Continuous Glucose Monitoring Versus Capillary Self-Monitoring In Gestational Diabetes: Protocol for a Randomised Controlled Trial with a Neonatal Primary Outcome

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Abstract

Background: Continuous glucose monitoring improves neonatal outcomes in pregnancies complicated by type 1 diabetes, and its use is expanding into gestational diabetes on the assumption that the same benefit follows. Gestational diabetes differs in pathophysiology, in glycaemic variability, in the proportion of women requiring insulin, and in the duration of exposure, so the extension is an assumption rather than a finding. Trials in gestational diabetes have generally been small and have reported glycaemic rather than neonatal outcomes.

Methods: We describe a protocol for a multicentre, open-label, parallel-group randomised controlled trial. Women with gestational diabetes diagnosed between 24 and 30 weeks will be randomised 1:1 to continuous glucose monitoring or to capillary self-monitoring according to usual care, with identical glycaemic targets and treatment algorithms in both arms. The primary outcome is large for gestational age at birth, defined as birthweight above the 90th customised centile. Assuming a control-arm rate of 20 % and a relative reduction to 14 %, 822 participants per arm give 90 % power at a two-sided 5 % level; allowing 10 % attrition, 1,827 women will be randomised. Secondary outcomes include neonatal hypoglycaemia requiring treatment, neonatal unit admission, caesarean birth, shoulder dystocia, insulin initiation, hypertensive disorders and maternal-reported burden of monitoring.

Discussion: The design is deliberately conservative in two respects. Both arms use identical glycaemic targets, so the trial tests the monitoring technology rather than a combined package of monitoring and intensified targets, which is the design flaw that makes several existing studies difficult to interpret. And the primary outcome is a neonatal one rather than a glycaemic surrogate, because the justification for the technology rests on neonatal benefit and because improvements in glycaemic metrics have repeatedly failed to translate. The protocol states in advance that the trial is underpowered for a control-arm rate below about 17 %, and the interpretation of a null result is fixed before any data are seen.

Keywords: Gestational Diabetes, Continuous Glucose Monitoring, Large For Gestational Age, Randomised Controlled Trial, Study Protocol, Maternal–Fetal Medicine.

1. BACKGROUND AND RATIONALE

Gestational diabetes affects a substantial and rising proportion of pregnancies, and its management rests on achieving glycaemic targets that are themselves derived from observational associations with neonatal size. The monitoring technology used to pursue those targets has been essentially unchanged for decades: intermittent capillary sampling, four to six times daily, recorded by the woman and reviewed at intervals.

Continuous glucose monitoring offers a different picture of the same physiology — interstitial glucose measured every few minutes, with time in range, variability and nocturnal excursions all visible. In type 1 diabetes in pregnancy it has been shown to improve neonatal outcomes, and that finding has understandably increased interest in its use in gestational diabetes.

The extension is not obvious. Type 1 diabetes in pregnancy involves absolute insulin deficiency, exposure from conception, wide glycaemic variability and universal insulin use, and the mechanism by which continuous monitoring helps is plausibly the detection and correction of excursions that intermittent testing misses. Gestational diabetes involves insulin resistance arising in the second half of pregnancy,

exposure measured in weeks, much narrower variability, and a majority of women managed without insulin. Whether the same technology confers the same benefit in that setting is an empirical question that the type 1 evidence does not answer.

Existing trials in gestational diabetes have been mostly small, have often used glycaemic endpoints such as time in range or mean glucose, and have in several cases applied different glycaemic targets in the two arms, which conflates the effect of the device with the effect of a more intensive treatment goal. The result is a literature that reports improvements in glucose metrics without establishing that anything happens to the baby.

1.1 Objectives

Primary. To determine whether continuous glucose monitoring, compared with capillary self-monitoring under identical glycaemic targets, reduces the proportion of infants born large for gestational age to women with gestational diabetes.

Secondary. To compare the arms with respect to neonatal hypoglycaemia requiring treatment, neonatal unit admission, birthweight centile as a continuous measure, caesarean birth, shoulder dystocia, initiation of insulin, hypertensive disorders of pregnancy, gestational weight gain, and the burden of monitoring reported by participants.

2. DESIGN

2.1 Trial design

This is a multicentre, open-label, parallel-group, individually randomised controlled trial with 1:1 allocation and a superiority framework. Blinding of participants and clinicians is impossible because the intervention is a visible wearable device; outcome ascertainment is from measurements made routinely at birth, which limits the scope for detection bias in the primary outcome.

