Assessment of the Impact of Real-time Continuous Glucose Monitoring on People Presenting with Severe Hypoglycaemia (AIR-CGM)

V1.0

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Protocol authorised by:

Name & Role	Date	Signature

Study Management Group

Chief Investigator: Professor Nick Oliver

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Project Manager: Maria Thomas

Clinical Queries

Clinical queries should be directed to Professor Nick Oliver who will direct the query to the appropriate person

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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This protocol describes the study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

CGM	Continuous glucose monitoring
T1DM	Type 1 diabetes mellitus
PAID	Problem Areas in Diabetes
CGMSS	Glucose Monitoring System Satisfaction Survey
HFS	Hypoglycaemia Fear Survey
HbA1c	Haemoglobin A1 C
NHS	National Health Service
ECG	Electrocardiogram
SMBG	Self-monitoring of blood glucose
RT CGM	Real-time continuous glucose monitoring

KEYWORDS
Type 1 diabetes, continuous glucose monitoring, glucose, insulin, hypoglycaemia

STUDY SUMMARY

TITLE	**Assessment of the Impact of Real-time Continuous Glucose Monitoring on People Presenting with Severe Hypoglycaemia**
DESIGN	Randomised open-label parallel group study
AIMS	This study aims to assess the impact of real-time continuous glucose monitoring on the frequency, duration, awareness and severity of hypoglycaemia in people with type 1 diabetes and a recent history of severe hypoglycaemia, compared to usual care.
OUTCOME MEASURES	The primary outcome is % time spent in hypoglycaemia (<3.0mmol/L, 55mg/dL). Secondary outcomes include other measures of hypoglycaemia, time in euglycaemia, overall glucose status and patient reported qualitative measures.
POPULATION	Adults with type 1 diabetes, who are CGM naïve, and having a recent episode of severe hypoglycaemia (<72hrs).
ELIGIBILITY	Participants with type 1 diabetes and severe hypoglycaemia requiring ambulance call-out or emergency department attendance within 72 hours.
DURATION	12 weeks for each participant, 52 weeks in total.

1. INTRODUCTION

1.1 BACKGROUND

Type 1 diabetes (T1DM), which affects 300,000 in the UK, is characterised by autoimmune destruction of the pancreatic beta cells, leading to absolute deficiency of insulin. Management of T1DM requires exogenous insulin administration, aiming for glucose concentrations as close to physiological values as possible. Intensive management of T1DM improves glucose control and reduces the risk of microvascular diabetes complications and cardiovascular disease [1]. In the UK diabetes consumes more than 10% of the National Health Service budget [2] and in the USA a relatively greater amount is spent on type 1 compared with type 2 diabetes (8.6% of the diabetes budget compared with 5.6% of diabetes prevalence) [3]. Medication and insulin pump therapy accounts for less than 10% of diabetes expenditure with the majority of costs incurred in the treatment of complications [4].

Optimal control remains challenging to achieve and intensive insulin treatment increases the risk of severe hypoglycaemia, with lower glucose values also associated with an increased frequency and severity of moderate hypoglycaemia [5, 6]. Severe hypoglycaemia is defined as any episode of hypoglycaemia requiring the assistance of a third party actively to treat. Hypoglycaemia is associated with morbidity and even mortality, and places a financial burden on health systems.

Severe hypoglycaemia costs £13million per year in NHS costs [7]. Between 4 and 10% of deaths in people with type 1 diabetes are attributed to hypoglycaemia and the risk of severe hypoglycaemia increases 6-fold in people with impaired awareness of hypoglycaemia. Avoidance of hypoglycaemia is associated with restoration of hypoglycaemia awareness and this may be enabled by the use of continuous glucose monitoring.

In type 1 diabetes real-time continuous glucose monitoring (CGM) improves overall glucose control in all age groups when used continuously, reduces hypoglycaemia in people with an HbA1c <7.0%, and may reduce severe hypoglycaemia [8-10].

