will consist of a cost-consequence analysis (primary analysis) and a cost-utility analysis (secondary analysis) of more relaxed and tight glucose control under intention-to-treat principle. The time horizon for both analyses is from the hospital admission to give birth up to 6 weeks post birth. We do not expect the impact of the intervention on costs and health utilities to extend beyond the 6 week follow-up of the trial. An NHS perspective will be adopted, and the outcomes will not be discounted (as follow-up <1 year). Cost-consequence analysis will present resource use, costs and selected outcomes (e.g. co-primary trial outcome, maternal health-related quality of life) in a disaggregated manner. Maternal health-related quality of life collected using EQ-5D-5L at baseline/hospital discharge/6 weeks and valued following NICE guidance (27). The cost-utility analysis will be conducted from a maternal perspective and estimate the incremental cost per quality-adjusted life year (QALY) of more relaxed relative to tight glucose control. Maternal EQ-5D data will inform the calculation of QALYs.

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ABBREVIATIONS

AE	Adverse Event
BAPM	British Association of Perinatal Medicine
BSS	Birth satisfaction Scale
CONSORT	Consolidated Standards of Reporting Trials
CGM	Continuous Glucose Monitor
CI	Chief Investigator
(e)CRF	(electronic) Case Report Form
DMC	Data Monitoring Committee
DoR	Delegation of Responsibilities
GCP	Good Clinical Practice
GDM	Gestational Diabetes Mellitus
HCP	Health Care Professional
HEAP	Health Economic Analysis Plan
HIE	Hypoxic Ischaemic Encephalopathy
ICF	Informed Consent Form
ITT	Intention To Treat
JBDS	Joint British Diabetes Societies
NCT	National Childbirth Trust
NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
NIHR	National Institute for Health and Care Research
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PP	Per Protocol
PPI	Patient and public involvement
QAYL	Quality-Adjusted Life Year
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAHA	South Asian Health Action
SWAT	Study Within A Trial
TSC	Trial Steering Committee
TMG	Trial Management Group
UKCRC	UK Clinical Research Collaboration

1. TRIAL BACKGROUND INFORMATION AND RATIONALE

Gestational diabetes (GDM) affects 8% (~50,000) of UK pregnant women/birthing people and is increasing (4). South Asian women/birthing people have a two-fold increased risk, compared to White European women/birthing people (5). If the mother/birthing person is hyperglycaemic, placental transfer of glucose leads to fetal hyperglycaemia which stimulates fetal hyperinsulinism. At birth, the placental supply of glucose is cut-off and persistent high insulin levels can cause neonatal hypoglycaemia. Neonatal hypoglycaemia occurs in 7-20% of babies born to women/birthing people with GDM (6, 7). In addition, around 10% of babies born to women/birthing people with GDM are admitted to the neonatal unit, causing anxiety, mother-baby separation and disruption to breastfeeding (8). Neonatal hypoglycaemia (the most important complication of intrapartum hyperglycaemia) 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 million to the NHS (9). Severe or prolonged hypoglycaemia can cause seizures and brain damage and though rare, litigation from such cases incurs a financial cost to the NHS (25 claims, total cost £162 million 2002-11).

Intensive or 'tight' maternal glucose control during pregnancy could reduce adverse outcomes in mother and baby (10). However, evidence about whether intrapartum tight glucose control is beneficial is lacking (6) with some advocating for more relaxed control during labour despite the absence of RCT evidence (7). Tight control, and therefore greater use of insulin to reduce blood glucose levels can lead to maternal hypoglycaemia in women/birthing people with pre-existing diabetes, though there is little data on the effect in GDM women/birthing people (estimates 2-28%) (10). The need for insulin to achieve tight control means that women/birthing people require an IV line, restricting their movement in labour. Women/birthing people have told us tight control negatively impacted on their birth experience. Currently 10% of women/birthing people with GDM require insulin during labour. More relaxed control could reduce maternal hypoglycaemia, empower diabetes self-management, improve birth experience and reduce midwifery workload: put simply reduce 'over treatment'.

The James Lind Alliance Diabetes in Pregnancy Priority Setting Partnership (JLA PSP) (involving 287 women/birthing people with lived experience, 11 support networks and 149 healthcare professionals) lists 'What are the labour and birth experiences of women/birthing people with diabetes, and how can their choices and shared decision making be enhanced?' in their top 10 priorities (11). This trial directly answers this research question. The trial also addresses the question 'In women/birthing people with diabetes, what is the best way to manage their blood sugar levels during labour and delivery?', ranked as 15/18.

During our patient and public involvement (PPI) work conducted as part of the GILD scoping study (Award ID: NIHR130175) women/birthing people have reinforced the importance of the study, telling us that they would prefer a more relaxed approach to glucose monitoring, to enhance their birth experience, but that they would like reassurance that this does not harm their baby.

Although the available observational studies suggest more relaxed (and thus, less frequent monitoring and less insulin) intrapartum glycaemic control could be safe, there is an urgent need for an adequately powered well designed randomised trial to ensure that there is no harm to the baby from more relaxed control and the effect of more relaxed control on maternal satisfaction/experience.

Traditionally tight intrapartum glucose control (target 4-7 mmol/L) (7, 10) has been recommended. 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/birthing people 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). 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 (12). Hourly intrapartum testing is also intrusive for women/birthing people and time consuming for health care professionals (HCPs).

The safety for the woman/birthing person of intensive control at the time of birth has recently been questioned, with some researchers advocating more relaxed targets e.g., 8 mmol/L (13) citing evidence in other disciplines in medicine that intensive control is associated with increased morbidity and mortality. The Joint British Diabetes Societies (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/birthing people in labour and reduce the risk of maternal hypoglycaemia (7).

The target ranges for the intervention group have been determined by extensive discussions held during the GILD scoping study (NIHR funding award 130175) and subsequent discussions during trial development. There was a broad consensus amongst experts from those discussions that a target range of 4-10 mmol/l and testing every 2-4 hours was felt to be safe in this group of women/birthing people.
The target population is pregnant women/birthing people with a singleton, term pregnancy and GDM. We have chosen not to include women/birthing people with multiple or preterm births as both are independent risk factors for neonatal hypoglycaemia and therefore management in this group of women/birthing people may preclude more relaxed control in labour and women/birthing people with a multiple pregnancy are offered timed birth prior to 38 weeks.
Whilst neonatal hypoglycaemia is common ($\geq$1 readings in the hypoglycaemia range recorded in 12% of infants of mothers with GDM (14)), there is no universally agreed definition. A 2015 survey of all 161 neonatal units in England (15) found the majority (88%) used a value of <2.6 mmol/L, but values ranged from 2.0-3.0 mmol/L. 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 2024 (1) which defines the operational threshold of neonatal hypoglycaemia using the cut off of a blood glucose level of <2.0 mmol/L in well babies. This is supported by the evidence from the recent HypoEXIT study which compared

two threshold values (<2.0 mmol/L vs. 2.6 mmol/L) in otherwise healthy babies born at >35 weeks' gestational age. They found that, at 18 months, the lower threshold was non-inferior to the higher with regards to the babies psychomotor development (16).

GILD will provide the NHS with evidence to potentially change policy. If more relaxed glucose control is non inferior to tight control AND is acceptable to both midwives and pregnant women/birthing people, it is highly likely to be introduced across the NHS. Its introduction would be anticipated to reduce the workload for midwives and improve the birth experience for women/birthing people with GDM. Training on more relaxed control for maternity staff will be required but no further funding would be needed to achieve this.

2. TRIAL OBJECTIVES AND PURPOSE

Purpose
To investigate whether in pregnant women/birthing people with gestational diabetes (Population) around the time of birth, is more relaxed blood glucose control (Intervention) non-inferior to tight control (Comparison) in relation to the incidence of neonatal hypoglycaemia and neonatal unit admission (Outcome).

Primary Objective
To establish whether more relaxed blood glucose control is non inferior to tight control around the time of birth for women/birthing people with GDM for risk of neonatal hypoglycaemia and neonatal unit admission.

Secondary Objectives
1. To investigate the benefits and harms of more relaxed control compared to tight control in relation to maternal experience, other maternal outcomes (inc., admission to critical care, feeding and fluid intake during labour) and other neonatal outcomes (inc., neonatal death and breastfeeding)
2. To undertake an economic evaluation of more relaxed control versus tight control
3. To conduct an internal pilot phase to evaluate key trial processes to inform progression from pilot to main trial
4. To assess the acceptability of a more relaxed or tight blood glucose monitoring strategy, from the perspectives of women/birthing people and health professionals, by conducting a qualitative sub-study
5. To conduct a Study Within a Trial (SWAT) to evaluate the effectiveness of an 'inclusivity package', aimed at increasing participation of South Asian women/birthing people

3. TRIAL DESIGN

3.1 TRIAL CONFIGURATION

Multi-centre, open-label, randomised, controlled, two-arm parallel group non-inferiority trial, with an internal pilot phase, and alongside economic and qualitative evaluation.

Participants	Pregnant women/birthing people with a singleton fetus, at term (≥ 37 weeks) who have GDM
Intervention	'More relaxed' blood glucose control around the time of birth, i.e. blood glucose monitoring every 2-4 hours, target blood glucose level 4-10 mmol/L
Comparator	'Tight' blood glucose control around the time of birth, i.e. blood glucose monitoring every hour, target blood glucose level 4-7 mmol/L
Outcome	Co-primary outcomes: • Neonatal hypoglycaemia, defined as a blood glucose level of <2 mmol/L at any time and / or a single value of <2.5 mmol/L in a baby with abnormal clinical signs • Neonatal unit admission (any level; 1-3).

