Real Time Continuous Glucose Monitoring in Neonatal Intensive Care

Evaluation of Real Time Continuous Glucose Monitoring in the very preterm infant

Version 5.0

24 April 2019

Clinical Trial Protocol

Trial Title:	Real Time Continuous Glucose Monitoring in Neonatal Intensive Care
Protocol Number:	REACT RCT
IRAS Project ID:	168042
ISRCTN Number:	12793535
Investigational Product:	Evaluation of real time continuous glucose monitor using glucose sensors with paper based algorithm
Protocol Version:	5.0

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I give my approval for the attached protocol entitled Real Time Continuous Glucose Monitoring in Neonatal Intensive Care dated 24 April 2019

Chief Investigator

Name: Dr Kathryn Beardsall

Signature: 

Date: 24 April 2019

Site Signatures

I have read the attached protocol entitled Real Time Continuous Glucose Monitoring in Neonatal Intensive Care 24 April 2019 and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and the GCP Directive 2005/28/EC.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

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3 Abbreviations

BAPM	British Association of Perinatal Medicine
BG	Blood Glucose
BPD	Bronchopulmonary Disease
CA	Competent Authority
CCTU	Cambridge Clinical Trials Unit
CE	Conformité Européenne (European conformity)
CGM	Continuous Glucose Monitor
CRF	Case Report Form
CT	Computed Tomography
DMEC	Data Monitoring Ethics Committee
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECHO	Echocardiogram
EDD	Expected Date of Delivery
EEG	Electroencephalography
EME	Evaluation, Trials and Studies Coordinating Centre
FU	Follow Up
GP	General Practitioner
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
LMP	Last Menstrual Period
LOS	Length of Stay
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NIHR	National Institute for Health Research
NICU	Neonatal Intensive Care Unit
pCRF	Paper Case Report Form
PI	Principal Investigator
rCGM	Real Time Continuous Glucose Monitoring
R&D	Research and Development
RA	Regulatory Agency
REC	Research Ethics Committee
ROP	Retinopathy of Prematurity
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SG	Sensor Glucose
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMC	Trial Management Committee
TMF	Trial Master File
TSC	Trial Steering Committee
USADE	Unanticipated Serious Adverse Device Effect
USS	Ultra Sound Scan

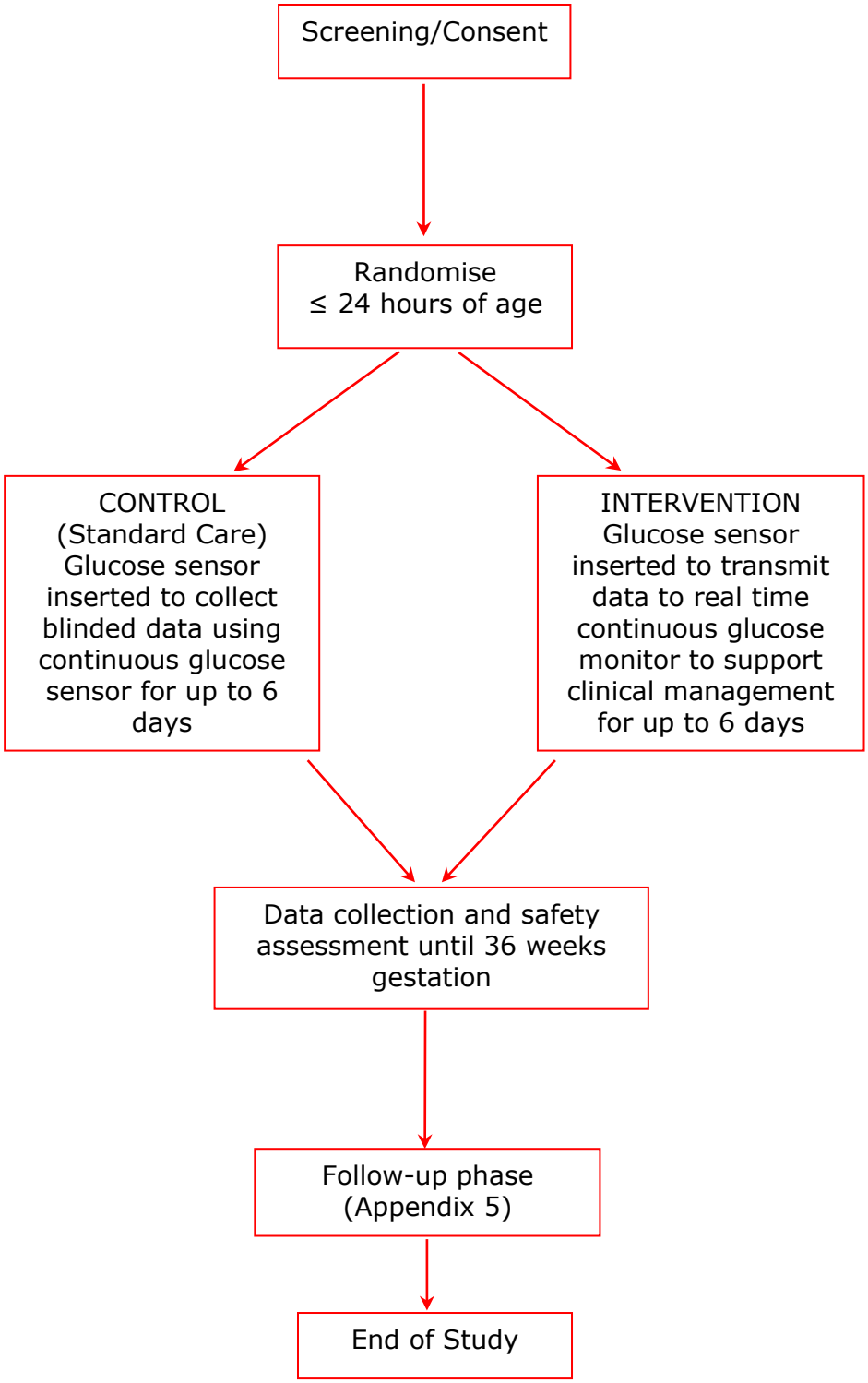
4 Trial Synopsis

Title of clinical trial	Real Time Continuous Glucose Monitoring in Neonatal Intensive Care (REACT)
Sponsor name	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
Medical condition or disease under investigation	Hyperglycaemia in preterm infants
Purpose of clinical trial	To evaluate efficacy, safety and utility of real time continuous glucose monitoring (rCGM) in Neonatal Intensive Care (NICU)
Primary objective	• To evaluate the efficacy of rCGM in helping control levels of glucose in the preterm infant • To evaluate clinical acceptability in the preterm infant • To assess safety in terms of risk for hypoglycaemia in the preterm infant
Secondary objective (s)	• To evaluate the cost-effectiveness and NHS importance of such an intervention
Trial Design	Multicentre Randomised Controlled Trial
Trial Outcome Measures	**Primary Outcome** Percentage of time sensor glucose (SG) in target range of 2.6-10mmol/l within the first 6 days of life in preterm infants **Secondary Outcome** **Efficacy** 1) Mean SG in first 6 days. 2) Percentage of time SG in target of 4-8mmol/l within the first 6 days of life 3) SG variability within individuals as assessed by within-patient standard deviation 4) Percentage of time glucose levels in hyperglycaemic range - SG >15mmol/l **Acceptability** 1) Clinical staff rating score of impact on clinical care 2) Frequency of blood glucose monitoring 3) Clinical use of algorithm

	Safety 1) Incidence of hypoglycaemia defined as any episode of blood glucose >2.2mmol/l and <2.6mmol/l 2) Incidence of hypoglycaemia defined as continuous episode of SG <2.6mmol/l for >1hour 3) Incidence of severe hypoglycaemia defined as any episode of BG ≤2.2mmol/l **Health Economics** ▪ Cost-effectiveness expressed in terms of incremental cost per additional case of adequate glucose control between 2.6mmol/l – 10mmol/l
Sample Size	200 babies
Summary of eligibility criteria	Inclusion Criteria: ▪ Parental informed consent ▪ ≤ 33+6 weeks gestation ▪ ≤ 24 hours of age ▪ Birth weight ≤1200g Exclusion Criteria: ▪ A lethal congenital abnormality known at trial entry ▪ Any congenital metabolic disorder known at trial entry ▪ Neonates who, in the opinion of the treating clinician at trial entry, have no realistic prospect of survival
Randomisation	1:1 ratio between intervention and control Intervention: Real time continuous glucose monitoring (rCGM)with paper based algorithm Control: Standard clinical management with continuous glucose monitoring data blinded to the clinical team
Investigational Medical Device	Real Time Continuous Glucose Monitoring with paper based algorithm
Standard Clinical Management Device	Clinical management according to standard unit protocols with blinded continuous glucose monitoring
Position and site of medical device	Glucose sensor will be placed in subcutaneous tissue
Duration of intervention of a participant	6 days
Maximum duration of assessment of a participant	Until equivalent to 36 weeks corrected gestational age. Appendix 5 details follow-up phase.

Procedures: Screening & enrolment	Participants will be screened within 24 hours of life and informed parental consent will be obtained prior to the performance of any study specific procedures
Baseline	▪ Inclusion/Exclusion criteria ▪ Randomisation ▪ Demography ▪ Clinical condition
Intervention period	Cases Day 1 – Day 6 ▪ Insertion of glucose sensor ▪ Glucose data collection using continuous real time glucose monitor ▪ Glucose control guided with modified paper based algorithm ▪ Clinical details will be recorded ▪ Day 3 – Clinician questionnaire Controls Day 1 – Day 6 ▪ Insertion of glucose sensor ▪ Glucose data collection using continuous glucose monitor blinded to the clinical team ▪ Glucose control according to standard clinical practice ▪ Clinical details will be recorded
Follow up period post intervention	**Day 7 to 36 weeks gestation** Day 7 Removal of glucose sensor Clinician questionnaire Cases will have parent questionnaire Day 14 Sensor site check Clinical details will be recorded Length, weight, head circumference
End of study	36 weeks corrected gestational age Clinical condition Length, weight, head circumference Assessment of resource use Level of care received (BAPM classification)
End of Trial	The trial will end when all participants have completed the 36 week gestation assessment. Appendix 5 details follow-up phase.
Procedures for safety monitoring during trial	Measurement of blood glucose by point of care technology
Criteria for withdrawal of patients from Intervention	Participant has an SAE/SADE that, in the opinion of the CI, PI or parent would affect their ability or would be harmful for them to continue participating in the trial.