Two design decisions distinguish this protocol from much of the existing literature and are stated here because they determine what the trial can conclude.

Identical glycaemic targets in both arms: Fasting and postprandial targets, the thresholds for initiating pharmacological therapy, and the escalation algorithm are the same in both groups and are specified in the protocol. The trial therefore isolates the effect of the monitoring modality. A design in which the intervention arm is also given tighter targets tests a package and cannot attribute any benefit to the device.

A neonatal primary outcome: Glycaemic metrics are secondary. The clinical case for the technology is that better information leads to better glycaemic control which leads to a better-grown baby, and the last link in that chain is the one that has not been demonstrated in this population. A trial powered on time in range would very probably succeed and would not answer the question.

2.2 Setting and participants

Table 1. Eligibility criteria

Inclusion	Exclusion
Gestational diabetes diagnosed by the local standard oral glucose tolerance test criteria	Pre-existing type 1 or type 2 diabetes
Singleton pregnancy	Multiple pregnancy
Gestation 24 weeks 0 days to 30 weeks 6 days at randomisation	Known major fetal anomaly or growth restriction at randomisation
Age 18 years or older	Already using continuous glucose monitoring
Able to use the device and give informed consent	Planned birth before 34 weeks; skin condition precluding sensor wear

The gestational window is deliberately narrow. Randomising before 24 weeks would include women whose diagnosis followed early testing for other indications and whose pathophysiology may differ; randomising after 31 weeks would leave too short an exposure for any effect on fetal growth to be plausible, since the majority of fetal fat accretion occurs in the final weeks.

2.3 Interventions

Intervention arm: A continuous glucose monitoring sensor is applied at randomisation and worn continuously until birth, with sensors replaced according to manufacturer instructions. Participants and clinicians have real-time access to readings. Review occurs at scheduled antenatal visits using the device summary.

Control arm: Capillary self-monitoring as per usual care, with the same recommended testing frequency, the same recording method and the same schedule of review.

Common to both arms: Identical glycaemic targets, identical criteria and algorithm for initiating and escalating metformin or insulin, identical dietary and activity advice, identical schedule of fetal growth assessment, and identical criteria for timing of birth. Any protocol-driven difference other than the monitoring modality is a threat to the trial's interpretability and will be recorded as a deviation.

3. OUTCOMES AND SAMPLE SIZE

3.1 Outcomes

Table 2. Outcomes

Outcome	Definition	Timing	Source
Primary: large for gestational age	Birthweight above the 90th customised centile for gestation, sex and parity	At birth	Delivery record
Birthweight centile	Customised centile as a continuous measure	At birth	Delivery record
Neonatal hypoglycaemia	Blood glucose below the local treatment threshold requiring intervention	First 48 hours	Neonatal record
Neonatal unit admission	Admission to a neonatal unit for any duration	Birth admission	Neonatal record
Shoulder dystocia	Recorded by the accoucheur using the standard definition	At birth	Delivery record
Caesarean birth	Any caesarean, with planned and intrapartum reported separately	At birth	Delivery record
Insulin initiation	Any insulin started after randomisation	To birth	Clinical record
Hypertensive disorders	Gestational hypertension or pre-eclampsia by standard criteria	To birth	Clinical record
Monitoring burden	Participant-reported measure at 34 weeks	34 weeks	Questionnaire
Glycaemic metrics	Time in range and mean glucose, intervention arm descriptively	To birth	Device and diary

The primary outcome uses a customised rather than population centile because the question concerns fetal overgrowth relative to a baby's own growth potential, and because population centiles misclassify in the directions that matter here — by maternal size, ethnicity and parity, all of which are distributed unevenly among women with gestational diabetes.

3.2 Sample size

The sample size is computed for a two-group comparison of proportions with a two-sided 5 % significance level and 90 % power, using the standard expression

$$n = [z_{1-\alpha/2}\sqrt{(2\bar{p}(1-\bar{p})} + z_{1-\beta}\sqrt{(p_0(1-p_0) + p_1(1-p_1))}]^2 / (p_0 - p_1)^2 \quad (1)$$

with a control-arm rate of large for gestational age of 20 % and a target rate of 14 %, a relative reduction of 30 %. This gives 822 participants per arm, 1,644 in total; allowing 10 % attrition from withdrawal, loss to follow-up and birth outside a participating unit, 1,827 women will be randomised.