3.1.1. Co-Primary outcomes

(safety outcomes are indicated by an asterisk*)

Objective	Outcome measure	Time point	Method of collection
To establish whether more relaxed blood glucose control is non inferior to tight control around the time of birth for women/birthing people with GDM for risk of neonatal hypoglycaemia.	Neonatal hypoglycaemia* - defined by a blood glucose level of <2 mmol/l at any time and/or a single value of <2.5 mmol/l in a baby with abnormal clinical signs Neonatal blood glucose levels will be tested using the blood gas analyser or a capillary blood glucose meter suitable for the neonatal population and shown to be precise and accurate at low glucose levels that are routinely available in neonatal units and labour suites and aligned with the current guidance (inc. operational thresholds) from the British Association of Perinatal Medicine (BAPM). These are more accurate than other point of care testing such as via other hand-held cot-side devices used for maternal blood glucose levels and provides real-time glucose levels. Management of neonatal hypoglycaemia will follow usual care (irrespective of randomised allocation), as per BAPM recommendations and will be recorded and reported as process outcomes.	At any point between birth and discharge from hospital	Extracted from paper or electronic patient records and entered into the trial database.
To establish whether more relaxed blood glucose control is non inferior to tight control around the time of birth for women/birthing people with GDM for risk of neonatal unit admission.	Neonatal unit admission (any level; 1-3)*	At any point between birth and discharge from hospital	Extracted from paper or electronic patient records and entered into the trial database

3.1.2. Secondary outcomes

(safety outcomes are indicated by an asterisk*)

Objective	Outcome measure	Time point	Method of collection
To investigate the benefits and harms of more relaxed control compared to tight control in relation to maternal outcomes	Maternal hypoglycaemia* defined as blood glucose <3.5 mmol/L. Measured by capillary blood glucose values from the commencement of capillary blood monitoring until birth (see 4.2 BLOOD GLUCOSE MONITORING).	At any point during admission for birth	Extracted from paper or electronic patient records and entered into the trial database
	Maternal admission to critical care, around the time of birth*	At any point between admission for birth and discharge from hospital	Extracted from paper or electronic patient records and entered into the trial database
	Postnatal depression. Measured by the Edinburgh Postnatal Questionnaires (validated questionnaire completed by the woman/birthing person). A score of ≥13 indicates postnatal depression. (17)]	6 weeks postnatal	Questionnaire completed by the woman/birthing person
To investigate the benefits and harms of more relaxed control compared to tight control in relation to maternal experience.	Maternal satisfaction with childbirth experience. Measured by the Birth Satisfaction Scale (BSS) Revised (validated questionnaire (18) completed by the woman/birthing person) and selected questions from the Childbirth Experience Questionnaire Version 2 (where not covered by the BSS).	6-week postnatal	Questionnaire completed by the woman/birthing person
	Maternal satisfaction with blood glucose monitoring strategy. Measured by a study-specific questionnaire about satisfaction with blood glucose monitoring strategies.	At maternal hospital discharge	Questionnaire completed by the woman/birthing person
To investigate the benefits and harms of more relaxed control compared to tight control in relation to feeding and fluid intake during labour.	Woman/birthing person able to eat/drink what they want (food/volume) around the time of birth.	At maternal hospital discharge	Captured by the woman/birthing person/ birth partner/midwife on a case report form (CRF)

To investigate the benefits and harms of more relaxed control compared to tight control in relation to other neonatal outcomes.	Outcome of birth (live/stillbirth)*	Day of birth	Extracted from paper or electronic patient records and entered into the trial database
	Symptomatic neonatal hypoglycaemia*, measured on a 'symptoms' checklist	At any point between birth and discharge from hospital	Symptoms checklist completed by healthcare professionals
	Treatment for neonatal hypoglycaemia* (e.g. buccal glucose, peripheral or central line IV dextrose)	At any point between birth and discharge from hospital	Extracted from paper or electronic patient records and entered into the trial database
	Neonatal hypothermia* (any episode <36.5°C)	At any point between birth and discharge from hospital	Extracted from paper or electronic patient records and entered into the trial database
	Duration of Neonatal Unit admission*	On discharge from hospital	Extracted from paper or electronic patient records and entered into the trial database
	Breastfeeding (any maternal breast milk prior to maternal hospital discharge, breastfeeding initiation defined as initiated breastfeeding within 1 hour of birth, breastfeeding at maternal hospital discharge, breastfeeding at 6 weeks)	At maternal hospital discharge and 6 weeks postnatal	Captured in the eCRF and on a study-specific questionnaire
	Hypoxic ischaemic encephalopathy (HIE) requiring active therapeutic hypothermia*	At any point between birth and discharge from hospital	Extracted from paper or electronic patient records and entered into the trial database

	Neonatal death* (death ≤ 28 days)	If the baby dies post-discharge, this will be captured at the time of the 5-week 'wellbeing check'	Extracted from paper or electronic patient records and entered into the trial database
To undertake an economic evaluation of more relaxed control versus tight control	Maternal health-related quality of life measured by EQ-5D-5L	At baseline prior to randomisation, maternal hospital discharge and 6 weeks	Questionnaire completed by the woman/birthing person
	Resource use. The main resources to be monitored include: 1. The costs associated with glucose monitoring in labour for both more relaxed control and tight control groups 2. Time and resource use incurred in NHS secondary care due to maternal or neonatal hypoglycaemia, admission of mothers or babies to high dependency/ICU and neonatal intensive care unit (NICU) or to treat any other adverse events 3. Duration of hospital stay 4. Maternal or neonatal re-admissions to secondary care or attendances at primary care or unscheduled postnatal outpatient contacts due to complications attributable to GDM	On discharge from hospital and at 6 weeks postnatal	Extracted from paper or electronic patient records and entered into the trial database, and questionnaire completed by the woman/birthing person
To conduct an internal pilot phase to evaluate key trial processes to inform progression from pilot to main trial	Progression criteria (see 3.2 STOPPING RULES AND DISCONTINUATION)	9 months after the first woman/birthing person is randomised	

To assess the acceptability of a more relaxed or tight blood glucose monitoring strategy, from the perspectives of women/birthing people and health professionals, by conducting a qualitative sub-study	Acceptability of a more relaxed or tight blood glucose monitoring strategy from the perspective of women/ birthing people	Within 6-12 weeks of birth	1:1 semi-structured interview (conducted remotely via telephone or video call)
Inclusivity package evaluation	The number of South Asian women/birthing people i) approached for participation in the trial, ii) who give consent to participate, (iii) who are randomised. All outcomes are proportionate to the number of South Asian women/birthing people at each site (ONS/site level data).		Extracted from trial management database

Secondary outcomes were determined by our scoping study. We will also collect and report the following outcomes from the core outcome set for evaluating interventions for GDM that did not reach consensus in our scoping study to facilitate comparison with other studies (3):

- Maternal: Mode of birth; hypertensive disorders of pregnancy; type of pharmacological therapy for hyperglycaemia; *(note `outcomes' prior to the time of birth will be reported as baseline data)*
- Neonatal: Birthweight, large for gestational age, small for gestational age, gestational age at birth

Process outcomes for the woman/birthing person:
Adherence with the allocated strategy including:

- Frequency of blood glucose monitoring
- Number of blood glucose tests conducted
- Use of intravenous insulin

Obtained from continuous glucose monitor

- Percentage of time blood glucose is in target according to randomised allocation from point of commencement of capillary blood monitoring (see 4.2 BLOOD GLUCOSE MONITORING) to birth
- Percentage of time blood glucose is 7-10mmol/l
- Percentage of time blood glucose is >10mmol/l
- Percentage of time blood glucose is < 4mmol/l

Process outcomes for the baby:
(all are usual care for neonatal hypoglycaemia, as per BAPM guidelines)

- Mother and baby received support for early feeding within the first hour of birth including
  - Dry and place the baby skin-to-skin care in draught free room
  - Encourage and support early breastfeeding within the first hour after birth
  - For women/birthing people who choose to formula feed, feed within first hour of birth and give a volume appropriate for 40-60 ml/kg/day
- Verbal and written information was given to parents to explain how to prevent hypoglycaemia, need for baby's glucose monitoring, listing signs that may indicate hypoglycaemia, and advice to inform a member of the healthcare team if they are concerned about the baby's well being
- Baby's pre-feed glucose was measured before second feed (within 2-4 hours after birth)
- Baby's pre-feed glucose monitoring was continued until two consecutive values ≥2mmol/L on regular feeding was obtained

3.1.3. Safety endpoints

Safety endpoints are included in the primary and secondary outcomes. Please refer to 3.1.1. Co-Primary outcomes and 3.1.2. Secondary outcomes.

3.2 STOPPING RULES AND DISCONTINUATION

There are no planned formal interim analyses. The Sponsor reserves the right to discontinue the trial (in part or whole) at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the independent Trial Steering Committee (TSC), independent Data Monitoring Committee (DMC) and the funder (National Institute for Health and Care Research Health Technology Assessment - NIHR HTA) before making this decision.

Discontinuation criteria for individual women/birthing people will follow the PeRSEVERE principles (19) and will include withdrawal of informed consent. See 3.9 CHANGES TO LEVEL OF PARTICIPATION/WITHDRAWAL for more information.

Internal pilot phase

An internal pilot phase is included to allow a feasibility assessment which will examine recruitment, retention, and adherence. These progression criteria, outlined below, will be continuously monitored by the Trial Management Group (TMG) and a formal review will take place 9 months after the first woman/birthing person is randomised, and reported to the funder.

Progression criteria	**Red**	**Amber**	**Green**
Recruitment rate per site per month	<2.25	2.25 to <3.75	≥3.75
Number of sites opened	<14	15 to 22	23
Total number of women/birthing people recruited	<293 (<60%)	293 to <488 (60 to <100%)	≥488 (100%)
% of primary outcome data available	<90	90 to <98	≥98
Adherence to randomised allocation, defined as:			
For women/birthing people allocated to tight control:			
% having capillary blood glucose measured hourly (+/- 15 minutes) at least 80% of the time for blood glucose ≥ 4mmol/L and ≤ 7mmol/L.	<80	80-94	≥95
% having a capillary blood glucose level ≥ 7 mmol/L on 2 consecutive occasions receiving insulin	<85	85-94	≥95
For women/birthing people allocated to more relaxed control:			
% having a capillary blood glucose measured every 2-4 hours (+/- 15 minutes) at least 80% of the time for blood glucose ≥ 4mmol/L and ≤ 10mmol/L	<80	80-94	≥95
% having a capillary blood glucose level between 7-10 mmol/L on 2 consecutive occasions receiving insulin	≥15	10-14	<10
% having a capillary blood glucose level > 10 mmol/L on 2 consecutive occasions receiving insulin.	<85	85-94	≥95

Internal pilot categorisation and synthesis rules:

Green	If all criteria met, continue the trial
Amber	If at least one criterion met, improvement needed. Present action plans to TSC with clear, achievable strategies to overcome barriers. With input from TMG, TSC and PPI group, make modifications to the trial. Depending upon the issues identified, this could include providing additional support to sites, opening new sites, providing additional training of trial documentation.
Red	If at least one criterion met, very substantial improvement needed. Discuss rescue and closure options with DMC, TSC and funder considering all aspects of the trial and actual recruitment, adherence and primary outcome data achieved. Consideration and strong likelihood of trial not progressing from internal pilot phase to main trial if progression criteria for participant recruitment is red even if other criteria or amber or green.