5 Trial Flow Chart



6 Introduction

6.1 Background

Increasing numbers of infants are being born preterm. These infants require intensive care and have a high risk of early mortality and short term morbidity [1]. Surviving infants have a high incidence of long term health problems, including learning difficulties with significant long term costs to the NHS and society [2]. Treatable neonatal causes of long term health problems have been difficult to establish. National Priorities for Research have highlighted investigation of the management of babies born too early or too small, and evaluation of the reasons for variations in outcome of "high risk" neonates. Early postnatal glucose control may be an important modifiable risk factor for clinical outcomes. In utero, glucose levels are normally maintained between 4-6mmol/l [3], but infants born preterm are at risk of both hyperglycaemia (20-86%, depending on how it is defined) and hypoglycaemia (<2.6mmol/l, 17%) [4].

Existing Research

Hyperglycaemia and hypoglycaemia in the preterm baby

Hyperglycaemia and hypoglycaemia have both been associated with increased mortality and morbidity of preterm babies [5, 6]. Hyperglycaemia can lead to acute problems of a persistent osmotic diuresis and metabolic acidosis which can be difficult to control and has been associated with increased risk of intraventricular haemorrhage [7]. Hyperglycaemia has also been associated with increased long term morbidity including increased risk of retinopathy of prematurity [6, 8, 9]. Pivotal single centre studies in adult intensive care demonstrated that tight glycaemic control can reduce both mortality and morbidity [10]. However these results have been difficult to replicate due to the risk of hypoglycaemia [11]. A trial in paediatric intensive care targeted to reduce hyperglycaemia, demonstrated a reduction in length of intensive care admission and mortality but a significant increase in hypoglycaemia [12]. This is of particular concern in attempts to translate these advances to the study of very preterm infants who have very varied insulin sensitivity which increases the risk of hypoglycaemia. In addition the developing brain appears to be particularly vulnerable to both hyperglycaemic [13], and hypoglycaemic insults. A recent Cochrane review has highlighted the need for further studies into the impact of interventions to improve glucose control in these infants [5].

Current Glucose monitoring

Although glucose monitoring is undertaken in all very preterm infants, it is currently limited to intermittent blood sampling, with long periods when glucose levels are unknown. In contrast other physiological parameters such as oxygen saturation, blood pressure and heart rate are all monitored continuously to prevent wide fluctuations. It is increasingly thought that fluctuations in glucose levels may also have a significant impact on long term outcomes [14]. The reason for the intermittent nature of glucose measurement is that current methodologies for measurement of glucose levels is by blood sampling either from a central arterial line or by heel prick and current practice in neonatal intensive care aims to reduce the frequency of handling of babies as this has been shown to improve outcomes. Due to the very small circulating volumes it is also important to minimize the amount of blood samples that are taken. In order to fully understand the clinical significance of hyperglycaemia and hypoglycaemia it is imperative that robust data is available on their true prevalence throughout the period of intensive care. In addition if clinical interventions to optimise glucose control are to be safe and effective in the intensive care setting robust methods of monitoring glucose levels in real time need to be in place.

Continuous glucose monitoring

A range of methods have been attempted to develop the possibility of continuous glucose monitoring. Currently the only method used in clinical practice for the management of patients with diabetes mellitus involves measurement of interstitial glucose levels which are calibrated against blood glucose measurements. These devices comprise a disposable subcutaneous oxidase-based platinum electrode that catalyses interstitial glucose generating an electrical signal which is transmitted to a monitor for recording or display. There are 3 companies with devices on the market for continuous glucose monitoring: Dexcom (San Diego CA, USA), Abbott (Berkshire, UK) and Medtronic (Northridge, CA, USA). However due to the size of preterm infants, issues of insertion and attachment to these small babies only the Medtronic devices are currently practical for use in the preterm infant. Early models collected data in real time but this data could only be downloaded retrospectively to be reviewed and used to guide clinical treatment. This is useful in the setting of research and for stable patients with diabetes to review patterns of glucose control over time. As such these devices have been used in the preterm infant without side effects and have demonstrated significant periods of both hyperglycaemia and hypoglycaemia that were undetected clinically [15-17]. Newer models have been developed in which the data can be viewed in real time, providing information on glucose trends with the potential for both identifying episodes of hyperglycaemia and hypoglycaemia and the possibility of earlier intervention and prevention.

Development of real time CGM

The development of real time continuous glucose monitors (rCGMs) provides the opportunity for updated data on glucose levels to be recorded every 5 minutes and viewed continuously. A number of different devices are available for clinical use and are increasingly found to help reduce HbA1c and glycaemic variability in patients with type I diabetes without increasing the risks of hypoglycaemia. These devices allow patients to monitor their glucose levels by displaying both absolute glucose concentrations as well as trends. Their use has been trialled in adult intensive care and in patients requiring cardiac surgery. These studies have been limited but have shown accuracy and safety in the cardiac surgical patients, and the ability to reduce the risk of hypoglycaemia in adult intensive care [18]. Some have raised concerns about the lack of absolute sensitivity of individual readings at glucose thresholds whilst emphasising the potential importance of rCGM as an early warning system for both hyperglycaemia and hypoglycaemia [19]. However the studies have highlighted the need for methodologies that can provide real time data and allow adjustment of clinical management in the setting of a rapidly changing clinical picture of intensive care [20]. These benefits have been seen in adult intensive care where blood glucose levels are routinely measured much more frequently than in neonatal intensive care (NICU). Therefore the potential for benefits in the setting of NICU where the frequency of blood glucose measurements is dramatically more limited is likely to be more clinically significant. Key recent developments in these devices include extended life of sensors (previously 72 hours) which can now remain in situ for 6 days and have been used up to 7 days in the REACT feasibility study (REC Ref: 14/EE/0127). In addition there have changes to the sensor construction and the calibration algorithms which have led to improved overall accuracy [21]. This is particularly important in terms of sensitivities to detect threshold levels of hypoglycaemia and hyperglycaemia.

Previous use of CGM in neonates

There is limited use of continuous glucose monitoring in neonatal intensive care. We have used blinded CGM devices as part of an international multicentre trial in the preterm infant and assessed the accuracy of these devices compared to current clinical practice [4, 22]. These studies suggested that the value of the CGM would be in providing early warning of fluctuations in glucose levels to guide the need for blood glucose assessment and that by providing a continuous read out episodes of hyperglycaemia and

hypoglycaemia could be anticipated and therefore avoided [22]. We have also undertaken single centre pilot studies of the real time monitors in preterm infants requiring intensive care. These studies have demonstrated that the sensor glucose values are comparable with blood glucose values (REACT feasibility study REC Ref: 14/EE/0127). These studies also provide provisional data that the use of continuous glucose monitoring could help to reduce periods of hyperglycaemia without increasing the prevalence of hypoglycaemia (improving glucose control in the preterm IMPP REC Ref: 11/EE/0445). The current study will help to determine whether real time continuous glucose monitoring with support from a paper-based algorithm can help improve the management of glucose control as part of a randomised controlled trial before being considered as standard clinical care.

6.2 Clinical Data

Safety and Efficacy

This is a low risk study involving devices that have been CE marked (manufacturer's declaration that the product meets the requirements of the applicable EC directives) for use in both adults and children with diabetes. The main safety issues are around nursing staff using rCGM to guide clinical management rather than checking blood glucose levels if required when glucose levels are outside the normal range. However, the feasibility study (REACT feasibility study REC ref: 14/EE0127) helped to develop clear clinical guidelines and staff will be trained to ensure that rCGM is seen to augment normal blood glucose assessment not to replace it. Early mortality and short term morbidity data will be recorded as part of the CRF

7 Rationale for Trial

Detecting fluctuations in glucose levels in real time has the potential to reduce the prevalence of both hyperglycaemia and hypoglycaemia in the preterm infant. Real time devices have been shown to be beneficial in adult intensive care and need validation in the NICU. The use of rCGM alone may help to optimise glucose control but validation of its use would also assist in the trial of alternative interventions which otherwise may put babies at risk of either hyperglycaemia or hypoglycaemia. This will not only enhance the short term management of glucose control in infants requiring intensive care but by reducing the risks associated with both hyperglycaemia and hypoglycaemia may impact on long term clinical outcomes.

8 Trial Design

8.1 Statement of design

This is a multicentre interventional, randomised controlled trial of rCGMS with paper based algorithm (Appendix 1) compared to standard clinical management (control).

8.2 Number of Centres

The study will identify eligible participants through a minimum of 5 level 3 NICUs in Europe. However, if after 10 months of active recruitment the trial is struggling to recruit babies, then further sites will be approached to join the study to ensure that the recruitment target is met within the planned and agreed timescale.

8.3 Number of Participants

Based on data from a feasibility study and historical control data, we conservatively assume that the SD of the primary endpoint is 22%. A sample size of 200 participants will enable a treatment effect of a 10% increase in the mean value of the primary endpoint to be detected with 90% power using a two-sided 5% significance test in the primary analysis. Based on a consensus of expert opinion drawn from the TSC, DMC and TMG, a difference of 10% is believed to be of minimal clinical relevance.

It is expected that a small number of patients will be withdrawn from the study. Reasons for withdrawal from intervention include transfer to participant's local NICU, withdrawal of parental consent or death. Therefore, recruitment will continue until 200 babies have provided a minimum of 5 days recorded data, captured by the CGM or rCGM.