In England continuous glucose monitoring is supported by NICE for people with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimised use of insulin therapy and conventional blood glucose monitoring [11]:

- More than 1 episode a year of severe hypoglycaemia with no obvious preventable precipitating cause.
- Complete loss of awareness of hypoglycaemia.
- Frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities.
- Extreme fear of hypoglycaemia.
- Hyperglycaemia (HbA1c level of 75 mmol/mol [9%] or higher) that persists despite testing at least 10 times a day

Addressing severe hypoglycaemia, reducing the risk of further episodes and acting promptly to optimise hypoglycaemia awareness are critical in people at high risk.

1.2 RATIONALE FOR CURRENT STUDY

This clinical study proposes to assess the impact of real-time continuous glucose monitoring supported remotely by a specialist healthcare team on the frequency, duration, awareness and severity of hypoglycaemia in people with type 1 diabetes and a recent history of severe hypoglycaemia.

1.3 HYPOTHESIS

Real-time CGM with adjunctive healthcare professional support provided within 72 hours of an episode of severe hypoglycaemia has a beneficial impact on hypoglycaemia frequency, duration, severity and awareness in those at highest risk of significant morbidity and mortality, compared with self-monitoring of blood glucose with adjunctive support.

2. STUDY OBJECTIVES

Primary outcome: % time spent in hypoglycaemia (<3.0mmol/L, 55mg/dL)

Secondary outcome: Number of episode of serious hypoglycaemia (defined as a sensor glucose <3.0mmol/L (55mg/dL) for >20 minutes)
% time spent in hypoglycaemia (<3.9mmol/L, 70mg/dL)
% time in euglycaemia (3.9-7.8mmol/L, 70-140mg/dL)
% time spent in target (3.9-10mmol/L, 70-180mg/dL)
% time spent in hyperglycaemia (>10mmol/L, 180mg/dL)
Number hypoglycaemic excursions
Severe hypoglycaemia
MAD%
Glucose variability
HbA1c
Ambulance call-out rates
Diabetes treatment satisfaction questionnaire
CGM usability
PAID
Gold score
Fear of hypoglycaemia survey score (HFS2)
Cost effectiveness

3. STUDY DESIGN

Randomised controlled study comparing the impact of real-time CGM with usual care following severe hypoglycaemia (Figure 1).