3.3. RANDOMISATION AND BLINDING

3.3.1. Randomisation procedure

Randomisation will be provided by REDCap, a secure online randomisation system at the Nottingham Clinical Trials Unit (NCTU). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been appropriately trained and delegated the role of randomising woman/birthing people into the study as detailed on the GILD Trial Delegation Log. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance, for which sites will be notified in advance.

After eligibility has been confirmed and informed consent has been received, the woman will have an appointment (telephone or face to face) at ≥37 weeks gestation to reaffirm consent and provide baseline data items. Once the baseline data has been collected, the woman/birthing person can be randomised into the trial and a trial number allocated. Following randomisation, a confirmatory email will be sent to the randomising clinician and local Principal Investigator. A blinded randomisation notification will be sent to the Chief Investigator, the Deputy Chief Investigator and NCTU. The woman/birthing person will receive an email, or letter if preferred, confirming their allocation and instructions on what to do when arriving at hospital to birth their baby

The woman/birthing person's consultant will be informed which glucose monitoring strategy the woman/birthing person has been randomised to and an alert placed on the woman/birthing person's electronic maternity health records, or a sticker placed on the front of their paper records. Women*/birthing people* will be provided with an ID card with their allocated glucose monitoring strategy at the time of continuous glucose monitor (CGM) fitting to keep on their person at all times. When the woman/birthing person comes into hospital to birth their baby, the clinical team providing intrapartum care will follow the glucose monitoring strategy as per randomised allocation.

Eligible women/birthing people will be individually randomised to more relaxed or tight control on a 1:1 ratio. Dynamic randomisation will use a probabilistic minimisation algorithm to balance across randomised groups by:

- recruitment site,
- antenatal treatment for GDM:
    - insulin or oral hypoglycaemics
    - diet alone
- treatment with beta-blockers during the third trimester, and
- fetal growth restriction as defined by fetal size or abdominal circumference <3rd centile or <10th centile with Doppler abnormalities (20, 21).

These factors have been selected as they are risk factors for neonatal hypoglycaemia in the BAPM guidelines.

3.2.2. Blinding and concealment

Trial role	Blinding status	Comments
Woman/birthing person	Not blinded	Blinding of women/birthing people is not possible due to the nature of the intervention
Neonatologists	Not blinded	Neonatologists will have access to maternal records and so blinding will not be possible. However, the British Association of Perinatal Medicine (BAPM) guidance will be followed to reduce the risk of detection bias.
Principal Investigator and other site staff	Not blinded	Blinding not possible due to the nature of the investigation
Chief Investigator/Deputy Chief Investigator	Blinded	The Chief Investigator and Deputy Chief Investigator will remain blinded to treatment allocation overall
Database Programmer	Not blinded	The database programmer will be responsible for the management of the randomisation system and will have access to unblinded datasets within the trial database
GILD Trial Management staff within NCTU	Not blinded	GILD Trial Management staff within NCTU will have access to the unblinded datasets within the trial database
Data Management	Not blinded	Data management staff will have access to the unblinded datasets within the trial database to ensure data quality and undertake central monitoring activities
Trial Statistician and Senior Trial Statistician	Blinded	The trial and senior trial statistician will not have access to treatment allocations or data

		which has the potential to unblind until after the database lock for the analysis
Independent Statistician	Not blinded	A statistician, independent to the trial team, will be responsible for the generation of closed reports for the Data Monitoring Committee (DMC) and other potentially unblinding data and will therefore be unblinded to treatment allocation
Health economist	Blinded	The Health Economist will not have access to treatment allocations or data which has the potential to unblind until after the database lock for the analysis

Blinding of women/birthing people and health professionals is not possible, due to the nature of the intervention. It is possible that decisions about the baby's care could be influenced by knowledge of randomised allocation, however the risk of this considered low since the neonatologist and other healthcare professionals involved in the care of the baby are unlikely to be involved in the care of the woman/birthing person during labour. Even where they are aware of the allocation, their decision making will be guided by the hypoglycaemia policy and is very unlikely to be influenced by awareness of how maternal blood glucose levels were managed.

The co-primary outcome will be based on neonatal blood glucose tested using blood glucose analysers on neonatal units and labour suites by a midwife/neonatologist who will not usually have been involved in intrapartum care and neonatal unit admission decided by a neonatologist who will not have been involved in intrapartum care. Process outcomes around baby blood glucose testing will be collected to monitor if this is being done as per BAPM guidance and will be monitored by allocated group by an independent Data Monitoring Committee (DMC). The primary outcome for neonatal hypoglycaemia is defined as any blood glucose level <2mmol/l or a blood glucose level 2-<2.5mmol/l with abnormal clinical signs.

Abnormal clinical signs include:

- Lethargy
- Abnormal feeding behaviour especially after a period of feeding well
- High pitched cry
- Altered level of consciousness
- Hypotonia
- Seizures
- Hypothermia (<36.5 degree C)
- Cyanosis
- Apnoea

Many of these clinical signs are subjective and therefore have the potential for bias due to knowledge of the treatment allocation. However, again these will be assessed by clinicians not involved in the intrapartum care of the women/birthing people reducing the potential for this. In addition, to avoid that their decision-making is influenced by knowledge of maternal treatment they will follow the symptoms list given in the BAPM guidance to diagnose symptomatic hypoglycaemia.

3.2.3. Maintenance of randomisation codes and procedures for breaking code

Interventions are open-label so healthcare professional responsible for care of the woman/birthing person will be aware of the treatment allocation. Therefore, there is no requirement for blind breaking procedures where needed for clinical care.

3.4 TRIAL MANAGEMENT

3.4.1. Sponsor

The University of Nottingham is the sponsor and grant host organisation of the GILD trial. The role and responsibilities of the Sponsor are outlined in the trial Delegation of Responsibilities (DoR) agreement, in the Trial Master File.

The Chief Investigator and Deputy Chief Investigator have overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator.

3.4.2. Clinical Trials Unit

The trial is co-ordinated by the Nottingham Clinical Trials Unit (NCTU), a UK Clinical Research Collaboration (UKCRC) registered Clinical Trials Unit. NCTU are responsible for trial design, set-up and management, coordination of public involvement, database development/maintenance, data management, statistical analyses and dissemination. NCTU will ensure all necessary approvals are in place prior to the start of the trial and will work closely with the sponsor to ensure all relevant contracts are in place, including agreements between sponsor and NHS Trusts. The role and responsibilities of the Clinical Trials Unit are outlined in the Delegation of Responsibilities (DoR) agreement.

3.4.3. Trial Management Group

The Trial Management Group (TMG) will include individuals responsible for the day-to-day management of the trial, including the Chief Investigator, Deputy Chief Investigator, Statistician, Trial Manager, Data Manager, with other members of the trial team attending as required. The role of the group is to ensure high quality trial conduct, to time and within budget, to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard women/birthing people, their babies, and the quality of the trial itself. Site training will be provided by the Trial Manager and Chief Investigator/Deputy Chief Investigator, via group-training sessions. The TMG will report to the Independent Trial Steering

Committee (TSC) who are responsible for oversight of the trial. The role of the TMG is outlined in the TMG terms of reference.

3.4.4. Trial Steering Committee

The role of the Trial Steering Committee (TSC) is to provide overall oversight for the trial on behalf of the Sponsor and Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's UK Policy Framework for Health and Social Care Research and the Guidelines for Good Clinical Practice. The TSC should monitor trial progress and conduct. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent and ultimately carries the responsibility for deciding whether a trial needs to be modified or stopped on grounds of safety or efficacy.

The TSC includes members who are independent of the Investigators, their employing organisations, funder and Sponsor. The TSC will operate in accordance with a trial specific charter. The TSC will meet prior to the start of the trial to agree the protocol, during the internal pilot phase and at least annually until trial completion. The TSC may meet more frequently as requested by the committee, dependent on trial activity or phase. More information on the TSC can be found in the current version of the trial TSC charter.

3.4.5. Data Monitoring Committee

The role of the Data Monitoring Committee (DMC) is to monitor unblinded trial data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should stop or aspects of the trial design be amended. This is to safeguard the interest of the women/birthing people and their babies, investigators and Sponsor. Members of the Data Monitoring Committee (DMC) should be independent of the trial (i.e. should not be involved with the trial in any other way or have any competing interest that could impact on the trial).

Reports will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further women/birthing people. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet annually at a minimum but more frequently as requested by the committee, dependent on trial activity or phase.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Trial Steering Committee (TSC) who will convey the findings of the DMC to Trial Management Committee, funders, and Sponsors as applicable. More information on the DMC can be found in the current version of the trial DMC charter.

3.4.6 Student involvement

Naomi Taylor, a Clinical Research Fellow/Specialty trainee in Obstetrics and Gynaecology has assisted in drafting the GILD trial protocol and will join trial meetings, as considered appropriate by the investigators, as part of skills development.

3.5 DURATION OF THE TRIAL AND WOMAN/BIRTHING PERSON INVOLVEMENT

Study Duration: 40 months
Participation Duration: Most women/birthing people will be involved in the main trial for a maximum of 10 weeks, depending upon when they are approached for participation antenatally. They will receive the randomised blood glucose monitoring strategy during their labour and will receive follow-up questionnaires until 6 weeks post-birth. Some women/birthing people will be approached to take part in the qualitative sub-study at 6-12 weeks post-birth. For these women/birthing people, their participation in both the main trial and qualitative study will last for up to 16 weeks in total.

3.6 END OF THE TRIAL

The end of trial will be the final database lock. This will allow sufficient time for the completion of protocol procedures, data collection and data input. NCTU will notify the Research Ethics Committee (REC) that the trial has ended within 90 days of the end of trial. Where the trial has terminated early, NCTU will inform the REC within 15 days of the date of early termination.