8.4 Participants Trial Duration

We will recruit potential participants within 24 hours of birth and continually monitor their glucose levels for 6 days. Data will be collected until 36 weeks corrected gestational age. Therefore the duration of the study will vary in length but be from the participant's birth date up to 36 weeks corrected gestational age.

8.5 Trial objectives

8.5.1 Primary objectives

- To evaluate the efficacy of rCGM in helping control levels of glucose in the preterm infant
- To evaluate clinical acceptability in the preterm infant
- To assess safety in terms of risk for hypoglycaemia in the preterm infant

8.5.2 Secondary objective

- To evaluate the cost-effectiveness and NHS importance of such an intervention

8.6 Trial Outcome Measures

8.6.1 Primary outcome measure

Percentage of time sensor glucose (SG) in target of 2.6-10mmol/l within the first 6 days of life in preterm infants

8.6.2 Secondary outcome measures

8.6.2.1 Efficacy

1) Mean SG in the first 6 days of life
2) Percentage of time SG in target of 4-8 mmol/l within the first 6 days of life
3) SG variability within individuals as assessed by within-patient standard deviation
4) Percentage of time glucose levels in hyperglycaemic range – SG >15mmol/l

8.6.2.2 Acceptability

1) Clinical staff rating score of impact on clinical care
2) Frequency of blood glucose monitoring
3) Clinical use of algorithm

8.6.2.3 Safety

1) Incidence of hypoglycaemia defined as any episode of blood glucose >2.2mmol/l and <2.6mmol/l
2) Incidence of hypoglycaemia defined as continuous episode of SG <2.6mmol/l for >1hour
3) Incidence of hypoglycaemia defined as any episode of BG ≤2.2mmol/l

8.6.2.4 Health Economics
Cost-effectiveness expressed in terms of incremental cost per additional case of adequate glucose control between 2.6mmol/l – 10mmol/l

8.6.3 Exploratory outcome measures

1) Mortality before 36 weeks corrected gestational age
2) Maximum severity of ROP across all retinal examinations (International Classification of Retinopathy of Prematurity, 2005).
3) Bronchopulmonary dysplasia (BPD: need for supplemental oxygen or respiratory support at 36 weeks corrected gestational age)
4) Microbiologically confirmed or clinically suspected late onset invasive infection from trial entry until hospital discharge
5) Necrotising enterocolitis requiring surgical intervention (including peritoneal drainage) or causing death
6) Patent ductus arteriosus requiring medical or surgical treatment
7) Maximum grade of intracranial haemorrhage before discharge (Papile and Burstein grading)
8) Growth (weight, length and head circumference at the end of week 1 and at 36 weeks corrected gestation)
9) Nutritional intake during the first week of life (carbohydrate, protein and lipid)
10) Use of insulin during the first and second week of life
11) Follow-up phase described in Appendix 5

9 Selection and withdrawal of participants

9.1 Inclusion Criteria

To be included in the trial the patient needs:

- Parental informed consent
- ≤ 33+6 weeks gestation
- To be ≤ 24 hours of age
- Birth weight ≤ 1200g

9.2 Exclusion Criteria

The presence of any of the following will preclude patient inclusion:

- A lethal congenital abnormality known at trial entry
- Any congenital metabolic disorder known at trial entry
- Neonates who, in the opinion of the treating clinician at trial entry, have no realistic prospect of survival

9.3 Treatment Assignment and Randomisation Number

Babies will be randomised in a 1:1 ratio into control and intervention arms of the study using a web based randomisation system, Tenalea. Prior to randomisation, investigators will need to confirm that eligibility criteria are met and exclusion criteria do not apply. The randomisation will use blocked stratified randomisation. The stratification factors will be to recruiting centres and gestation (<26 weeks gestation, >=26 weeks gestation). A detailed specification of the randomisation system will be prepared in advance. This is an open study in which the clinical staff, research team and parents will be aware of the study arm and intervention.

Standard care (Control)
These infants will have their glucose control monitored and managed according to standard clinical practice using point of care blood glucose monitoring. Glucose and insulin delivery will be prescribed according to the standard guidelines within each unit. For

consistency across sites these point of care glucose measurements will be standardized by providing all units with Nova StatStrip® meters and training staff in their use.

These babies will in addition have a subcutaneous sensor inserted – Enlite® (Medtronic) inserted that will be linked to a Medtronic MiniMed® 640G System. The infusion functionality of the MiniMed® system will NOT be used. The device will collect glucose data continuously but the clinical team will be blinded to the data – the display screen will be obscured by a cover fastened by a tamper proof seal. All sensors will be inserted by appropriately trained staff.

Real Time Continuous Glucose Monitoring Device with paper based algorithm (Intervention)
These infants will have the same subcutaneous glucose sensor inserted Enlite® (Medtronic) but it will be linked to a device with real time read outs - using the monitoring function of the Medtronic MiniMed® 640G System. The infusion functionality of the MiniMed® system will NOT be used. Clinical management of glucose control will then be guided by specifically designed paper based algorithm to support staff to use the additional data available from real time monitoring to guide timing of blood glucose measurement and changes in clinical management. This algorithm was developed during the REACT feasibility study (REC Ref: 14/EE/0127) (Appendix 1). All sensors will be inserted by appropriately trained staff. To ensure consistency between neonatal units point of care blood glucose levels will be measured on the Nova StatStrip® glucose monitoring system which will be provided as part of the study.

9.4 Participant withdrawal criteria

The parent of a participant may terminate their baby's participation in the study at any time without necessarily giving a reason and without any personal disadvantage to themselves or the baby. An investigator can stop the participation of a participant after consideration of the benefit/risk ratio. Reasons for participant withdrawal including death will be recorded in the CRF and reported to the coordinating centre within 48 hours of awareness.

Data from withdrawn, consented participants will be kept and may be included in the trial analysis unless the parents specifically request for the data to be destroyed. If the baby moves to another hospital the research team, with parental consent, will use NHS databases or contact other hospitals involved in the baby's care to obtain follow up data. Parents themselves may also be contacted for information to complete data collection. Primary reasons for withdrawal may include: Serious Adverse Event (SAE), withdrawal of consent, loss to follow up or trial closed or terminated.

Participants withdrawn from the study will be replaced.

10 Medical Devices

10.1 Enlite® sensor

The Enlite® sensor (Medtronic, Northridge, CA, USA) is a CGM sensor which received CE mark in 2013 (CE certificate No. 21024). The sensor comprises a disposable subcutaneous oxidase-based platinum electrode that catalyses interstitial glucose generating an electrical current every 10 seconds which is transmitted to a monitor for display and/or recording. The data are recorded and/or displayed as an averaged value every 5 minutes, giving a total of 288 readings per day. Glucose values outside the range 2.2-24.0 mmol/l (40-430 mg/dl) are reported as < 2.2 mmol/l (40 mg/dl), or >24 mmol/l (430 mg/dl) respectively.

Figure 1: Enlite® sensor

The sensor is inserted subcutaneously (into the thigh) by hand, NOT using the standard insertion device, thus ensuring the sensor is inserted into the subcutaneous tissue. The sensors are soft and flexible, approximately 8.75mm in length and are mounted inside a hollow needle to allow for subcutaneous insertion. Once the sensor is inserted the introducer needle is withdrawn, and the sensor is attached to a small Guardian™ Link transmitter (CE Mark 2013; Certificate No. 8858) for data transfer to the MiniMed® 640G System for data viewing. The sensor is then secured with a clear occlusive dressing (again trimmed to ensure minimal contact with the infant's skin), so that the insertion site can be inspected daily. A blood sample is required every 12 hours to ensure calibration of the sensor. Sensors will be removed at the end of 6 study days.

Figure 2: The Enlite® sensor with Guardian™ Link transmitter attached

10.2 MiniMed® 640G System

The MiniMed® 640G System is indicated for glucose monitoring and for continuous delivery of insulin, for the management of diabetes mellitus in persons requiring insulin. **Monitoring equipment only will be used for this study**. The system being used comprises linking the Enlite® sensor (Medtronic, Northridge, CA, USA) using the Guardian™ Link transmitter to the MiniMed® 640G which then displays the glucose data in real time. The MiniMed® 640G as well as displaying continuous glucose values stores this data so that it can be analysed to track patterns and improve glucose management. Glucose data can be downloaded to a computer for analysis of historical glucose values. The continuous glucose values provided by the MiniMed® 640G are intended to provide an indication that a confirmation blood glucose measurement may be required. This device received CE mark in 2014 (CE certificate No. 8857).

Figure 3: MiniMed® 640G System

11 Procedures and assessments

Data collection will be undertaken from birth to 36 weeks corrected gestational age. If the participant is discharged, follow up assessments may take place in the clinical setting or at research facilities of approved participating sites or in the home setting. Data will be collected at each participating site and sent to the coordinating centre in Cambridge. Study procedures and assessments are listed in Table 1.

11.1 Screening evaluation

11.1.1 Screening/Baseline Assessments

Screening will be undertaken in collaboration with the clinical team. Families will be approached after the clinical team have confirmed eligibility and that the family is happy for them to do so.

11.1.2 Participant Registration

Prior to registration informed consent will be taken from the participant's parent/legal guardian by a suitably qualified person designated by the PI. Following this procedure, the randomisation system Tenalea will be used to randomise patients. This procedure will be explained in detail in the Trial Manual and produced prior to the trial initiation.

11.2 Baseline Assessments

All participants will have a clinical assessment on Day 1. The mother's pregnancy and delivery history will also be recorded in addition to the data points listed in the schedule of assessments (11.4).

11.3 Trial Assessments

11.3.1 Assessment of Efficacy

This will be assessed by comparison of data collected by real time CGMS in the intervention arm and blinded CGMS in the control infants. Clinically recorded BG measurements will also be recorded

11.3.2 Assessment of Clinical Acceptability

Parents, nurses and medical staff, caring for babies in the study will be asked to complete study specific questionnaires. Compliance using the study algorithm will be monitored and recorded as part of study procedure.