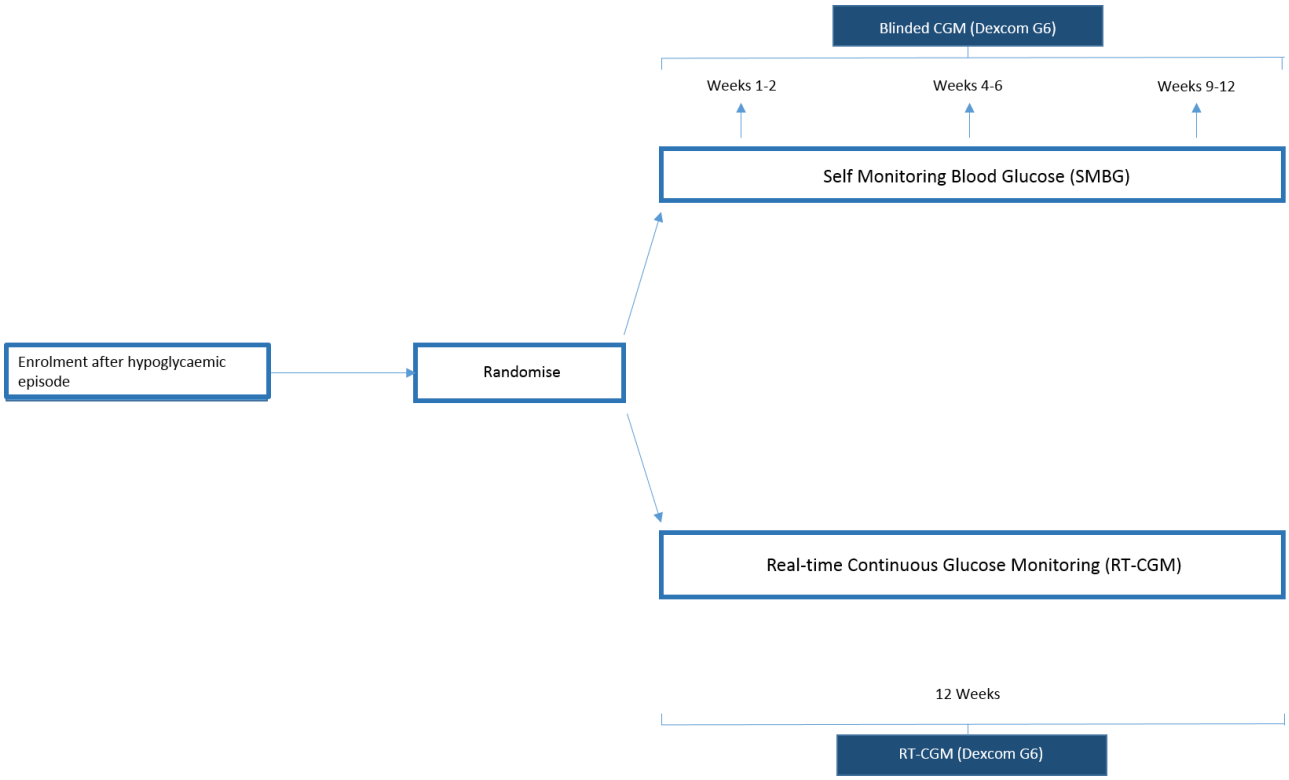

Figure 1. Study design

3.1 RECRUITMENT

Recruitment will be undertaken in collaboration with the London Ambulance Service and from the Accident and Emergency departments of St Marys Hospital and Charing Cross Hospital in London (recruitment flow chart below). Participants will be identified following an episode of severe hypoglycaemia and participant information sheets will be given to potential subjects. Following any questions, London Ambulance Services and Emergency Departments will seek verbal consent to share details with study investigators, and send details to principal investigator through a secure website (NHS.net account).

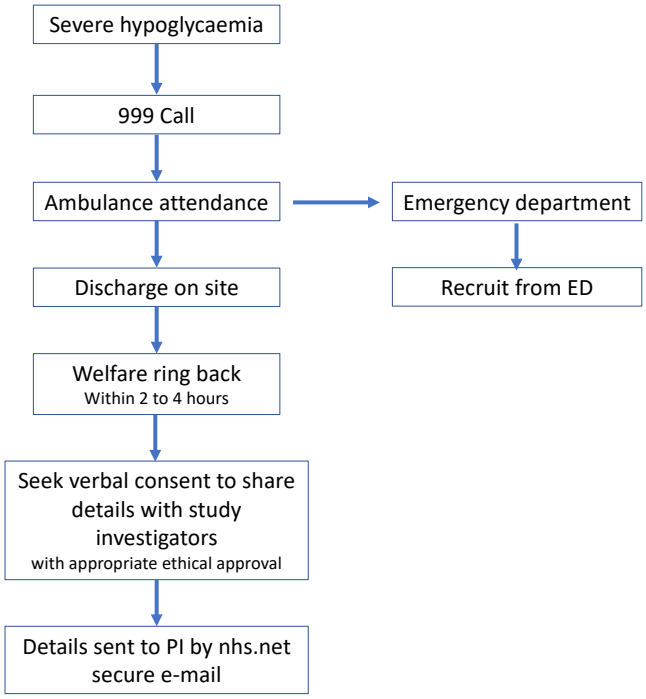

Figure 2. Recruitment Flow Chart

3.2 FEASIBILITY

London Ambulance Service call outs for hypoglycaemia in selected geographical areas of North West London in 2015 calendar year are as follows:

Region	Number of call outs	Conveyed to emergency department
NWL London (Harrow)	286	160
Hillingdon	468	321
Brent	499	335
North Central	311	174
Hounslow	343	210
Hammersmith/ Fulham	245	167
TOTAL	**2152**	**1367**

Between 1st March 2014 and 28th February 2015, 236 people attended the emergency departments of Imperial College Healthcare NHS Trust with a coded diagnosis of hypoglycaemia.