3.7 SELECTION AND WITHDRAWAL OF WOMEN/BIRTHING PEOPLE

3.7.1. Screening and recruitment

The clinical care teams based at recruiting sites will review personal patient information to identify and screen potential women/birthing people for the trial during routine hospital antenatal appointments. Women/birthing people will be recruited from antenatal clinics held in secondary care settings.

Potentially eligible women/birthing people will be approached by appropriately trained clinic staff at each recruiting site (including both clinical team members or research midwives) between 28+0 and 36+6 weeks' gestation during a routine face-to-face antenatal appointment (or closer to the time of birth if clinical staff have the capacity to accommodate this). Women/birthing people will be given an information sheet/leaflet and a link to a short video, which will explain the aims of the trial and what will be involved if they choose to participate. The woman/birthing person will be given sufficient time to consider participating or not and will be encouraged to discuss the trial with family and friends. Women/birthing people who are under 16 will be encouraged to discuss the study with a parent/guardian, though consent will only need to be provided by the woman/birthing person. The Investigator, or their delegate, will inform the woman/birthing person of all aspects pertaining to participation in the study

and answer any questions that the woman/birthing person has concerning study participation. Sites will raise awareness amongst community midwives for them to be able to answer questions and support women/birthing people with early information about the trial. Information about the trial will be on display in the relevant clinical areas.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial. Recruitment materials, such as the consent forms and information sheets, will be translated into the top five languages at each site. For sites randomised to the inclusivity package as a part of the SWAT (see 6. STUDY WITHIN A TRIAL (SWAT) REGIMEN), translated documents will also include the developed bespoke recruitment materials, focused on the inclusion of South Asian women/birthing people.

It will be explained to the potential woman/birthing person that entry into the trial is entirely voluntary and that their and their baby's treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time, however attempts will be made to avoid this occurrence. In the event of their withdrawal, it will be explained that their data collected to date cannot be erased and we will use the data in the final analyses where appropriate.

For further details on the consent process, see 3.10 INFORMED CONSENT.

3.7.2 Eligibility criteria

Inclusion criteria

1. Women/birthing people with gestational diabetes mellitus
2. Aged 16 years or over (or <16 years if deemed Gillick competent).
3. Singleton pregnancy
4. Able to provide informed consent
5. Planned birth ≥37 weeks gestation

Exclusion criteria

1. Known lethal fetal anomaly
2. At time of consent, known clinical indication to recommend birth <37 weeks

3.8 EXPECTED DURATION OF PARTICIPATION

Women/birthing people will be participating in the main study for approximately 10 weeks (from 37 weeks of pregnancy to 6 weeks after birth). For women/birthing people who provided optional consent to take part in the embedded qualitative evaluation an additional 1:1 semi-structured interview will take place 6-12 weeks after birth. For these women/birthing people, their participation in both the main trial and qualitative study will last for up to 16 weeks in total.

3.8.1 Co-enrolment

There is a chance that women/birthing people may be approached for participation who are already enrolled in another trial. Our experience is that this can be conducted appropriately and sensitively, and that patients and research teams in this situation can make an informed decision about whether participation is appropriate.

3.9 CHANGES TO LEVEL OF PARTICIPATION/WITHDRAWAL

We will follow the principles of the PeRSEVERE guidance when considering changes to women/birthing peoples' level of participation in the trial. Women/birthing people have the right to withdraw their consent at any time, without having to give a reason and without any negative effect on their usual care. This will be made clear at recruitment. In practice, women/birthing people's level of involvement can stop, reduce or change. It is primarily for women/birthing people to decide how their level of involvement will change. An exception to this is where someone else decides it is no longer in a woman/birthing person or their baby's interests to continue taking part in some part of the study. All normal standard hospital care safeguarding procedures will apply in the event of concerns about a participant's or other person's health and/or safety. An additional exception is where continued participation would no longer be feasible or no longer relevant to the study objectives.

Women/birthing people will be made aware that, should they change their level of participation or withdraw consent, the data collected to date cannot be erased and may still be used in the final analysis.

A woman/birthing person's decision(s) about changing their level of involvement should be informed and freely-given. We will include a contact number for a research nurse as a point of contact for all women/birthing people to use in the event they are experiencing problems during the study or considering early withdrawal. Site staff will discuss with the woman/birthing person how they want their participation to change and will make reasonable efforts to find ways to continue some follow-up, where the woman/birthing person is willing.

Interactions with women/birthing people will be conducted in a balanced way, providing sufficient information about different options, not pressuring women/birthing people to take further part in aspects of the trial but also not assuming they want to stop all aspects.

The NCTU must be informed of all requests by women/birthing people to stop or change their involvement in the trial; appropriate action will be taken to ensure that the woman/birthing person's wishes are followed promptly and safely.
Collecting as much as possible of a trial's planned data can help the trial reach a reliable conclusion. This should be kept in mind by all trial staff during the trial.

Sites will be trained to determine which activities women/birthing people may wish to discontinue. Levels of discontinuation will include, but are not limited to:

	Type of participation change	Action required at the time of participation change	Use of data
1	Discontinuation from intervention only	Any woman/birthing person that requests to change the way in which their blood glucose levels are monitored during labour will be marked as discontinued from intervention on the trial database. Woman/birthing person will revert to the local hospital guidance on intrapartum glycaemic control.	Data collection to continue as per protocol.
2	Discontinuation from 6-week follow-up questionnaires only	Any woman/birthing person that requests stop receiving trial questionnaires will be marked as discontinued from questionnaire collection on the trial database and no further contact will be made with the woman/birthing person for the purpose of obtaining questionnaire follow-up data.	Any data collected prior to change in participation will be retained and used. No contact will be made for further follow-up data collection. Data from routine hospital sources will still be collected.
3	Discontinuation from intervention and from follow-up questionnaires	As per (1) **and** (2) above.	Any data collected prior to change in participation will be retained and used. No contact will be made for further follow-up data collection. Data from routine hospital sources will still be collected.
4	Discontinuation from intervention, follow-up questionnaires and the collection of routine hospital data	This would constitute a withdrawal of consent from all further trial related activities, the woman/birthing person should therefore be withdrawn from the trial and marked as withdrawn on the trial database. The participant will be asked to confirm if they would still like to be contacted about the study results.	Any data collected prior to change in participation will be retained and used. No contact will be made for further follow-up data collection. No further data from routine hospital sources will be collected.
5	Withdrawal of consent prior to randomisation	Any women/birthing people that request to withdraw their consent prior to randomisation will not be randomised and will be withdrawn from the trial completely. The woman/birthing person's blood glucose monitoring will follow the local	Data recorded will be used, but no further study data collected after change in participation. No contact will be made for further

		hospital guidance on intrapartum glycaemic control.	follow-up data collection. No data from routine hospital sources will be collected.
6	Change in eligibility prior to randomisation	Any women/birthing people that give birth, or are otherwise deemed not eligible, between consent and randomisation will not be randomised and will be withdrawn from the trial completely. The woman/birthing person's blood glucose monitoring will follow the local hospital guidance on intrapartum glycaemic control.	Data recorded will be used, but no further study data collected after change in participation. No contact will be made for further follow-up data collection. No data from routine hospital sources will be collected.

3.10 INFORMED CONSENT

Informed consent will be sought between 28^{+0} and 36^{+6} gestation during a routine hospital antenatal appointment (or closer to the time of birth if clinical staff have the capacity to accommodate this). All women/birthing people will provide informed consent (electronic consent to be completed at the appointment, or paper-based where access to an electronic device is unavailable). Any women/birthing people aged under 16 must be deemed Gillick competent to take part. The Informed Consent Form will be signed and dated by the woman/birthing person before they enter the trial.

Consent will be obtained by a member of the research team at the recruiting site, in accordance with the responsibilities delegated by the Principal Investigator as captured on the Site Delegation Log. It remains the responsibility of the Principal Investigator to ensure informed consent is obtained appropriately.

Informed consent will be collected from each woman/birthing person before they undergo any interventions (including physical examination and history taking) related to the trial.

Potential women/birthing people will consent electronically via REDCap (where access to an electronic device is not possible, a paper written consent form will be used). On completion, this will be reviewed by the person taking consent who will review and approve the consent form (electronic signature within REDCap, or wet ink signature on paper consent form). Once signed by both parties, a copy of the complete consent form will be saved in REDCap and a copy put in the woman/birthing person's medical records. For those consented electronically, a copy of the completed consent form will be sent to the woman/birthing person via email, along with an electronic copy of the PIS for their records. Where the consent form is completed on paper, a copy will be made so that both the investigator and woman/birthing person have a copy each. Details of the informed consent discussions will be recorded in the woman/birthing person's medical notes.

The woman/birthing person will give explicit consent for the regulatory authorities, members of the research team and representatives of the Sponsor to be given direct access to the woman/birthing person's medical records. Explicit consent will be provided for use of the woman/birthing person's and their baby's information held by their GP, NHS England Digital and other central UK NHS bodies. At the time of providing consent to participate in the trial, women/birthing people will be asked to give their optional consent to be contacted after birth to take part in a 1:1 semi-structured interview (conducted remotely via telephone or video call). This interview will form part of the embedded qualitative evaluation. Optional consent will be sought for women*/birthing people* to be contacted for long-term follow-up to assess neurodevelopment of the baby at 2 years and during childhood. Further funding for this will be sought and details are not included in this version of the trial protocol.

If the woman/birthing person provides their consent for participation, a member of the site research team (as per delegation log) will contact the woman/birthing person at approximately 37 weeks gestation by telephone to re-affirm consent, collect baseline data and randomise them via the web-based randomisation system. If it is discovered at this time that a woman/birthing person is no longer eligible to take part in the trial, for example due to giving birth prior to randomisation, this should be noted on the screening log and no baseline data should be collected and randomisation should not take place.