11.3.3 Assessment of Safety

This will be assessed in 3 areas: incidence of hypoglycaemia measured as part of clinical care (blood glucose levels) and after review of sensor glucose data; device safety through adverse device effect reporting; and acute mortality and morbidity outcomes as part of the CRF.

11.3.4 Assessment of Costs for Economic Evaluation

Data will be collected on the health service resources used in the treatment of infants during the period between randomisation and 36 weeks gestation. Data collection forms will record the duration and intensity of neonatal care, based on standard criteria for level of care, as well as neonatal complications. Details of the resources associated with glucose monitoring, as well as staff time, tests, procedures, drugs and equipment will be recorded. Current UK unit costs will be applied to each resource item to value total resource use in each arm of the trial. A *per diem* cost for each level of neonatal care will be based on Department of Health reference costs calculated on a full absorption costing basis. The unit costs of clinical events that are unique to this trial will be derived from the hospital accounts of the trial participating centres, although primary research that uses

established accounting methods may also be required. Assessments are listed in 11.4.

11.3.5 Timing of Assessments

All participants will already be hospitalised in a level 3 NICU and it is expected that the majority of participants will still be hospitalised at 36 week gestation assessment. In the event where participants have been discharged from the recruiting centre, a time window of +/- 7 days will apply to both follow up assessments.

11.3.6 Assessments at Time Point

Time points are listed in the schedule of assessments (11.4) and described further in the Trial's study manual. Data will be collected from birth to 36 weeks corrected gestational age. It is expected that approximately 50% of babies will be transferred to local hospitals or home prior to 36 weeks corrected gestational age. At UK sites the local study team will follow progress and complete data collection of each participant recruited in their site through BadgerNet UK which collects live perinatal patient data whilst endeavouring to keep in contact with the parents and/or local paediatrician to gather information to complete data collection. In non UK sites the local study team will follow progress and complete data collection of each participant recruited in their site through locally available databases whilst endeavouring to keep in contact with the parents and/or local paediatrician to gather information to complete data collection.

11.3.7 End of Trial Participation

Participants enrolled into this trial will already be receiving the appropriate standard of care, and this care will be continued following the end of the trial. Participants will finish the study at 36 weeks corrected gestational age. Confirming follow-up contact with families and capturing subsequent neurodevelopmental outcomes including weight and height of participants is described in Appendix 5.

Parental consent will be sought upon joining the study to confirm that parents are happy to be contacted for future follow up assessments of their baby and about future research studies organized by the University of Cambridge.

11.4 Schedule of Assessments

	≤ 24 Hours of Age	Trial Assessments			Final Assessment
Day	Study Day 1	Study Days 2 - 6	Study Day 7	Study Day 14	36 weeks corrected gestation
Assessments					
Informed Consent	×				
Inclusion/Exclusion	×				
Demography - NICU admission date - Name of referring Unit, if applicable - Date & time of birth - Sex - Gestational age at time of birth - Ethnicity	×				
Randomisation - Date of randomisation/person randomising - Case or control	x				
Maternal Pregnancy & Delivery History - Date of LMP - Date of EDD - Antenatal history - Singleton/Multiple birth – ranking - Method of delivery - Apgar scores - Resuscitation history - Temperature on Admission - Base excess on Admission - Birth weight/Length/Head Circumference	×				

	≤ 24 Hours of Age	Trial Assessments			Final Assessment
Day	Study Day 1	Study Days 2 - 6	Study Day 7	Study Day 14	36 weeks corrected gestation
AE/SAE/ADE/SADE	**x**	**x**	**x**	**x**	**x**
Specific Concomitant Medications	**X**	**x**	**X**		
Clinical care - Medication - Oral/IV intake – protein, lipid and dextrose - Total daily dose of Insulin - Record hypoglycaemia BG >2.2 - <2.6mmol/l - Record hypoglycaemia BG <2.2mmol/l - Record time and result of BG, POC, lactate & ketones - Record hypoglycaemia SG <2.6mmol/l - Record hypoglycaemia SG <2.2mmol/l - Insulin requirement from Day 7	**X** **x** **x** **x** **x** **x** **x** **x**	**X** **x** **x** **x** **x** **x** **x** **x**		**x**	
Baby's clinical condition/Care Record - Cardiovascular - PDA - Respiratory support - Gastrointestinal - NEC - Intraventricular Haemorrhage - Sepsis					**x**
Growth Assessment - Weight/Length/Head Circumference			**x**	**x**	**x**

	≤ 24 Hours of Age	**Trial Assessments**			**Final Assessment**
Day	Study Day 1	Study Days 2 - 6	Study Day 7	Study Day 14	36 weeks corrected gestation
Insertion of Glucose Sensor - Date & time of insertion - Insertion site - Sensor Lot no. - Sensor expiry date - Monitor details	**x**				
Sensor site check	**x**	**x**	**x**	**x**	**x**
Removal of Glucose Sensor Date of removal			**x**		
Data Monitoring with rCGM/CGM	**x**	**x**			
Recording use of paper based algorithm (Appendix 1) regarding administration of Insulin & 20% Dextrose	**x**	**x**			
Parent & Clinician Questionnaires[1]		**X**	**x**		
Assessment of Resource Use - Mode of transport for admission/transfer - LOS (in days) at each level of neonatal care - Record number(s) of USS, EEG, MRI, ECHO, ECG, CT Scan - Record number of any other diagnostic tests/ procedures/ reviews carried out - Number of surgical procedures carried out					**x**
ROP – Maximum grade of ROP and confirmation of vascularised/not vascularised					**x**
Record number of days of each level of care required using BAPM definition					**x**
Discharge date/transfer date (record destination)/Details of Death if applicable	**x**				

[1]Clinician questionnaire given on Day 3 and Day 7. Parent questionnaire given on Day 7.

11.5 Trial Restrictions

There are no trial restrictions for this study population.

12 Assessment of Safety

Definitions from 'Guidelines on Medical Devices, Clinical Investigations: Serious Adverse Event Reporting' (under directives 90/385/EEC and 93/42/EEC).
Defined in 8.6.2.3.

Recording of all adverse events must start from the point of Informed Consent (beginning of the trial) regardless of whether a patient has yet received any study procedure until completion of 36 weeks corrected gestation assessment. Appendix 5 provides details of simple follow up at 2 years corrected gestational age and as such adverse event reporting will not apply to this study period from 36 weeks corrected gestational age until end of study.

12.1 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

- This includes any adverse event resulting from insufficiencies or inadequacies in the instruction for use, the deployment the implantation, the installation, the operation, or any malfunction of the investigational medical device.
- This includes any event that is a result of a use error or intentional misuse.

12.2 Adverse Event (AE)

12.2.1 Definition of Adverse Event

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device.

- This includes events related to the investigational device or the comparator.
- This includes events related to the procedures involved (any procedure in the clinical investigational plan)
- For users or other persons this is restricted to events related to the investigational medical device.

12.2.2 Device Deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

12.2.3 Investigational Medical Device

Medical device being assessed for safety or performance in a clinical investigation, this includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

12.3 Serious Adverse Device Effect (SADE)

12.3.1 Definition of Serious Adverse Device Effect

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

12.4 Serious Adverse Event (SAE)

12.4.1 Definition of Serious Adverse Event

Adverse event that:

a) led to death
b) led to a serious deterioration in health that either:
    1) resulted in a life-threatening illness or injury, or
    2) resulted in a permanent impairment of a body structure or a body function, or
    3) required in-patient hospitalisation or prolongation of existing hospitalisation, or
    4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

12.5 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

- Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

12.6 Expected Adverse Device Effects/Expected Adverse Events

12.6.1 Expected Adverse Device Effects

Insertion failure - the sensor may be withdrawn into the needle hub at time of insertion. This will result in absence of signal and mean that the sensor will need replacement.

Localised infection at sensor site - although not previously reported, this would not be unexpected due to prematurity of babies recruited. The site will be examined prior to insertion of the sensor to check for cuts, abrasions and broken skin. The sensor will be inserted using aseptic technique and a clear dressing will be used to secure the sensor thus enabling daily checks for signs of infection.

12.6.2 Expected Adverse Events

Hypoglycaemia is a foreseeable adverse event in premature babies. If blood glucose level falls below 2.6 mmol/l, intravenous lines should be reviewed and additional dextrose given. This should prevent BG falling to less than 2.2mmol/l. Please refer to section 12.7.3 when recording and reporting BG <2.6mmol/l during study days 1-7.

12.6.3 Recording Expected Adverse Device Effects/Expected Adverse Events

Expected adverse device effects will be assessed and managed by the site PI and recorded in the medical notes and CRF (safety log). All episodes of hypoglycaemia <2.6mmol/l will be recorded in the CRF (safety log) during the intervention period (study day1-7) of the trial and reported to the coordinating centre (section 12.7.3). Following the intervention period the number of episodes of hypoglycaemia <2.6mmol/l will be captured in the CRF at day 14 and at the 36 weeks corrected gestation assessment.

12.7 Expected Serious Adverse Device Effects (SADE)/Expected Serious Adverse Events (SAE)

12.7.1 Expected Serious Adverse Device Effects

There are no known Expected Serious Adverse Device Effects.

12.7.2 Expected Serious Adverse Events

In this study population of preterm infants, the 'natural' mortality and morbidity is expected to be high. This includes death, culture positive infection, severe hypoglycaemia (falling less than 2.6mmol/l), seizures, necrotising enterocolitis or focal, intestinal perforation, Broncho-pulmonary dysplasia, persistent pulmonary hypertension, thrombocytopenia, intracranial abnormality (haemorrhage or focal white matter damage) on cranial ultrasound scan or other imaging and secondary hydrocephalus, pulmonary haemorrhage, patent ductus arteriosus, renal failure, retinopathy of prematurity requiring retinal surgery, jaundice, apnoea, hypothermia, recurrent desaturations, re-ventilation, hypotension, hypertension, arrhythmias and coagulopathy.