3.3 STUDY DURATION

12 weeks for each participant, 52 weeks in total.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Episode of severe hypoglycaemia
Age >18 years
Diagnosis of type 1 diabetes

4.2 INCLUSION CRITERIA

Adults over 18 years of age
Severe hypoglycaemia requiring ambulance call-out or emergency department attendance within 72 hours
Type 1 diabetes confirmed on the basis of clinical features
Type 1 diabetes for greater than 3 years

4.3 EXCLUSION CRITERIA

Use of CGM or Abbott Freestyle Libre device within the last 6 months (except short periods of diagnostic blinded use under clinic supervision)
Use of pre-mixed insulin
Use of regular paracetamol
No access to smartphone or computer
Pregnant or planning pregnancy
Breastfeeding
Have active malignancy or under investigation for malignancy
Severe visual impairment
Reduced manual dexterity
Unable to participate due to other factors, as assessed by the Chief Investigators

4.4 WITHDRAWAL CRITERIA

Participants will be withdrawn if their ability to give informed consent is impaired. Participants will also be withdrawn, at the chief investigators discretion, if glucose control is negatively impacted by the use of either intervention.

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the NRES Committee xxx where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
Fax: 0207 594 2432, attention Prof Nick Oliver
Please send SAE forms to:
Diabetes, Endocrinology and Metabolism Medicine
Imperial College
Room G3, Medical School Building
St Mary's Campus
Norfolk Place
London, W2 1PG
Tel: 0207 594 2460 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

6.1 CLINIC VISIT 1: Screening and Randomisation

Following informed consent study participants will give a full medical and medication history, as well as undergo a physical examination and ECG. Venous blood tests will be taken and sent to assess HbA1c, plasma glucose, renal function, serum C-peptide, thyroid function test, 9 am cortisol and coeliac screen (tissue transglutaminase antibody). Women of childbearing age will have a urine pregnancy test. If participants meet the inclusion criteria they will be enrolled on to the study and will complete a semi-structured participant interview and questionnaires (Diabetes treatment satisfaction questionnaire, CGM usability, PAID, and Fear of hypoglycaemia survey score (HFS2)). A Gold Score questionnaire will also be completed.

Participants enrolled will be randomised to real-time continuous glucose monitoring (RT CGM) or self-monitoring blood glucose (SMBG) group. Randomisation will be done using sealedenvelope.com and stratified by insulin delivery modality.

The RT CGM group will receive a Dexcom G6 transmitter and sensors, as well as a structured education refresher focusing on hypoglycaemia avoidance, recognition, and management. Participants in the SMBG group will receive the same structured education refresher focusing on hypoglycaemia avoidance, recognition, and management. All education will be delivered by the research nurse from a predefined curriculum and will be supported by independent written materials.

Participants will be instructed to test their capillary blood glucose if symptoms of hypo- or hyperglycaemia occur, in case of sensor failure or if the sensor glucose is out of the desired range. Participants using the G6 sensor will change sensor every ten days (or sooner in the event of sensor failure). Low glucose alert settings will be standardised at 4.4 mmol/L (80mg/dL) for all participants at the start of the study and can be reduced to 4 mmol/L (70mg/dL) at week 2 during the telephone visit depending on participant preference. High glucose alerts may be personalised.

The SMBG group will additionally undergo blinded CGM at weeks 1 and 2, weeks 4 to 6 and weeks 9 to 12 using the Dexcom G6 system. Participants in this group will be shown how to insert the Dexcom G6 at the first clinic visit and sensors provided so they can do this at home.

6.2 FOLLOW-UP: Telephone follow-up during study period

Participants will be provided telephone support twice in the first week, then weekly for the next 3 weeks, and every 2 weeks thereafter, to optimise glucose and reduce the risk of further hypoglycaemia.

Participants in the CGM group with an iOS or Android smartphone will be able to upload and share data with the Research team through the “Dexcom Share app”. Participants who do not have a smartphone can upload their CGM data to and online platform named “Tidepool” using a PC or Mac desktop computer. In total, participants will use CGM for 12 weeks.

Participants in the SMBG group will be asked to self-monitor a minimum of 4 times daily and upload data to Tidepool, an online not-for-profit platform for individuals to selectively share data with clinicians to optimize diabetes management. They will receive telephone support from the research team, based on their Tidepool data, at the same time points as the RT-CGM group to optimise glucose and reduce the risk of further hypoglycaemia. Blinded CGM data from the SMBG group will be uploaded at the end of week 2, end of week 6 and end of week 12.