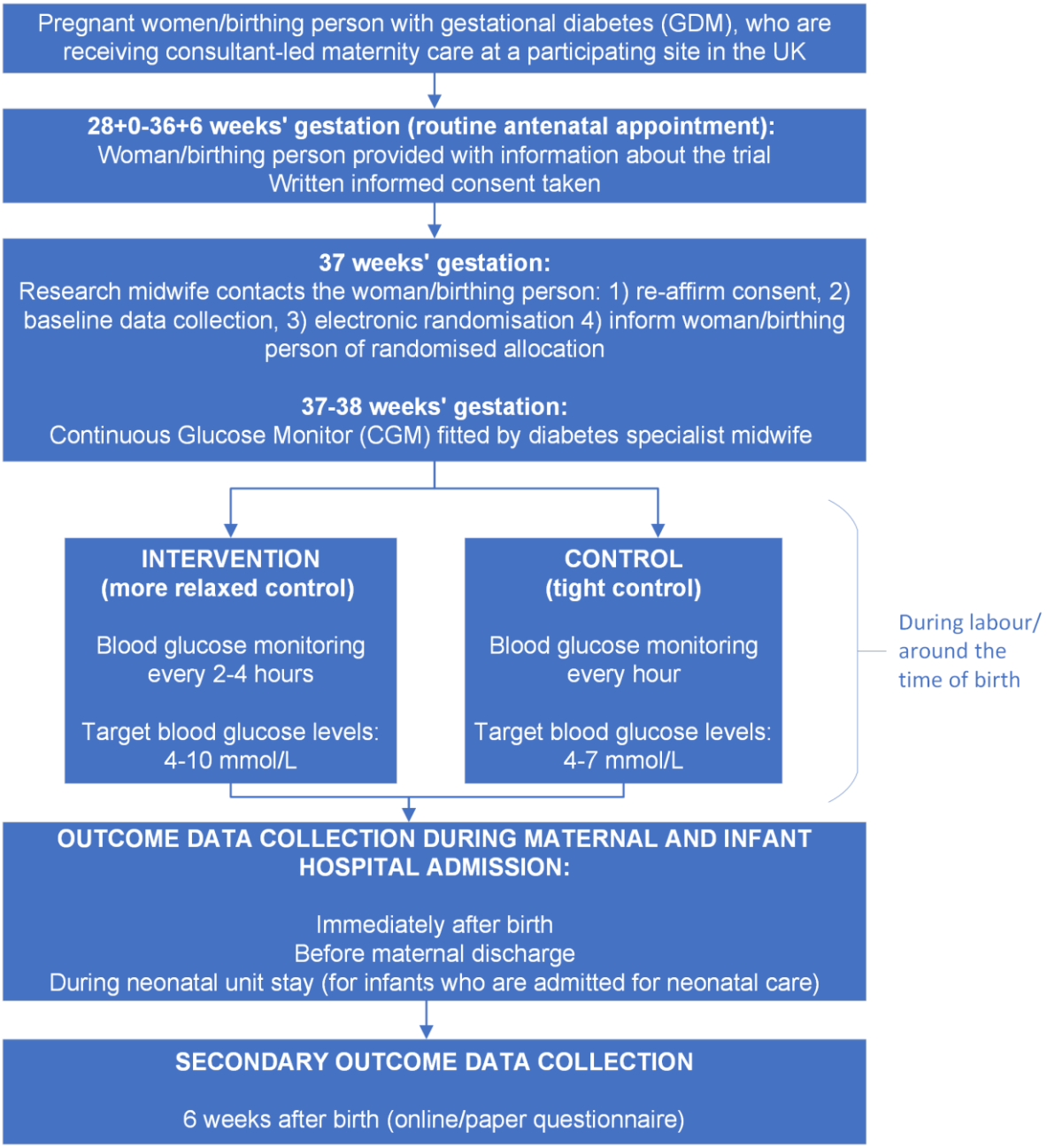
Throughout the trial the woman/birthing person will have the opportunity to ask questions about the trial. Any new information that may be relevant to the woman/birthing person's continued participation will be provided. The woman/birthing person's right to withdraw from the trial will remain.

4. TRIAL TREATMENT AND REGIMEN

4.1 TRIAL REGIMEN

Figure 1 summarises the study regimen that each woman/birthing person will receive depending on the monitoring type they are randomised to.

Figure 1: Participation flow chart



4.2 BLOOD GLUCOSE MONITORING

A suitable healthcare professional, such as a diabetes specialist midwife, will fit a CGM to the woman/birthing person between 37-38 weeks' gestation at a routine appointment (or closer to the time of birth if clinical staff have capacity to accommodate this). The CGM will not be used for women/birthing people to monitor their blood glucose levels because it is not currently licenced for intrapartum use and is not part of routine clinical care for women/birthing people with GDM. Finger-prick blood glucose testing is used as standard care and will be used in both the intervention and control groups. Women/birthing people will be unable to view the CGM data during their pregnancy or labour, and health professionals will only be able to view the data collected by the CGM during labour after the woman/birthing

person has given birth. The CGM is being used purely to facilitate trial data collection in real-time as our previous scoping study showed that recording of glucose values around the time of birth in clinical records can be poor. However, where it is not possible or the woman/birthing person is unwilling to have a CGM fitted, capillary blood glucose levels (recorded in medical notes) will be used. In the unlikely event that a woman already has a CGM fitted for clinical reasons then this CGM will be used for trial data collection.

A CGM is fitted by 1) cleaning and drying the skin 2) loading the sensor in the sensor applicator 3) applying the sensor applicator to the skin 4) pushing down firmly on the sensor applicator. We will use a blinded version of a CGM for research use – called the LibreProIQ. This will be fitted to the woman/birthing person and collects continuous blood glucose measurements every 15 minutes. The device is removed after being scanned by the research team, using a central reader at site. The woman/birthing person is unable to view the data during data collection, but may be sent a copy after birth if requested.

A CGM can collect continuous data for 14 days. If a woman/birthing person has not given birth within 14 days of the initial CGM fitting, the site should contact the woman/birthing person by day 11 to arrange for them to return to the hospital by day 14 to have the initial device removed and a new device fitted following the procedures outlined above. The removed device will be stored securely at site until the baby has been delivered. At this point, the study CGMs worn by the woman/birthing person will be scanned and data uploaded to the trial

When the woman/birthing person comes into hospital to birth their baby, the clinical team providing intrapartum care will follow the glucose monitoring strategy as per randomised allocation.

Glucose testing by finger prick testing will commence from the point of:

- admission in spontaneous established labour or
- following artificial rupture of membranes or onset of regular contractions following induction of labour or
- admission for elective caesarean section

Data collected during the woman/birthing person and baby's admission in hospital will be collected via a variety of methods, as outlined in 3. TRIAL DESIGN.

4.2.1. Tight Glucose Monitoring (control)

Women/birthing people randomised to receive tight glucose monitoring will have capillary blood glucose measured via finger prick every hour during labour, or between admission and birth for planned caesarean. Target glucose levels for these women/birthing people is between 4-7mmol/L, and intravenous insulin will be administered if the woman/birthing person's glucose levels are above 7mmol/L on two consecutive occasions.

4.2.2. More Relaxed Glucose Monitoring (intervention)

Women/birthing people randomised to receive more relaxed glucose monitoring will have capillary blood glucose measured via finger prick every 2-4 hours during labour, or between admission and birth for planned caesarean. Target glucose levels for these women/birthing people is between 4-10mmol/L, and intravenous insulin will be administered if the woman/birthing person's glucose levels are above 10mmol/L on two consecutive occasions.

4.2.3. Both groups

For both randomised groups management of blood glucose levels (i.e. frequency of testing and treatment) for blood glucose < 4 mmol/L and when general anaesthesia is used during a caesarean will be according to the local hospital guideline or national guidance (22). Similarly, frequency of blood glucose testing when capillary blood glucose levels are greater than the target glucose level (i.e. 7mmol/L in tight control group and 10 mmol/L in more relaxed control group) will be according to the local hospital guideline or national guidance.

4.3 ADHERENCE

Blood glucose values from finger prick testing and subsequent treatment will be recorded. CGMs will be used for trial purposes to calculate the percentage of time in target range for both groups. The proportion of time blood glucose values in range from 7-10mmol/l will also be derived to check there is separation between the groups.

4.3.1. Adherence with tight glucose monitoring plan

For women/birthing people allocated to the tight glucose monitoring plan, adherence (during labour/between admission and delivery for a planned C-section) will be determined by:

1. Having capillary blood glucose measured hourly (+/- 15 minutes) at least 80% of the time for blood glucose ≥ 4mmol/L and ≤ 7mmol/L.
2. Receiving insulin only if capillary blood glucose level is >7mmol/L on two consecutive occasions

4.3.2. Adherence with more relaxed glucose monitoring plan

For women/birthing people allocated to the more relaxed glucose monitoring plan, adherence (during labour/between admission and delivery for a planned C-section) will be determined by:

1. Having capillary blood glucose measured every 2-4 hours (+/- 15 minutes) at least 80% of the time for blood glucose ≥ 4mmol/L and ≤ 10mmol/L
2. Receiving insulin only if capillary blood glucose level is >10mmol/L on two consecutive occasions

Monitoring of adherence (blood glucose values and frequency of testing) will reduce bias. The above criteria will be monitored by the NCTU trial team as part of central

monitoring procedures, and sites identified as having unacceptable adherence with the monitoring plans may be offered additional training, have a triggered monitoring visit, or the trial may be ceased at the site. Adherence to the randomised allocation is one of the progression criteria for the internal pilot phase.

4.4 POST-BIRTH

Post-birth management of the woman/birthing person will be as per local policy.
After birth, usual care for neonatal hypoglycaemia should be followed, as per BAPM guidelines.

At the time of maternal hospital discharge, women/birthing people will complete a questionnaire and will be provided with printed information as a reminder about the trial. The leaflet will clearly state that they should expect to receive follow-up questionnaires 6 weeks after birth with a link to the GILD website and information about who to contact if they have any questions.

Site research staff will check routine hospital systems at ~5 weeks post-birth for a "wellbeing check", to confirm there have been no significant maternal and/or newborn events that would mean a standard approach at 6 weeks post-birth is inappropriate. With site staff confirmation that it is appropriate, an email with a personalised link to the online questionnaire will be sent, or a paper copy of the questionnaire will be posted to the woman/birthing person's home address. Text messages with a personalised link to the online questionnaire may also be sent if a participant has agreed to received text communications. These texts will be sent in addition to the email/paper copies. If an event has taken place (e.g. woman/birthing person/baby death or significant health issue), an alternative/tailored approach will be made, with appropriately worded communications that have had input from patient and public involvement representatives. For women/birthing people who prefer not to receive a questionnaire via electronic methods, a paper copy will be provided which will be returned to NCTU for data entry.