Therefore, following discussions with the MHRA the following reporting requirements have been agreed (12.7.3)

12.7.3 Recording and Reporting Expected Serious Adverse Events

12.7.3.1 During the Intervention period of the study (study days 1-7)

The following expected SAEs will need to be recorded in the CRF (safety log) and reported using the safety report form to the sponsor within 24 hours of awareness of the event:

1. Death
2. Culture positive infection
3. Severe hypoglycaemia (falling less than 2.6mmol/l)
4. Seizures
5. Any other SAE related to blood glucose levels

12.7.3.2 Post intervention period (study day 7 until 36 weeks corrected gestation assessment)

Important medical outcomes for the trial will be captured in the CRF at the 36 weeks corrected gestation assessment. Other SAEs listed in 12.7.2 are anticipated events for this study population and do not need to be recorded or reported separately as an SAE.

12.8 Recording and Reporting of Adverse Device Effects and Adverse Events

12.8.1 Adverse Device Effects

Safety will be assessed continuously during each baby's stay in the neonatal unit. Any ADE will be recorded in the CRF (safety log) and reported to the coordinating centre. The investigator at each site will be responsible for managing all device deficiencies and determine and document in writing whether they could have led to a SADE. All device deficiencies that might have led to a SADE if suitable action had not been taken; intervention had not been made; or if circumstances had been less fortunate, must be reported to the Sponsor as for SAEs/SADEs.

12.8.2 Adverse Events

The frequency of adverse events is expected to be very high in this study population of preterm infants. AEs will be captured and recorded in the medical notes and some also recorded as expected adverse events as described in section 12.6.3; as exploratory outcomes (8.6.3) in the CRF; or in the CRF (safety log)at the discretion of the PI.

12.9 Recording and Reporting Serious Adverse Device Effects and Serious Adverse Events/Unanticipated Serious Adverse Device Effects

Safety will be assessed continuously during each baby's stay in the neonatal unit. Any serious adverse device effect or serious adverse event which requires expedited reporting will follow the system outlined below and Appendix 2.

Each recruiting site needs to report serious adverse device effects (SADE) and serious adverse events (SAEs*), if not excluded as outlined in section 12.7.2,* to the Chief Investigator using the trial specific SADE or SAE form within 24 hours of their awareness of the event.

The Chief Investigator is responsible for ensuring the assessment of all reported SADEs/SAEs for expectedness and relatedness is completed and the onward notification of all SADEs/SAEs to the Sponsor immediately but not more than 24 hours of first notification. If applicable, the sponsor will notify the competent authority in line with legal requirements. The Sponsor has to keep detailed records of all SADEs/SAEs reported to them by the trial team.

For UK sites the Sponsor, with the assistance of the Chief Investigator and trial team, is responsible for prompt reporting of all serious adverse device effects and serious adverse events to the MHRA. For non UK sites the PI is responsible to report all SADEs/SAEs to the relevant competent authority and to the CI. The CI will be responsible for notifying DMEC and the MHRA of all SADEs/SAEs that occur during the trial through regular DSURs to the MHRA. This refers to events that could:

- adversely affect the health of participants
- impact on the conduct of the trial
- alter the risk to benefit ratio of the trial
- alter the competent authority's authorization to continue the trial in accordance with Directive 2001/20/EC.

For UK sites the Chief Investigator is responsible for prompt reporting of all serious adverse device effects and serious adverse events that are related or unexpected to the Ethics Committee within 15 days. For non UK sites it is the responsibility of the PI for prompt reporting of all serious adverse device effects and serious adverse event findings to the Ethics Committee according to local regulations.

The completed SADE/SAE form can be faxed or emailed. Details of where to report the SADE's/SAEs can be found on the 'REACT RCT' SADE/SAE form and the front cover of the protocol.

SADEs/SAEs considered to be related to the study intervention by the investigator will be followed up until resolution or the event is considered stable. The investigator may be asked to provide follow-up information.

All related SADEs/SAEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an SADE/SAE is of sufficient severity to require the participant's removal from treatment. A participant may also be voluntarily withdrawn from treatment due to what the attending clinician or the parents perceive to be an intolerable SADE/SAE.

12.10 Adverse Reactions and Suspected Unexpected Serious Adverse Reaction

An IMP is not included in this protocol; therefore Adverse Reactions and Unexpected Serious Adverse Reactions will not occur.

12.11 Reference Safety Information (RSI)

This study will be using devices that have CE mark approval for glucose monitoring in patients with diabetes. The devices used for this study will be used 'off label'. The manufacturer's user guidelines will be used for reference only.

12.12 Evaluation of Adverse Events

The Sponsor expects that adverse events are recorded from the point of Informed Consent regardless of whether a patient has had a CGMS device attached. Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, causality and any relationship between the intervention and the adverse event.

12.12.1 Assessment of Seriousness

Seriousness is assessed against the criteria in section 12.1.4. This defines whether the event is an adverse event, device effect, serious adverse event or a serious adverse device effect

12.12.2 Causality and Expectedness

Investigators will be asked to record their opinion as to whether an SAE as defined above was related to the intervention. The assignment of causality should be made by the investigator responsible for the care of the participant. If any doubt about the causality exists the principal investigator should inform the study coordinating centre who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and others the DMEC and sponsor will be informed and a final decision made before the sponsor submits report to the MHRA.

13 Analysis

13.1 Statistical methods

The primary endpoint will be analysed using linear regression to estimate the absolute difference in time SG in target of 2.6 - 10mmol/l within the first 6 days of life, adjusting for baseline variables (centre, gestation). Estimates of treatment effect, with 95% confidence intervals and p-values will be provided. Secondary endpoints that are continuous variables will be analysed in a similar fashion. Secondary endpoints that are counts or binary variables will be analysed using an appropriate regression framework.

Multiplicity of data is potentially an issue in this study due to the fact that there are multiple secondary endpoints to be tested. Therefore, methods will be used to reduce the likelihood of a type I error.
All of the efficacy endpoints will be ranked with one being the most important (the primary endpoint), two being the next most important and so on.

The rankings of the efficacy endpoints in order of importance are:
Primary:

1) Percentage of time sensor glucose (SG) in target range of 2.6-10mmol/l within the first 6 days of life in preterm infants

Secondary:

2) Mean SG in first 6 days.

3) Percentage of time SG in target of 4-8mmol/l within the first 6 days of life

4) SG variability within individuals as assessed by within-patient standard deviation

5) Percentage of time glucose levels in hyperglycaemic range - SG >15mmol/l

The primary endpoint and the two top-ranked secondary endpoints are seen as the most important and so will be tested. The Benjamini-Hochberg procedure will then be applied to these three endpoints [23]. The p-values are ranked in order of significance (smallest first), p_1, p_2,…, p_n. The highest ranked p-value such that $p_i < 0.05*i/n$ is used as the significance level and any p-values lower than this value are considered as significant.
For example, suppose the three hypothesis had p-values of 0.01, 0.04 and 0.08. As 0.01<0.05*1/3 (0.017) and 0.04>0.05*2/3 (0.033), the only hypothesis in this example to be rejected would be the one producing the p-value of 0.01. By doing this, if only one endpoint is significant at the 5% level, there needs to be stronger evidence to claim a significant result but if all three are significant at the 5% level, a 5% level remains for each individual hypothesis.

The remaining two secondary endpoints will then be tested using a gatekeeping procedure. The next secondary endpoint down the list will be tested. If the p-value is >0.05, none of the other endpoints are tested. However, if the p-value is <0.05, the next hypothesis will then be tested. The same logic is then used; if the p-value is >0.05 the next endpoint is not tested, but if <0.05 it is. This continues until a p-value>0.05 is produced or all of the predefined endpoints are tested. By employing this method of only testing some of the endpoints if all of the previous p-values are<0.05 it decreases the probability of obtaining a false positive result.

Using both of these rules, ensures that the risk of obtaining a type I error is kept to a minimum. The results from all five efficacy endpoints will be reported. However, the discussion of the results will focus on the first three outcomes rather than the two endpoints further down the list. Any of the endpoints that are significant using the Benjamini-Hochberg method will be seen as important but consideration will be given to the fact that the study was designed to test the primary outcome and not the two most important secondary outcomes.

The safety analyses will all be tested regardless of the results of the primary outcome and any secondary outcomes tested. Both the direction of the effect estimate and the strength of the association will be considered when making any safety decisions. For all safety analyses the intervention does not need to be shown to be better than the control but there must not be evidence that the intervention has worse safety outcomes. The safety outcomes are:

1) Incidence of hypoglycaemia defined as any episode of BG > 2.2mmol/l and <2.6mmol/l
2) Incidence of hypoglycaemia defined as continuous episode of SG <2.6mmol/l for >1hour
3) Incidence of severe hypoglycaemia defined as any episode of BG ≤2.2mmol/l

Exploratory analyses will be performed to assess whether metrics derived from the raw CGM data such as but not limited to, mean glucose and time spent within target (2.6-10mmol/l), impact on clinical outcomes listed in section 8.6.3. The primary and secondary outcomes investigate whether the intervention leads to better glucose control whereas the exploratory analyses investigate whether better glucose control leads to better clinical outcomes.

Summary statistics will be provided broken down by treatment arm for all endpoints. Continuous variables will report the mean, median, SD, range, max and min. Binary or categorical endpoints will be represented using frequency tables in the "p% (r/n)" format.

The analysis will look for a treatment interaction effect with the following baseline variables: centre, sex, corrected gestational age, birth weight SDS, use of antenatal steroids, maternal chorioamnionitis and maternal diabetes using the regression framework in an exploratory, non-confirmatory manner.

A detailed statistical analysis plan will be produced before the final data base lock.