Table 3. Sample size across assumed effect sizes (control rate 20 %)

Relative risk	Intervention rate	Per arm	Total	Total with 10 % attrition
0.60	12.0 %	440	880	978
0.70 (assumed)	14.0 %	822	1,644	1,827
0.75	15.0 %	1,212	2,424	2,694
0.80	16.0 %	1,937	3,874	4,305
0.85	17.0 %	3,519	7,038	7,820

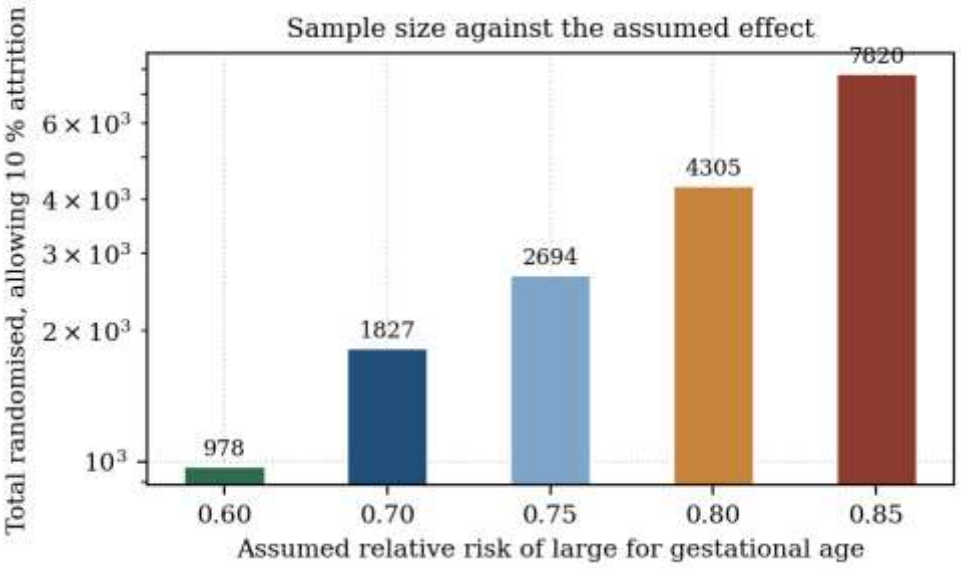

Figure 1. Total randomised against the assumed relative risk, on a logarithmic scale

Table 3 states the design's principal vulnerability plainly. The sample size is exquisitely sensitive to the assumed effect: a relative reduction of 30 % requires 1,827 women, while a reduction of 20 % requires 4,305 and a reduction of 15 % requires 7,820. A 30 % relative reduction in large for gestational age from a monitoring technology alone, with glycaemic targets held constant, is optimistic, and the protocol records that judgement rather than concealing it.

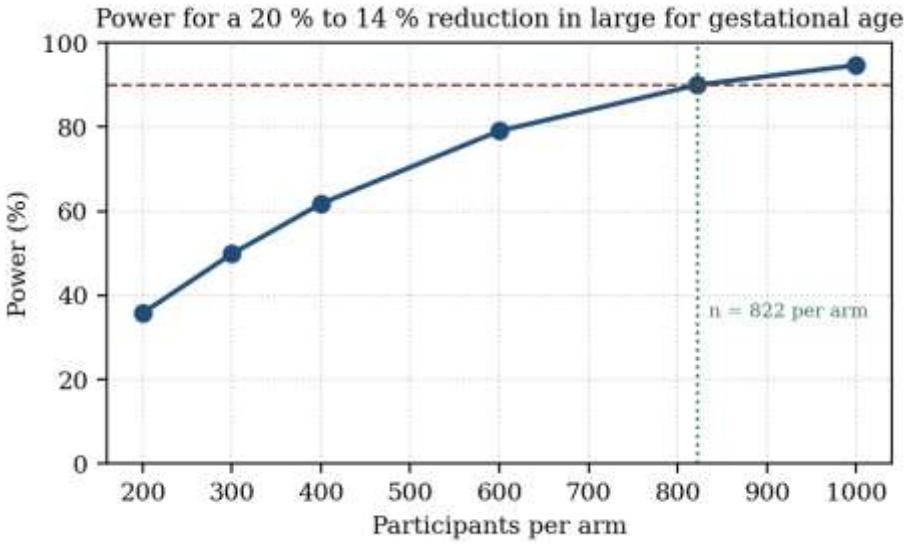

Figure 2. Power against sample size per arm for the assumed effect

Table 4. Power at the planned sample size if the control rate differs from 20 %

Actual control-arm rate	Per-arm sample size that would be required	Power at the planned 822 per arm
14 %	1,247	74.9 %
17 %	997	83.7 %
20 % (assumed)	822	90.0 %
25 %	624	96.1 %
30 %	491	98.7 %