6.3 CLINIC VISIT 2: End of study

At the end of the study (i.e. at end of 12 weeks), repeat blood tests to assess HbA1c will be performed. Participants will be asked to complete questionnaires and a semi-structured interview will be conducted, similar to that at baseline. Participants will return study equipment and return to their standard care.

7. STATISTICS AND DATA ANALYSIS

Baseline data will be taken from the first 14 days of monitoring and outcomes will be calculated from the last 30 days of the treatment period.

Power calculation: Based on findings from our 'I HART CGM trial', we would expect percentage time spent in hypoglycaemia (<3.0mM) to be 64% lower in the CGM group compared to the self-monitoring group [mean (SD): CGM group 2.1% (2.3%); self-monitoring group 5.8% (5.9%)]. To demonstrate that difference as significant at $p<0.05$ and with 80% power, 25 participants would be needed in each group. To allow for a 10% drop-out 55 participants will be recruited.

Analysis: Intention to treat. The primary outcome will be assessed by two-tailed unpaired t-test. For secondary outcomes, parametric data will be compared between the two study arms by two-tailed unpaired t-test for continuous variables. Non-parametric data will be compared using a Wilcoxon Rank sum test.

Sub-analysis: Other outcomes assessed will include hypoglycaemia awareness by participant (Gold score). Hypoglycaemia outcomes will be assessed throughout the time period and nocturnal only.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the xxx Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. Confidentiality of data will be preserved during data transmission via the use of anonymised codes. Participants will be assigned codes based on order of enrolment and site at which they are enrolled (AIR-HH-001 etc. for those enrolled at Hammersmith Hospital, AIR-CX-001 etc. for those enrolled at Charing Cross Hospital and AIR-SM-001 etc. for those enrolled at St Mary's Hospital/. Identifiable personal information will be stored securely in a locked room at Imperial College Healthcare NHS Trust. Annonymised data will be held securely in swipe-card access room at Imperial College London and on Imperial College London computers. The latter will be encrypted with a password. Data will be accessible only to the Research Team and for audit. Pseudoanonymised data will be used for analysis. Confidentiality of data will be preserved when sending identifiable information from Imperial College Healthcare NHS trust and London Ambulance Service to the Imperial College London research team by using encrypted NHS.net email accounts. The data will be stored at Imperial College London for 10 years. App security is covered in Tidepool's privacy statement as they are a separate data controller. The data custodian is Professor Nick Oliver.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

Dexcom are funding this study. Participants will be fully reimbursed for travel expenses.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the Chief Investigator, Prof Nick Oliver.

10. PUBLICATION POLICY

Data from the study will be analysed then published in peer-reviewed scientific journals and presented at Scientific Conferences. A lay summary of the data will be disseminated to all participants and a summary of results will be publically available.

11. REFERENCES

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11. *Type 1 diabetes in adults: diagnosis and management | Guidance and guidelines | NICE.* 2017.

11. APPENDICES

- Summary of investigations, treatment and assessments
- Dexcom G6 instructions for use
- Validated questionnaires:
    - Diabetes treatment satisfaction questionnaire
    - CGM usability
    - PAID
    - Gold score
    - Fear of hypoglycaemia survey score (HFS2)

Tidepool Privacy Statement (https://tidepool.org/legal/privacy-policy-2-0/)

Appendix 1: Summary of investigations, treatment and assessments

	Clinic Visit 1 (Screening & Randomisation)	End of Week											
		1	2	3	4	5	6	7	8	9	10	11	Week 12 (Clinic Visit 2)
History	x												
Medication history	x												
ECG	x												
Physical examination	x												
Urine pregnancy test	x												
HbA1c	x												x
Glucose	x												
Renal function	x												
TFT	x												
9am cortisol	x												
Coeliac screen	x												
C-peptide	x												
Gold Score	x												x
Participant interview	x												x
QoL Questionnaires	x												x
Diabetes Education	x												
Randomisation	x												
CGM education	x												
CGM insertion	x	x	x	x	x	x	x	x	x	x	x	x	
Telephone consultation		x (twice)	x	x	x		x		x		x		
CGM group - CGM download		x (twice)	x	x	x		x		x		x		x
SMBG Group - Meter download		x (twice)	x	x	x		x		x		x		x
SMBG Group - Blinded CGM download			x				x						x
Research clinic visit	x												x