The trial coordinating centre will follow-up (via telephone, text message, post and/or email) outstanding questionnaires.

For around 20 women/birthing people who provided optional consent to take part in the embedded qualitative evaluation an additional 1:1 semi-structured interview will take place 6-12 weeks after birth.

We will seek optional consent for women/birthing people to be contacted for long-term follow-up to assess neurodevelopment of the baby at 2 years and during childhood. Further funding for this will be sought.

4.5 CRITERIA FOR TERMINATING TRIAL

There are no formal stopping rules. The Data Monitoring Committee will review unblinded data, adverse events and any other published data at least annually, and,

based on the cumulative data, may advise stopping if there is clear evidence of benefit or harm in one or other group.

5. QUALITATIVE SUB-STUDY

Qualitative study: A qualitative evaluation will determine the acceptability of the two blood glucose monitoring strategies, and barriers and facilitators to implementation.

Women/birthing people: We will interview ~20 women/birthing people (or until data richness is reached), who will be purposively sampled via a pre-defined sampling matrix to ensure we include women/birthing people with a range of characteristics, (ethnicity, age, location, randomised group and whether this is the woman/birthing person's first or subsequent GDM pregnancy). If the woman/birthing person has given consent to be contacted about taking part in an interview, they may be provided with an invitation letter/email and a participant information sheet (online or postal) explaining the interviews. They will be asked to register their interest by clicking a link or contacting the study team. If no response is received within 2 weeks, a member of the local research or central study teams may contact the participant by telephone call to confirm if they would like to take part and to arrange a mutually convenient time for the interview. They will be asked to give their verbal consent over the phone or video call before the start of the interview. The interviews will be conducted by midwifery researchers from the Essential Baby Company. Interviews will take place around 6-12 weeks after birth, last around ~30-45 minutes, and will follow an interview theme guide. A £25 shopping voucher will be offered as a token of appreciation upon interview completion.

Health professionals: 1:1 semi-structured interviews will be conducted with ~20-30 health professionals (e.g. clinical midwives, neonatologists, obstetricians, diabetes specialists) (or until data richness is achieved) from participating sites, who have experience of either caring for women/birthing people who have been randomised to the more relaxed blood glucose monitoring strategy or caring for infants born to women/birthing people who were randomised to more relaxed control. Purposive sampling will ensure health professionals of different career stages, ethnicities and locations are included. Some healthcare professionals may be approached via email and provided with the PIS for healthcare professionals. The PIS for healthcare professionals will also be given to research midwives at each site who may then approach colleagues with suitable experience who they think maybe suitable to participate. The health care professionals will then have time to consider the information in the PIS before consent is taken. A remote interview, via telephone or video call, will be convened at a mutually convenient time. Consent will be taken verbally and recorded electronically at the beginning of the interview. Health professionals will be offered the opportunity to enter into a £250 prize draw upon completion of interview.

All interviews will be audio recorded (including video for those that take place via video call) and transcribed (de-identified prior to analysis). Acceptability will be examined using the theoretical framework of acceptability (23) as a guide, which includes affective attitudes, burden, perceived effectiveness, ethicality, intervention coherence,

opportunity costs and self-efficacy. Site-specific contextual factors will be examined, including practical, environmental and organisational barriers and facilitators to implementing a more relaxed blood glucose monitoring strategy (24). Systematic thematic analysis will be conducted. The framework method will be used to provide a structured summary of the data. This type of thematic analysis is suitable for work with multidisciplinary teams and studies where data are compared within and between different sub-groups (25). A combined inductive-deductive approach will be used which enables specific research questions to be addressed, as well as identifying unexpected or new themes relating to acceptability and implementation of a more relaxed blood glucose monitoring strategy. Data will be analysed using NVivo software and reported in accordance with COREQ reporting guidance (26).

6. STUDY WITHIN A TRIAL (SWAT) REGIMEN

Title: Study Within A Trial (SWAT): Increasing participation of South Asian women/birthing people in gestational diabetes trials

Background: Gestational diabetes (GDM) affects 8% (~50,000) of UK pregnant women/birthing people. South Asian women/birthing people are twice as likely to develop GDM compared to White European women/birthing people.

Since South Asian women/birthing people are disproportionately affected by GDM, it is important that they are included in the GILD Trial, yet in the past may have been under-served by research.

We wish to understand the barriers and enablers to participation of South Asian women/birthing people with gestational diabetes trials to inform the design of an 'inclusivity package' to specifically target recruitment of South Asian women/birthing people into the GILD trial.

To facilitate recruitment of South Asian women, we will work with South Asian Health Action (a charity based in Leicester to support the physical and mental health needs of the local South Asian community) and the HaPPIE research group (a group dedicated to patient and public involvement to amplify the voices of Black and Brown skin people).

Aim: To increase trial participation amongst South Asian women/birthing people, who are more likely to develop GDM and have previously been underserved by research.

Method

Inclusivity package development

i) A package of study-specific recruitment materials with inclusive messaging have been developed following a number of focus groups conducted with South Asian woman/birthing people and their families to explore barriers to the research.

ii) Sites randomised to receive the SWAT materials above may also receive bespoke cultural-awareness training on how to approach, seek consent, recruit and retain South Asian women/birthing people in the trial.

iii) A small number of 'Community Connectors' (women/birthing people with lived experience of GDM) will be appointed to provide ad-hoc informal peer support and advice to women/birthing people who are in or considering joining GILD. Information and contact details of the Community Connectors will be given to South Asian women/birthing people by the research midwife, and they will be given the opportunity to connect for an informal chat.

Inclusivity package evaluation

Participating sites will be randomised on a 1:1 allocation to receiving the standard recruitment materials or standard recruitment materials plus the inclusivity package (including bespoke trial materials for South Asian women/birthing people and site training as detailed above), using a minimisation algorithm balancing on baseline South Asian ethnicity at site (ONS/site level data). Randomisation will be by NCTU prior to site initiation. Our collaborators will attend site training to deliver the cultural-awareness training. The research midwife and Principal Investigator will receive this training and arrangements will be made locally for this to be cascaded to other members of the local team.

Sites not randomised to receive the inclusivity package will receive standard trial recruitment materials. To ensure these sites are still supported to recruit underserved groups, including South Asian women/birthing people, standard trial materials will be translated to the top five languages at the participating sites.

Key SWAT outcomes are the number of South Asian women/birthing people who:

1. are approached for participation in the trial
2. give consent to participate
3. are randomised.

All outcomes are proportionate to the number of South Asian women/birthing people at each site (ONS/site level data). Other outcomes are number of randomised South Asian women/birthing people who complete the 6 week follow-up questionnaire.

The analysis of the SWAT will be specified in the GILD SWAT statistical analysis plan. Analyses will include appropriate descriptive statistics and between-group comparisons will use appropriate regression models with analysis at the site level.

7. STATISTICS

7.1 METHODS

Analyses and presentation of trial results will be in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines for non-inferiority trials (27). All

analyses will be specified in the Statistical Analysis Plan (SAP) finalised prior to database lock.

7.2 SAMPLE SIZE AND JUSTIFICATION

The sample size is based on the neonatal unit admission outcome with non-inferiority only concluded if non-inferiority is demonstrated on both primary outcomes. Assuming 10% of babies in both groups are admitted to the neonatal unit, an absolute non-inferiority margin of 5%, 90% power and 1-sided significance level of 0.025, a total sample size for analysis of 1594 is needed (using a using a continuity corrected Z test). Reported rates of neonatal hypoglycaemia in babies of women/birthing people with GDM are varied according to the definition used. Assuming that 7% of babies in both groups have neonatal hypoglycaemia (based on the GILD scoping study), a sample size of 1594 provides 97% power for an absolute non-inferiority margin of 5%. This means the overall power for the trial to conclude non-inferiority will be in excess of 87% (90x97). From our previous intrapartum clinical trials with pre-hospital discharge outcomes, we anticipate loss to follow-up will be minimal (2%), giving a target sample size for recruitment of 1630.

A 5% non-inferiority margin for neonatal hypoglycaemia is considered acceptable to clinicians and women/birthing people with GDM we have consulted. We surveyed 29 women/birthing people (14 white, 7 Asian, 5 black, 1 Hispanic, 1 Persian, 1 Kurdish): 21 (72%) found the 'trade-off' between more relaxed control and neonatal hypoglycaemia acceptable and 8 (28%) did not, citing reasons including they did not want to risk their baby having low blood sugars and they wanted to get home quickly after birth. We consulted 10 health professionals (including obstetricians, midwives, neonatologists): all considered the non-inferiority margin acceptable. Our PPI group also consider a 5% non-inferiority margin for neonatal unit admission acceptable, recognising the close association with neonatal hypoglycaemia.

7.3 ASSESSMENT OF EFFICACY

Analysis of the co-primary outcomes will be performed using a mixed effects model for binary outcomes adjusting for site as a random effect and other minimisation variables as fixed effects to estimate a risk difference for each outcome. Estimates of the adjusted risk difference and 95% confidence intervals (CIs) will be obtained by average marginal predictions in the fitted model.

There will be two analyses of the co-primary outcomes to allow assessment of the robustness of the results – an intention to treat (ITT) and a per protocol (PP) analysis. Conclusions will be based on the upper bound of the 95% confidence intervals for the risk difference for the two co-primary outcomes with non-inferiority inferred if this is no greater than the non-inferiority margin of 5% for the two outcomes. The ITT and PP analysis populations are sets defined in the Section 7.5. Definition of populations analysed0.

Secondary outcomes will be considered as supportive of the co-primary outcomes. Between-group comparisons will use appropriate regression models (depending on the outcome data type), using a generalised linear mixed model framework, adjusting for the minimisation variables as described for the primary outcomes. Analyses of

secondary neonatal and maternal safety outcomes will be conducted on the ITT and PP analysis sets as described for the primary outcome. Analyses of other secondary outcomes will be conducted on the ITT analysis set. Process outcomes will be summarised descriptively according to randomised allocation.