13.2 Economic Evaluation Methods: Analytical Strategies

An incremental cost-effectiveness analysis will be performed. In the baseline analysis, the economic evaluation will be expressed as the incremental cost per additional case of adequate glucose control. Adequate control will be considered as 80% of time in target. Results will be presented using incremental cost-effectiveness ratios and cost-effectiveness acceptability curves generated via non-parametric bootstrapping. This accommodates sampling (or stochastic) uncertainty and varying levels of willingness to pay for reductions in the primary health outcome of interest. Cost-utility analysis using QALYs is not ideal here due to the methodological constraints surrounding utility measurement in the perinatal context [24]. Given the multinational nature of the trial, the hierarchical structures of the cost and outcomes data will be taken into account in the analysis plan [25]. Due to the known limitations of within-trial economic evaluations [26] we will also construct a decision-analytical model to model the cost-effectiveness of rCGM beyond the time horizon of the trial. The model will be informed partly by data collected as part of the trial, but also by data collected from secondary sources. Long term costs and health consequences will be discounted to present values using discount rates recommended for health technology appraisal in the United Kingdom [27]. A series of probabilistic sensitivity analyses will be undertaken to explore the implications of parameter uncertainty on the incremental cost-effectiveness ratios and to consider the broader issue of the generalisability of the study results. In addition, cost-effectiveness acceptability curves will be constructed using the net benefits approach.

13.3 Interim analyses

An independent Data Monitoring Ethics Committee (DMEC) has been established, whose remit is to review the trial's progress as described in the DMEC charter. The DMEC will review safety data following recruitment of the first 50 babies and then 125 babies recruited and consider the need for any interim analysis advising the TSC regarding the release of data and/or information.

13.4 Criteria for the premature termination of the trial

The TSC will determine if it is in the best interests of the participants to terminate the study prematurely.

13.5 Procedure to account for missing or spurious data

We anticipate a very low rate of drop-out in the clinical setting; however the CONSORT diagram will illustrate any such drop-outs. Missing data at the individual variable level will be reported within the summary statistics by reference to the number of complete cases. The analyses will use complete cases unless the incidence of missing data is above 5% which implicitly assumes any missing data is missing completely at random. Additional methods will be implemented if the incidence of missing data is above 5%.

13.6 Definition of the end of the trial

The trial will end when the last participant completes their 36 week corrected gestation assessment. Confirming follow-up contact with families and capturing subsequent neurodevelopmental outcomes including weight and height of participants is described in Appendix 5.

14 Data handling and record keeping

14.1 CRF

Only non-patient identifiable data collected from the trial will be entered into a paper Case Report form (pCRF). All trial data in the CRF must be consistent with the relevant source documents. The pCRFs must be completed, dated and signed by the investigator or

designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy of the pCRF pages. The pCRF will be accessible to trial coordinators, data managers, the investigators, Clinical Trial Monitors, Auditors and Inspectors as required. Once the study is complete the original CRF will be stored at the coordinating centre.

The investigator will retain the original copy of each completed pCRF page at site. The investigator will also supply the trial coordination centre with any required, anonymised background information from the medical records as required

The investigators must ensure that the pCRFs and all other trial related documentation is sent to the trial coordination centre containing no patient identifiable data.

Registration forms with family contact details and anonymised data collection forms will be sent separately to the coordinating centre to avoid identity of participant.

All data from the pCRFs will be entered into a purpose designed trial database. Access to the database will be via a secure password protected web interface. Data will be entered promptly and data validation and cleaning will be carried out throughout the trial. Training will be provided for using the database and data validation and data cleaning procedures will be documented in the data management plan.

All pCRF pages must be clear, legible and completed in black ink. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections should be inserted and the change dated and initialled by the investigator or designee. If it is not clear why the change has been made, an explanation should be written next to the change. Typing correction fluid must not be used.

14.2 Source Data

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the pCRF pages.

Paper/electronic patient medical records of both mother and baby
Record of practical use of paper-based algorithm
Case report forms: Eligibility, Randomisation
Daily Insulin and glucose management record worksheet
Clinician and parent questionnaires
Signed consent forms
Data collected from Medtronic devices

14.3 Data Protection & Patient Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 1998 and Trust Policies with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Non UK sites must follow local legislation.

Data collected on pCRFs and data collection forms will be stored in an electronic database in which the baby will be identified by a study specific number. The baby's name, address and any other identifying detail will be recorded on the registration form and stored in a separate database linked only by the study number. This identifiable information will be collected with the parent(s)/legal guardian's consent to enable follow-up to be undertaken at a later date, if necessary. Identifiable data will be sent from Non UK sites to the coordinating centre.

Standard operating procedures are in place for the collection and handling of data received at the Trial Coordinating Centre. All data will be stored in secured servers and will be accessible only to named personnel on the delegation log. Information governance policies of the Trust and CCTU SOPs will be followed for handling data. For interim or final analysis, data will be encrypted and password protected before being sent to the statistician

15 Trial Steering Committee/Data Monitoring Committee

The constitution of both groups will follow the guidelines produced by the funding body – NIHR EME.

15.1 Trial Steering Committee

The EME Programme Director will formally appoint an Independent Chair and Members to the TSC after receiving nominees from the CI. Committee members are listed in section 2.0.

The TSC will provide overall supervision for the trial on behalf of the Trial Sponsor and Trial Funder and will ensure that the trial is conducted to the rigorous standards set out in the Medical Research Council's guidelines for Good Clinical Practice. In particular the TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and consider new information of relevance to the research question.

The TSC will provide advice, through its Chair, to the CI, and report to Trial Sponsor and Trial Funder. The TSC meetings will be organized by the CI in association with the Chair and be held prior to ethics submission and at least annually.

15.2 Data Monitoring and Ethics Committee (Membership provided p4)

The DMEC will have access to the comparative data and be responsible for monitoring these data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. The DMEC will be responsible for providing recommendations to the TSC regarding early termination of the trial for safety but decisions regarding early termination lie with the TSC.

Responsibility for calling and organizing the meeting lies with the Chief Investigator, in association with the Chair of the DMEC. The frequency of meetings should be at least annually and timely so reports can be fed to the TSC. The DMEC will consider the need for any interim analysis advising the TSC regarding the release of data and/or information. The project team are responsible for providing the DMEC with a comprehensive report, the content of which should be agreed in advance by the Chair of the DMEC.

16 Ethical & Regulatory considerations

16.1 Consent

The Informed Consent form must be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator must ensure that the baby's parent/legally acceptable representative is fully informed about the nature and objectives of the trial and possible risks associated with their baby's participation.

The investigator or a suitably qualified person designated by the principal investigator will receive written or verbal informed consent from the patient's parent/legally acceptable representative before any trial-specific activity is performed. The informed consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. The investigator will retain the original of each patients signed informed consent form and file a copy in the patient's health records.

Should the patient's parent/legally acceptable representative require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators.

Parent information leaflets will need to be available in Spanish and Dutch and be reviewed and approved by the Sponsor and appropriate participating site prior to use.

Any new information which becomes available, which might affect the patient's mother or legally acceptable representative willingness to continue allowing the baby to participate in the trial will be communicated to them as soon as possible by face-to-face or by telephone.

16.2 Ethical committee review

Before the start of the trial or implementation of any amendment the CI will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g. advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

The CI will delegate the responsibility for applying for and maintaining local ethical approval to the lead site of each non UK country.

16.3 Regulatory Compliance

The trial will not commence in the UK until MHRA approval is obtained. Non UK sites cannot commence the trial until their regulatory bodies, have approved the study. The sponsor will delegate the responsibility for applying for and maintaining local regulatory approval to the lead site of each country.

The protocol and trial conduct will comply with the Medical Devices Regulations 2002 and any relevant amendments.

Development Safety Update Reports (DSURs) will be submitted to the MHRA every 6 months unless indicated differently by the MHRA. It is the Chief Investigators responsibility to produce the annual reports as required.

The sponsor, with the assistance of the Chief Investigator, is responsible for reporting SADEs or USADEs that have occurred in the UK to the MHRA. SADEs or USADEs occurring at non UK sites should be reported by the site PI to the competent authority of that country and the CI at the coordinating centre.

16.4 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the REC and/or competent authority (ies).

The only circumstance in which an amendment may be initiated prior to REC and/or competent authority approval is where the change is necessary to eliminate apparent, immediate risks to the patients (Urgent Safety Measures). In this case, accrual of new patients will be halted until the national Ethics Committees and/or competent authority (ies) approval has been obtained.

In the event of an urgent safety measure the principal investigator or suitably qualified delegate at the participating site will be informed within 48 hours by the Chief Investigator or suitably qualified member of the study team.

16.5 Peer Review

The NIHR Evaluation, Trials and Studies Coordinating Centre, University of Southampton, Alpha House, Enterprise Road, Southampton, S016 7NS reviewed this study.

16.6 Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

16.7 GCP Training

Trial staff receiving consent must hold evidence of appropriate GCP training and ideally all other trial staff should undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with local hospital policy.

17 Sponsorship, Financial and Insurance

The trial is jointly sponsored by Cambridge University Hospitals NHS Foundation Trust and University of Cambridge. The study will be funded by NIHR: Evaluation, Trials and Studies Programme. An application for support will be made to Medtronic for supplying MiniMed® 640G System, Enlite® sensors and Guardian™ Link transmitters.

The University of Warwick will act as the Health Economic Evaluation Centre for the trial.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

Each participating site will be provided with Medtronic equipment and further costs will be listed in each participating site agreement.

Participants or their parents/legal representatives will not receive any payment for participating in this study, however, all reasonable travel costs will be reimbursed by the coordinating centre, in the unlikely event that parents/legal representatives need to travel to the recruiting centre to attend any study visit.

18 Monitoring, Audit & Inspection

The investigator must make all trial documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All patient data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the trial. However, face-to-face monitoring visits will be

undertaken, if required, within the first 6 months and following assessment of recruitment rate, number of data queries and SAE reports.

19 Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used at any participating site.

All participating sites must ensure that any substantial amendment is approved before implementation by an accredited Ethics Committee and the country's regulatory authority.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

20 Publications policy

Ownership of the data arising from this trial resides with the trial team. On completion of the trial the data will be analysed and tabulated and a Final Study Report prepared.