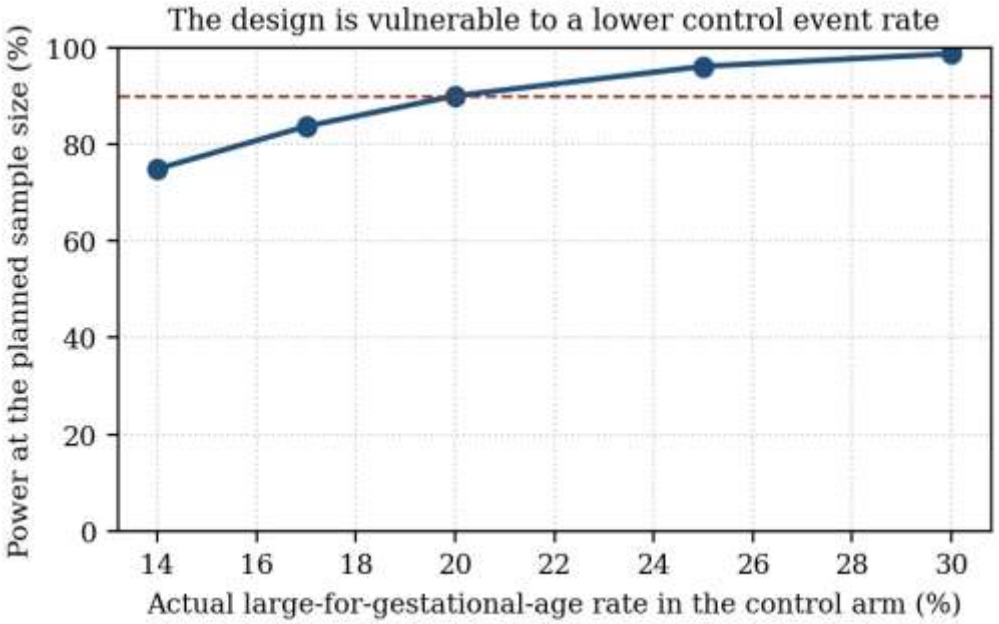

Figure 3. Power at the planned sample size as the control-arm event rate varies

The event rate in the control arm is the input most likely to be wrong and the one the investigators control least. Rates of large for gestational age in treated gestational diabetes vary substantially between populations and with the diagnostic criteria in use, and a rate of 14 % rather than 20 % would leave the trial with 74.9 % power. An internal pilot of the first 60 participants will estimate the control-arm rate from blinded pooled data, and if the observed pooled rate falls below 16 % the sample size will be revised upward by a pre-specified rule rather than by discussion after the fact.

For the principal secondary outcome, neonatal hypoglycaemia requiring treatment, a reduction from 15 % to 10 % would require 918 per arm, so the planned sample provides 86.6 % power. Secondary outcomes are otherwise not powered individually and will be reported with confidence intervals and without claims of confirmatory inference.

3.3 Randomisation and blinding

Participants will be randomised 1:1 by a central web-based system using permuted blocks of random size, stratified by centre, by gestation at randomisation (24–27 versus 28–30 weeks) and by body mass index above or below 30 kg/m^2. Stratification by gestation matters because duration of exposure to the intervention differs materially across the eligibility window, and by body mass index because it is a strong independent predictor of the primary outcome.

Blinding of participants and treating clinicians is not possible. The outcome assessor at birth will not be informed of allocation, although concealment cannot be guaranteed in an open trial; birthweight is measured routinely and is not susceptible to interpretation, which is a further reason for choosing it as the primary outcome. The trial statistician will remain blinded to allocation labels until the primary analysis is complete.