Exploratory subgroup analyses according to antenatal treatment for GDM (insulin or oral hypoglycaemics/diet alone and booking body mass index (≤ 25 or > 25) will be performed by including appropriate interaction terms in the analysis models for the co-primary outcomes.

7.3.1. Assessment of safety

In addition to the primary and secondary outcomes collected as safety outcomes, serious adverse events for women/birthing people and their babies will be collected. These will be summarised descriptively.

7.4 PROCEDURES FOR MISSING, UNUSED AND SPURIOUS DATA

We expect the co-primary outcomes to be able to be collected for nearly all babies, but if appropriate, sensitivity analyses will be conducted using multiple imputation for missing primary outcome data.

7.5 DEFINITION OF POPULATIONS ANALYSED

Intention to treat (ITT) population – randomised women/birthing people and their babies analysed according to randomised allocation regardless of adherence with allocated blood glucose monitoring strategy.

Per-protocol (PP) population - All randomised eligible women/birthing people and their babies with blood glucose monitoring around the time of birth conducted according to their randomised allocation0.

Note neonatal outcomes, other than outcome of birth, will be analysed in the population of liveborn babies.

Further details on analysis populations and definition of estimands for the trial will be specified in the SAP.

8. ECONOMIC EVALUATION

A health economic analysis plan (HEAP) will be drafted early in the trial and finalised prior to co-primary outcome analysis. The economic evaluation will consist of a cost-consequence analysis (primary analysis) and a cost-utility analysis (secondary analysis) of more relaxed and tight glucose control under intention-to-treat principle. The time horizon for both analyses is from the hospital admission to give birth up to 6 weeks post birth. We do not expect the impact of the intervention on costs and health utilities to extend beyond the 6 week follow-up of the trial. An NHS perspective will be adopted and the outcomes will not be discounted (as follow-up <1 year). Cost-

consequence analysis will present resource use, costs and selected outcomes (e.g. co-primary trial outcome, maternal health-related quality of life) in a disaggregated manner. Maternal health-related quality of life collected using EQ-5D-5L at baseline/hospital discharge/6 weeks and valued following NICE guidance (28). NHS resource use data, including primary care and outpatient contacts, and hospital admissions of the mother and infant collected via patient questionnaires and review of medical records, and valued using national costs (29). This will allow us to identify labour-related resource use data (e.g. diabetes medications provided, type of birth, admissions of mothers or babies to high dependency care/ICU and NICU). Descriptive statistics (means and SD) will be reported, for the outcomes at each follow-up point using complete data. Differences between trial groups will be reported as means and 95% CI estimated using mixed effects linear regression models. Missing EQ-5D and cost data will be imputed following best practice in cost-effectiveness studies (30), e.g. mean imputation of baseline data and multiple imputation at follow-up, if a missing at random mechanism is assumed to hold following examination of the patterns of missing data.

The cost-utility analysis will be conducted from a maternal perspective and estimate the incremental cost per quality-adjusted life year (QALY) of more relaxed relative to tight glucose control. Maternal EQ-5D data will inform the calculation of QALYs. Following multiple imputation, total costs and QALYs will be estimated as well as incremental costs and QALYs, using separate linear regression models controlling for treatment allocation and other variables of interest. Rubin's rule will produce the mean difference in costs and QALYs of more relaxed relative to tight glucose control. Incremental cost-effectiveness ratio (ICER) will be estimated by dividing the difference in costs by the difference in QALYs of the two treatments under analysis and will be depicted on the cost-effectiveness plane. Joint uncertainty around incremental costs and QALYs will be estimated using bootstrapping from each imputed dataset, running the estimation model and extracting the estimated treatment effects, producing confidence intervals for the difference in costs and QALYs and cost-effectiveness acceptability curve informing the probability of the interventions being cost-effective at different maximum willingness to pay values, e.g. £20,000 to £30,000 per QALY gained.

9. ADVERSE EVENTS

9.1 DEFINITIONS

An adverse event (AE) is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.

An AE **does** include a / an:

1. exacerbation of a pre-existing illness.
2. increase in frequency or intensity of a pre-existing episodic event or condition.
3. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE **does not** include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that led to the procedure is an AE.
2. pre-existing disease or conditions present or detected at the start of the study that did not worsen.
3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).
4. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.
5. overdose of concurrent medication without any signs or symptoms.
6. triage or day unit attendances for fetal monitoring, maternal hypertension, antepartum haemorrhage, preterm labour, preterm prelabour rupture of membranes, abdominal pain, transverse or oblique lie or placenta praevia.

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the treatment or intervention that results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalisation or prolongation of existing hospitalisation
4. A disability / incapacity
5. A congenital anomaly in the offspring of a participant
6. Other medically important event**

**Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

9.2 CAUSALITY

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment / intervention administration which makes a causal relationship incompatible or for which other treatments, chemicals or disease

provide a plausible explanation**.** This will be counted as “unrelated” for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, but which could also be explained by other interventions, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other interventions, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

9.3 REPORTING OF SERIOUS ADVERSE EVENTS

Serious adverse event reporting period

- **Maternal SAEs** will be reported from the point of admission in either spontaneous labour or for a planned induction of labour or caesarean birth until maternal discharge from hospital.

- **Neonatal SAEs** will be reported from the time of birth until neonatal discharge from hospital.

Events that do not require reporting

Adverse events that meet the definition of an SAE should be reported, with the exception of the below list of events that are expected in this population. These events should **not** be reported as an SAE, however, should be recorded in clinical records:

- ***Maternal events***
    - Birth (spontaneous labour, planned caesarean or induction of labour)
    - Elective treatment of a pre-existing condition
    - Common antenatal complications, such as: fetal monitoring, maternal hypertension, antepartum haemorrhage, preterm labour, preterm prelabour rupture of membranes, abdominal pain, transverse or oblique lie or placenta praevia

- Common postpartum complications such as maternal hypertension, perineal problems, mental health problems, urinary problems, or infections
- Inpatient hospitalisation solely for any of the above maternal events

- ***Neonatal events***
  - Admission to the Neonatal Unit
  - Respiratory distress syndrome/transient tachypnoea of the newborn needing respiratory support
  - Polycythaemia and jaundice
  - Congenital anomalies including congenital heart disease, neural tube defects, caudal regression syndrome, renal anomalies
  - Inpatient hospitalisation solely for any of the above neonatal events

All adverse events will be recorded in clinical records and closely monitored until resolution, stabilisation, or until it has been shown that the study intervention is not the cause. The Chief Investigator (or delegate) shall be informed immediately of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners. All normal standard hospital care safeguarding procedures will apply in the event of concerns about a participant's or other person's health and/or safety.

Investigators will report AEs that meet the definition of an SAE. AEs defined as serious and which require expedited reporting as an SAE, will be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE.

Causality of an event will be categorised as one of the following:

- Definitely related
- Probably related
- Possibly related
- Unlikely to be related
- Unrelated

SAE reporting procedure

On becoming aware that a participant has experienced an SAE, the Investigator (or delegate) must complete the electronic SAE form within the REDCap database. The form should be completed as soon as possible and no later than 24 hours after first becoming aware of the event. The site investigator will define the causality of the SAE and sign the form electronically.

Completion of the electronic SAE form will generate a unique SAE reference number and will trigger an alert, via email, to NCTU. The SAE reference number will be quoted on all correspondence regarding the SAE. NCTU will request Medical Monitor assessment via the REDCap database.

In the unlikely event that the electronic SAE reporting system is unavailable, a paper SAE form must be completed by the site investigator (or delegate). For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments.

Paper SAE forms (only in the unlikely event that the electronic SAE reporting system is unavailable) must be emailed to NCTU-SAE@nottingham.ac.uk as soon as possible and no later than 24 hours after becoming aware of the event. NCTU will request Medical Monitor assessment via email.

On receipt of an SAE form (either electronic or paper), seriousness and causality will be reviewed independently by the Medical Monitor (Chief Investigator or delegate) responsible for determining causality assessments. An SAE judged by the Investigator to have a reasonable* causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Chief Investigator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected, it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR). Any events classified as a SUSAR will trigger an immediate alert to the NCTU Quality Assurance team and to the trial Sponsor office.

*reasonable equates to possible, probable or definitely related in the opinion of either the Investigator or Chief Investigator

9.4 TRIAL TREATMENT / INTERVENTION RELATED SAES

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment or intervention shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment or intervention.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment or intervention shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required

9.5 PARTICIPANT REMOVAL FROM THE STUDY DUE TO ADVERSE EVENTS

Any woman/birthing person, or their baby, who experiences an adverse event may have their level of participation in the trial changed at the discretion of the Investigator to stop the intervention. See 3.9 CHANGES TO LEVEL OF PARTICIPATION/WITHDRAWAL for details.

10. ETHICAL AND REGULATORY ASPECTS

10.1 ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to women/birthing people, and their babies, may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the UK Department of Health Policy Framework for Health and Social Care, 2017.

10.2 INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced.

The investigator will inform the woman/birthing person of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for women/birthing people already enrolled in the trial).

For further details on the consent process, see 3.10 INFORMED CONSENT.

10.3 RECORDS

10.3.1. Case Report Forms

Each woman/birthing person will be assigned a trial identity code number, allocated at consent if appropriate, for use on CRFs, other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd-mm-yyyy). The woman/birthing person's trial identity code, initials, and date of birth will also be used for any reporting related to their baby's outcomes.

CRFs will be treated as confidential documents and held securely in accordance with regulations. To permit identification of all women/birthing people enrolled in the trial and for follow-up as required, women/birthing people's identifiers will be stored securely in the trial database in accordance with regulatory requirements.
CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

CRFs are used to record clinical trial data and are an integral part of the study and subsequent reports. The CRFs, therefore, must be legible and complete. All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

10.3.2. Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

10.3.3. Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. Department of Health and Social Care, Human Tissue Authority).

11. DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the individuals in the trial to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the trial. eCRFs will be stored securely on the trial database. Where used, paper CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Information about the trial in the woman/birthing person's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

12. QUALITY ASSURANCE & AUDIT

12.1 INSURANCE AND INDEMNITY

The University of Nottingham is the trial sponsor. Delegated responsibilities will be assigned to the NHS Trusts taking part and the NCTU. The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in of claims made by research subjects. Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

12.2 TRIAL CONDUCT

The Principal Investigator will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up.