Participating investigators will have no rights to publish any of the study data without permission by the CI.

The Trial Steering Committee will approve all publications generated from the trial and the Chief Investigator will ensure that the Consort Guidelines and checklist are reviewed prior to generating any publications.

NIHR Evaluation, Trials and Studies Coordinating Centre will be notified no less than twenty eight (28) days prior to any publication arising from the project. Publications shall acknowledge the Authority's full financial support and carry the following disclaimer: "The Efficacy and Mechanism Evaluation programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland, NISCHR in Wales and the HSC R&D, Public Health Agency in Northern Ireland. This report is managed by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) (Efficacy and Mechanism Evaluation, 11/133/07 – Real Time Continuous Glucose Monitoring in Neonatal Intensive care). The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NHS the National Institute for Health Research or the Department of Health".

The University of Warwick acting as the Economic Valuation Centre will be notified no less than thirty (30) days in advance of any publication submission.

Medtronic United Kingdom will be notified at least thirty days prior to any publication or presentation of the study's results in manuscripts, abstracts or other materials and

Prior to submission for publication, public dissemination, or review by a publication committee, Medtronic United Kingdom, will be notified at least (30) days in advance of any publication submission and at least twenty (20) days for any presentation submission.

Parents will be notified of the outcome of this study by a specifically designed newsletter, after the results have been published. Parents of babies who have died will also be asked if they would like to continue receiving information about the study because research suggests that they do wish to be notified. [28]

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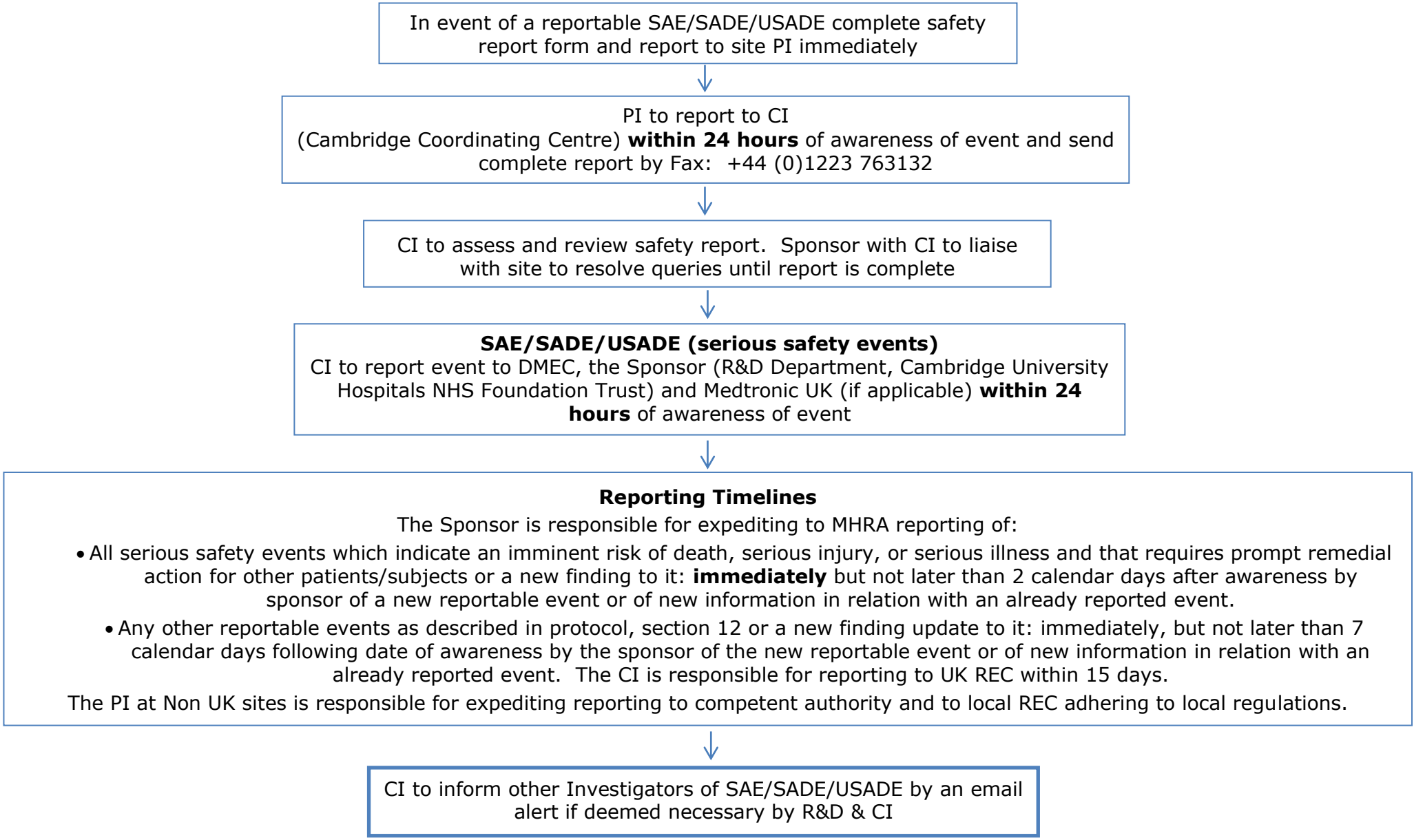
22 Appendices

Appendix 1: Paper based algorithm for use in intervention arm only

Sensor Glucose mmol/l	Falling	Stable	Rising
<2.6	**Check Blood Glucose** Stop any Insulin & Check all lines Give additional Dextrose Consider starting 20% Dextrose at 1ml/kg/hr	**Check Blood Glucose** Stop any Insulin & Check all lines Give additional Dextrose Consider starting 20% Dextrose at 1ml/kg/hr	**Check Blood Glucose** Review infusions & check lines Ensure Insulin is not running Consider starting/increasing 20% Dextrose at 1ml/kg/hr
2.6-4.0	**Check Blood Glucose** Stop any Insulin & Check all lines Give additional Dextrose Consider starting 20% Dextrose at 1ml/kg/hr	**Check Blood Glucose** Stop any Insulin & Check all lines Give additional Dextrose Consider starting 20% Dextrose at 1ml/kg/hr	**Observe the rate of rise** Review infusions & check lines Ensure Insulin is not running Consider need for additional Dextrose
Target Range 4.0 - 8.0	**IN TARGET** If the rate of fall means you will be <4.0mmol/l within 1 hour consider reducing Insulin	**IN TARGET**	**IN TARGET** Consider weaning any additional 20% Dextrose
8.0-10.0	**Observe the rate of fall** Consider ***reducing*** Insulin infusion rate by 25%	Stop any additional 20% Dextrose or Start Insulin at 0.05 units/kg/hr or if Insulin is already running ***increase*** Insulin infusion rate by 50%	Stop any additional 20% Dextrose or Start Insulin at 0.05 units/kg/hr or if Insulin is already running ***increase*** Insulin infusion rate by 50%
10-15.0	**Observe the rate of fall** Consider ***increasing*** Insulin infusion rate by 25%	Stop any additional 20% Dextrose or Start Insulin at 0.05 units/kg/hr or if Insulin is already running ***increase*** Insulin infusion rate by 50%	Stop any additional 20% Dextrose or Start Insulin at 0.05 units/kg/hr or if Insulin is already running ***increase*** Insulin infusion rate by 50%
> 15	**Observe the rate of fall** Consider ***increasing*** Insulin infusion rate by 50%	Start Insulin at 0.05 units/kg/hr **or** consider ***increasing*** Insulin infusion rate by 100% (that is: Double) **Always check infusion lines if there is little or no response to an intervention**	Start Insulin at 0.05 units/kg/hr **or** consider ***increasing*** Insulin infusion rate by 100% (that is: Double) **Always check infusion lines if there is little or no response to an intervention**
CRITICAL	Please remember continuous glucose sensor readings are provided to support clinical management. They provide additional information on trends in glucose levels which should be used to guide the need for blood glucose measurement. Capillary/venous blood glucose levels are more accurate. ***Always check infusion lines if there is little or no response to an intervention***		
CONCERN			
IN TARGET			

Appendix 2: Safety Reporting Flow Chart



Appendix 3: Study Management / Responsibilities

The study will be overseen by the TSC (16.0)

Chief Investigator: Dr Kathryn Beardsall

Coordinating Centre:
Cambridge Clinical Trials Unit (Paediatric Theme)
University Department of Paediatrics
University of Cambridge
Box 116, Level 8
Cambridge Biomedical Campus
Hill Road
Cambridge CB2 0QQ

Telephone: +44(0)1223 746414 / +44(0)7565 964631
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Email: REACT@paed.cam.ac.uk

Data Manager:
Cambridge Clinical Trials Unit
Box 401
Coton House, Level 6
Cambridge University Hospitals NHS Foundation Trust
Addebrooke's Hospital
Hills Road
Cambridge, CB2 0QQ

Patient registration/ Randomisation procedure
Prior to registration informed consent will be taken from the participant's parent/legal guardian. The registration and randomisation procedures will be explained in detail in the Trial Manual and produced prior to the trial initiation.

CRF Completion & Data management

The Senior Data Manager will be responsible for producing a Data Management Plan and a pCRF. Suitably qualified personnel designated by the PI and listed on the delegation of responsibility log will be responsible for completing the pCRF. The coordinating centre will be responsible for managing receipt of collected data and will be responsible for generating queries and liaising with participating sites to resolve these queries.

Preparation & submission of amendments

The coordinating centre at Cambridge will be responsible for the preparation and submission of all amendments in the UK. Each Non-UK site will be responsible for the preparation and submission of all amendments to the appropriate competent authority and ethics committee.

Preparation and submission of Annual Safety Report/Annual Progress Reports and reports for DMEC and TSC

The coordinating centre at Cambridge will be responsible for the preparation and submission of annual safety reports and annual progress reports. The Senior Data Manager will be responsible for producing the data necessary for these reports in a timely fashion.