4. CONDUCT AND ANALYSIS

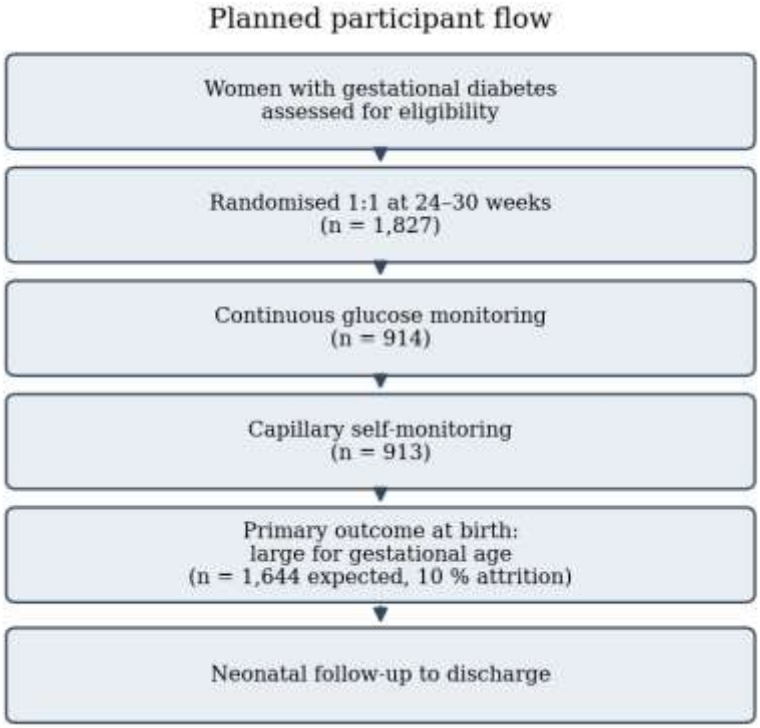

Figure 4. Planned participant flow

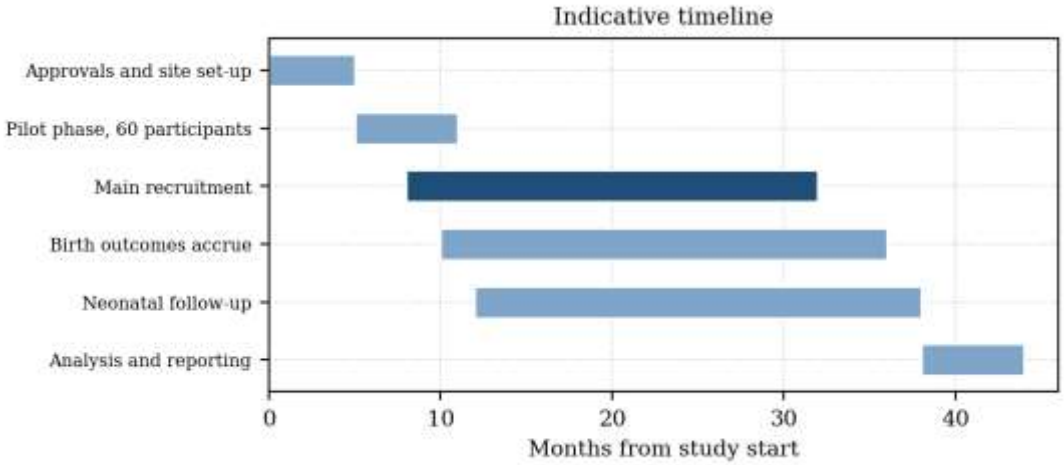

Figure 5. Indicative study timeline

4.1 Statistical analysis

The primary analysis will follow intention to treat, including all randomised participants with a primary outcome available, analysed in the group to which they were allocated. The primary outcome will be compared using a log-binomial model adjusted for the stratification variables, reporting a risk ratio and an absolute risk difference with 95 % confidence intervals. No interim analysis for efficacy is planned.