Trial conduct may be subject to a Sponsor systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

The Trial Master File and evidence of audits will be made available upon request for regulatory inspections.

12.3 TRIAL DATA

A member of NCTU, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity. All monitoring activities will be detailed in the trial Monitoring Plan and recorded in line with NCTU standard operating procedures.

Trial data and evidence of monitoring will be made available for inspection by regulatory authority as required.

12.4 RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the CI on behalf of the Sponsor shall be finally archived securely in the Microsoft cloud which has multiple redundant systems and backup services. This archive shall include all trial databases and associated meta-data encryption codes. Access to files once archived (e.g. for inspection purposes), will be managed by the NCTU archivist and will only be accepted on approval of the University of Nottingham sponsor.

12.5 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

12.6 STATEMENT OF CONFIDENTIALITY

Individual women/birthing people and their baby's medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the woman/birthing person and their baby's medical teams and all appropriate medical personnel responsible for their welfare.

If information is disclosed during the study that could pose a risk of harm to the woman/birthing person, their baby or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

12.7 PUBLICATION AND DISSEMINATION POLICY

All publication activities will be planned in close collaboration with our PPI representatives. Women/birthing people and their babies will not be identified in any publications. Manuscripts will be prepared by the Chief Investigator and TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the Chief Investigator and NCTU. Manuscripts must be submitted to both parties in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Nottingham.

During the trial, press releases may be issued from the Sponsor or NCTU. Presentations or other material prepared by local investigators to publicise the trial must be reviewed by the Chief Investigator and NCTU. No party will be entitled to submit any publicity material without prior approval of the NCTU.

Sites will be invited to a results meeting where the findings of the trial will be shared prior to publication.

All publications, including source and date of publication, will be detailed in a separate trial publication log.

De-identified individual participant data may be shared with researchers external to the trial research team in accordance with the NCTU's Data Sharing Standard Operating Procedure (SOP 33) wherein the request is considered by a data sharing committee which includes the CI and the sponsor and where a formal data sharing agreement is required between the trial sponsor (University of Nottingham) and the sponsor of the data requestor.

12.8 USER AND PUBLIC INVOLVEMENT

Patients and members of the public have made a significant contribution to the development of this trial, through several methods, described here.

In our NIHR-commissioned GILD scoping study, 151 women/birthing people with gestational diabetes (GDM) responded to a national survey about their experiences of having diabetes around the time of birth, blood glucose monitoring strategies, treatment during labour, and whether they would be willing to participate in a trial. A third of women/birthing people reported their biggest concern about unstable blood

glucose levels was it leading to complications in the baby, such as neonatal hypoglycaemia. Two thirds of women/birthing people said they'd be willing to participate in a trial, with a further 23% being unsure about participation. 102 parents with experience of diabetes in pregnancy also contributed to a Delphi survey to seek consensus on important aspects of trial design, including frequency of monitoring and outcomes. Parents also attended the subsequent online consensus meeting.

We have a well-established PPI group, formed in 2020, who were active in the design and delivery of the scoping study, which helped to develop the GILD trial. This group is led by co-investigator Plachcinski, an independent parent and public involvement consultant and former National Childbirth Trust (NCT) antenatal facilitator, based in West Yorkshire. She is now supported by co-investigator Aswat, a South Asian woman with experience of diabetes in pregnancy and of supporting women/birthing people in her community with dietary issues, who has joined as a co-investigator. The group also includes two white women with lived experience. Members communicate regularly via a WhatsApp group and attended meetings throughout the scoping study. The group will be expanded further with input from South Asian Health Action and the haPPIE research group to ensure members reflect the diversity of the UK population.

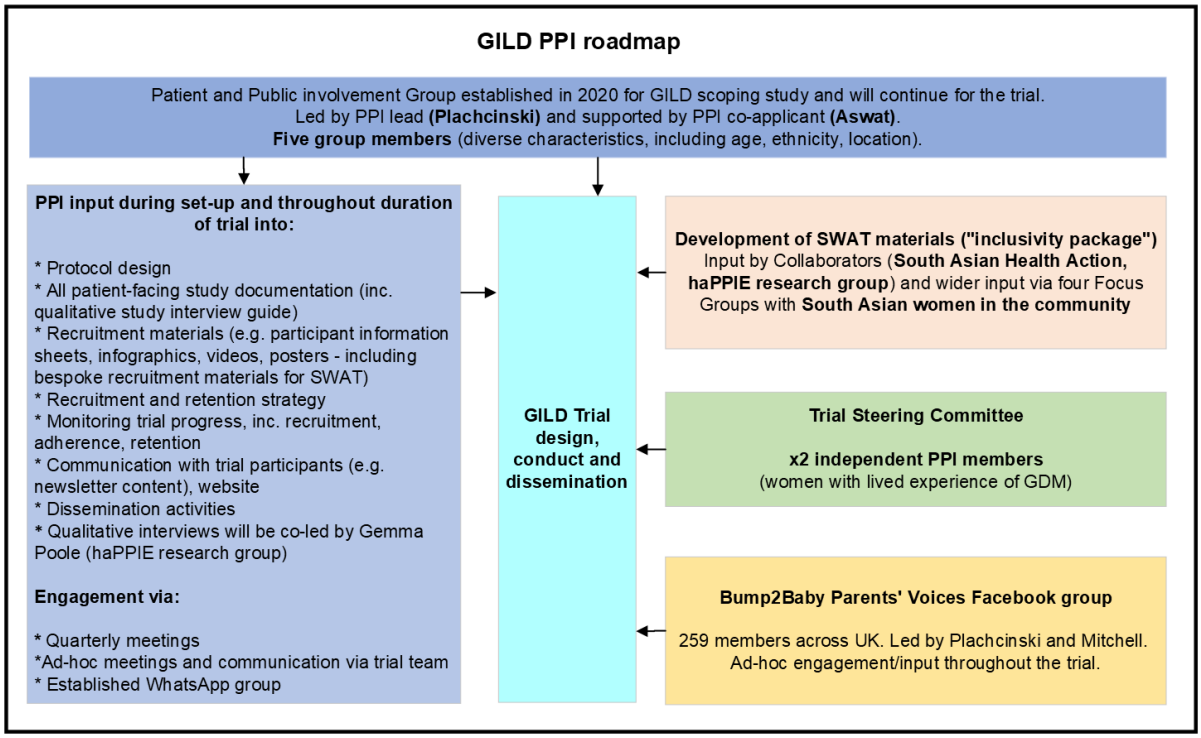
In addition, members of the Bump2Baby Parents' Voices Facebook group (led by Plachcinski and Mitchell) have given ad-hoc input into the development of the scoping study and trial proposal. This group currently has c.260 members, some who have experienced diabetes in pregnancy and other maternal and neonatal complications.

Parents have given substantial input into the outcomes that are being collected in the trial, in particular emphasising the priority of understanding the woman's experience during labour, due to the blood glucose monitoring strategy she is randomised to. They have also pushed the importance of measuring maternal food and fluid intake during labour. For the scoping study, the emphasis was on the language of 'permissive' blood glucose monitoring (as per previous NIHR commissioned call), however with PPI input, we have changed to describing the monitoring strategies as 'more relaxed' and 'tight' control, which is considered language that is more easily understood. Parents have also given input into the non-inferiority margin they would be comfortable with, as described in the Detailed Research Plan.

We have collaborated with the Leicester-based charity, South Asian Health Action (SAHA), to ensure we have considered ways in which we can increase participation of South Asian women. With input from SAHA, Gemma Poole (our collaborator from the haPPIE research group, who support underserved groups) and 3 members of our PPIE group, we have completed the NIHR INCLUDE ethnicity worksheets, to help us consider inclusivity in all aspects of our trial design.

Our PPI activities are visually described on our PPI roadmap (see below).

The GILD PPI roadmap:



Plachcinski and Aswat will lead PPI activities throughout the trial, supported by other members of the team. Whilst Aswat has been a member of the PPI group for some time, she has not previously been a co-investigator on a research study and will therefore be mentored and supported by Plachcinski. Gaps in training identified by PPI members will be supported by Plachcinski and other members of the team as necessary. A roles and responsibilities document will be drafted to ensure all PPI group members are aware of their role within the trial.

The PPI group will meet quarterly throughout the trial, inputting into all aspects. During the set-up phase they will contribute to protocol design, development of study documentation and recruitment materials, in particular considering 'messaging' to women/birthing people with GDM, and the recruitment and retention strategies needed to best engage with women/birthing people with GDM. Once trial recruitment has started, the PPI group will continue to meet quarterly to monitor trial progress, including recruitment, retention and adherence to the blood glucose monitoring strategy. They will help us to communicate with women/birthing people who have participated, by giving input into other communication such as participant newsletters. The PPI group will input into the dissemination and engagement strategy, particularly considering how to communicate the results of the trial with women/birthing people with GDM. In addition to quarterly meetings, the PPI group will continue to communicate via the WhatsApp group already established, and at ad-hoc meetings and via other communication methods as required. PPI members will also give input into the design and delivery of the qualitative component of GILD, in particular giving input into the interview topic guide.

The independent trial steering committee also includes two women/birthing people who have lived experience of GDM.

13. STUDY FINANCES

13.1 FUNDING SOURCE

This study is funded by NIHR Health Technology Assessment (HTA) Programme (Award ID: NIHR159223).
The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

13.2 PARTICIPANT STIPENDS AND PAYMENTS

Women/birthing people taking part in the main trial will receive a £10 token of appreciation. Women/birthing people taking part in the qualitative study will be offered a £25 shopping voucher as a token of appreciation upon interview completion. Health professionals taking part in the qualitative study will be offered the opportunity to enter a £250 prize draw upon completion of the interview.

14. SIGNATURE PAGES

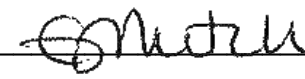
Signatories to Protocol:

Chief Investigator: Professor Kate Walker

Signature: 

Date: 03-Jul-2025

Deputy Chief Investigator: Dr Eleanor Mitchell

Signature: 

Date: 03-Jul-2025

Trial Statistician: Toyin Bello

Signature: ToyinBello
ToyinBello (Jul 3, 2025 12:24 GMT+1)

Date: 03-Jul-2025

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