Data protection/ confidentiality (see 15.3)

Data collected on the CRFs and data collection forms will be stored in an electronic database in which the baby will be identified by a study specific number. The baby's name and any other identifying detail will be recorded on the registration form stored in a separate database linked only by the study number. This information will be collected with the

parent(s)/legal guardian's consent to enable follow-up to be undertaken at a later date, if necessary. The Senior Data Manager will be responsible for insuring that all data is held in compliance with current legislation surrounding data protection.

Trial documentation & archiving

The Trial Master File (TMF) will be kept up to date by the coordinating centre and each participating site will be responsible for maintaining their Investigator Site Files (ISF). These files need to be complete at the end of the trial and archived for 25 years. The sponsor will be responsible for archiving the TMF and Cambridge ISF. Other participating sites will be responsible for archiving their ISF. Original copies of the CRF will be sent and stored at the coordinating centre.

All essential and trial documentation (e.g. TMF, ISF source data paper CRFs) will be securely archived after the last analysis of the trial data has been completed and the Final Trial Report has been submitted to the relevant authorities.

The Investigator must not destroy any documents or records associated with the trial without written approval from the Sponsor.

Appendix 4: Authorisation of Participating Sites

Required Documentation

Investigator Site File
Competent Authority Approval in addition and following home country approval
Ethics approval from each country in addition and following home country approval
Signed Participating Agreement
Protocol – signed protocol signature page
Patient Information leaflets including informed consent form and GP letter to be provided in English and translated to Home Country language
Delegation of Responsibility and Signature Log
PI signed and dated CV
Signed and dated CVs from everyone listed on the delegation of responsibility log
CRF pages
Study Manual

Procedure for initiating/opening a new site

The clinical study coordinator will organize the initiation meeting on behalf of the CI and invite all the participating site trial members. The CI, study coordinator and PI will be present throughout the meeting.

Principal Investigator Responsibilities

The Principal Investigator's (PI) legal responsibilities will be listed in the Participating Site Agreement but each recruiting site will have a nominated PI who will be expected to:

1. Read the REACT protocol and agree to follow it and future amended protocols in accordance with ICH Good Clinical Practice guidelines, legal and regulatory requirements
2. Understand that to deviate from the protocol without discussion or formal agreement with Cambridge University or Cambridge University Hospitals NHS Foundation Trust (sponsor) would be a violation of the protocol.
3. Supply a current CV and undertake GCP training or have a training session booked before the trial starts and/or update GCP training every 2 years
4. Attend initiation meeting and subsequent study meetings or delegate to a suitably qualified team member
5. Adhere to safety reporting timelines
6. Have overall responsibility of data collection and responsibility of maintaining ISF
7. Each PI will delegate responsibility for the recruitment of eligible babies to members of their team once they are satisfied that the relevant member(s) of staff is/are competent and confident in:
    - their knowledge of the study and their ability to answer questions raised
    - their competency in obtaining informed consent from the families
    - their comprehension of the randomisation procedure following training by the REACT study team or by a local team member who has received this training inserting CGMS sensors and have a thorough working knowledge of the study devices
    - collection and reporting of trial data following training provided by a member of the
    - REACT study team or by a local team member who has received this training they have adequately trained and received by experience or have received training in GCP relative to their role in the trial

APPENDIX 5: Follow-up phase

Purpose of follow-up phase
Preterm babies are at an increased risk of poor childhood growth, reduced insulin sensitivity in childhood and higher risk of the metabolic syndrome in later life. It is important therefore that we assess the longer-term impact of our intervention in terms of growth and neurodevelopmental outcome.

Primary objective
- Confirm consent for future follow-up

Secondary objective
- Neurodevelopmental outcome at 2 years of age
- Catch up Growth at 2 years corrected age – weight and length

Outcome measures
1. Number of families consenting to future follow-up
2. Neurodevelopment - assessed by PARCA-R (Parent Report of Children's Abilities-Revised for preterm infants).
3. Growth

Number of participants
182 preterm babies were recruited to the REACT randomised controlled trial. Parents agreed and consented to be contacted in relation to follow-up studies.

Selection and withdrawal of participants

Inclusion criteria
- Participated in either the REACT feasibility or RCT
- Confirmed parental consent

Exclusion criteria
- Deceased children

Making contact
Patient contact details for both studies are stored securely at the trial coordinating centre and at each recruitment site. Prior to making contact with families, each baby's health status will be checked, for example, through the spine web portal held by NHS digital or similar patient follow-up system. This is to prevent bereaved families from being contacted unnecessarily and help us confirm contact details are still valid. Contact will be made either by introductory letter/email or by telephone. Upon making contact with the family, on-going consent will be confirmed.

Participant registration
Follow up participation will be recorded on a patient log and contact details will be updated as necessary. The participant ID allocated to babies in the feasibility study will remain unchanged.

Assessments
A validated questionnaire called PARCA-R https://www2.le.ac.uk/departments/health-sciences/research/timms/parca-r will be sent for parental completion which will measure neurodevelopmental outcomes and is routinely used in clinical trials. A recent height and weight of the child will also be requested from either the family or the recruitment centre where they joined the REACT study.

End of trial participation
Receipt of last follow-up questionnaire.

Assessment of safety
Due to the completion of the interventional studies, this follow-up phase will not assess or record any safety events.

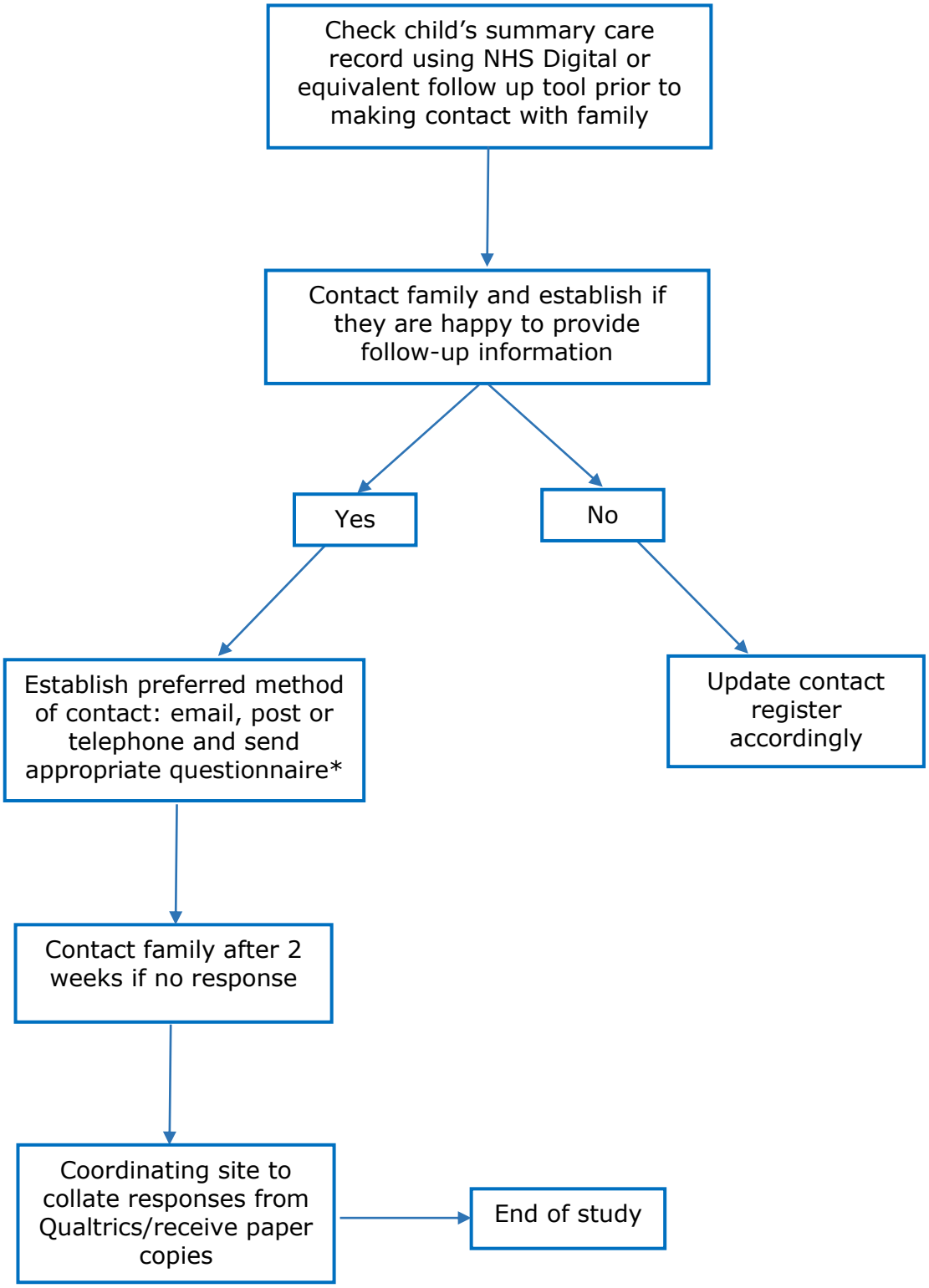
Data handling and record keeping
The PARCA-R questionnaire including height and weight measurements will be available to complete on paper or electronically by using Qualtrics which is the standard system used within the University of Cambridge to collect secured data. Qualtrics security brief can be found at https://www.qualtrics.com/security-statement/

Responses will be identified by the participant's study ID and we will ask confirmation of the parent completing the questionnaire.

Consent
Parents will be asked to confirm their ongoing consent either electronically, by telephone or by completing a paper form. Both consent form and questionnaires will be available in Spanish and Dutch and be reviewed by the Sponsor and appropriate recruitment site prior to use.

Withdrawal
Participation in this follow up phase is voluntary and parents are free to withdraw at any time, without giving any reason and without any personal disadvantage to themselves or their child.

Follow-up phase flow chart



*Confirmation of ongoing consent to be requested prior to start of questionnaire