Table 5. Pre-specified analyses

Analysis	Specification	Status
Primary	Log-binomial model adjusted for centre, gestation stratum and body mass index stratum	Confirmatory

Birthweight centile	Linear model on the continuous customised centile	Pre-specified secondary
Neonatal composite	Hypoglycaemia requiring treatment or neonatal unit admission	Pre-specified secondary
Subgroups	Insulin-treated versus diet-controlled; body mass index stratum; gestation stratum	Pre-specified, interaction tests, interpreted cautiously
Adherence	Sensor wear time in the intervention arm; testing frequency in the control arm	Descriptive; informs the per-protocol analysis
Per protocol	Restricted to participants with sensor wear above 70 % of days	Exploratory, with the limitation stated
Missing data	Multiple imputation if the primary outcome is missing in more than 5 %	Contingent
Glycaemic mediation	Whether any effect on the primary outcome is mediated by glycaemic metrics	Exploratory

The mediation analysis is exploratory and is included for a specific reason. If the intervention reduces large for gestational age without any detectable change in glycaemic metrics, the mechanism is not the one assumed, and that finding would be as informative as the primary result. If it changes glycaemic metrics without changing the primary outcome, that is the pattern already reported in the existing literature and would be worth documenting in an adequately powered trial.

4.2 Ethics, consent and dissemination

Both arms represent monitoring approaches in current use and neither exposes participants to an unlicensed intervention. Written informed consent will be obtained from every participant before randomisation. Approval from a research ethics committee will be obtained before enrolment begins. An independent data monitoring committee will review safety data at the mid-point of recruitment with authority to recommend suspension for evidence of harm only. The protocol, the statistical analysis plan and the results will be published irrespective of direction, and the analysis plan will be finalised before database lock.

Participants will be offered their own glucose data at the end of the trial in both arms, and the intervention arm will be informed at consent that sensors will be removed at birth and are not provided thereafter.

5. DISCUSSION

5.1 Rationale for the design choices

The two decisions described in Section 2.1 — identical targets and a neonatal primary outcome — are what make this trial worth conducting given the studies that already exist. A trial that permits tighter targets in the intervention arm can show a benefit and be unable to say what produced it, and a trial powered on time in range can show a benefit that does not reach the baby. Both designs are cheaper and both have been done.

The cost of these choices is a large sample. Isolating the device effect removes the most plausible route by which the technology might act, namely that better information prompts more aggressive treatment; the protocol accepts that, because a trial of monitoring-plus-tighter-targets tests a policy that could be implemented without the device by simply tightening the targets.

5.2 Anticipated difficulties

Three are worth naming. Sensor adherence will be imperfect and will attenuate any effect toward the null; wear time will be recorded and reported, and a pre-specified per-protocol analysis is included with its limitations stated. Contamination is possible in the other direction if control-arm participants obtain sensors privately, which will be asked about at 34 weeks. And clinicians treating intervention-arm participants may act on information the protocol does not require them to act on — a nocturnal excursion

visible only on continuous monitoring — which is a deviation in principle and is arguably the effect under study; such decisions will be recorded rather than prevented.

5.3 Limitations

The trial is powered for a 30 % relative reduction and would miss a 20 % one, as Table 3 shows. A null result will be reported alongside the minimum detectable effect, and the protocol records in advance that it should not be read as evidence that continuous monitoring is ineffective in gestational diabetes. This interpretation is fixed here so that it cannot be revised once the result is known.

Large for gestational age is an intermediate outcome. It is associated with shoulder dystocia, operative birth and neonatal morbidity, and it is not itself a harm; a trial powered for shoulder dystocia or for a composite of serious neonatal morbidity would be several times larger and is not feasible as a first study. The choice is a compromise and is stated as one.

The trial is open-label, single-country and recruits from participating maternity units, so its findings will describe the populations and diagnostic criteria of those units. Diagnostic thresholds for gestational diabetes differ internationally, and a population diagnosed by more inclusive criteria contains a larger proportion of women at low risk of the primary outcome, in whom any effect would be smaller. Finally, the technology is changing rapidly, and a sensor evaluated over a four-year trial may be superseded before the results are published — a general problem for trials of devices that the protocol manages, by recording the device generation used, rather than solves.

6. CONCLUSION

Continuous glucose monitoring is being adopted in gestational diabetes on the strength of evidence generated in a different disease, and the trials conducted in gestational diabetes itself have largely reported glycaemic outcomes or have confounded the device with a change in glycaemic targets. This protocol describes a trial that holds the targets constant, measures a neonatal outcome, and is powered to detect a 30 % relative reduction in large for gestational age with 1,827 women.

It is published before enrolment so that the assumed effect size, the vulnerability of the design to a lower control-arm event rate, the pre-specified analyses and the stated interpretation of a null result are all on the record in advance of any data.

Declarations

Ethical approval: Not applicable.

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Conflicts of interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions:

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Makbul Hussain Choudhury	✓				✓	✓		✓		✓				✓

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

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