# I HART CGM

## Impact on Hypoglycaemia Awareness of Real Time CGM and Intermittent Continuous Glucose Data

V2.0 30th August 2015

MAIN SPONSOR: Imperial College London
FUNDERS: Dexcom
STUDY COORDINATION CENTRE: Imperial College London
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**Protocol authorised by:**

| Name & Role | Date | Signature |
|---|---|---|
| Dr Nick Oliver | 30/August/ 2015 | |

## Study Management Group

Chief Investigator: Dr Nick Oliver

Co-investigators: Dr Ahmed El-Laboudi - Dr Monika Reddy

Statistician: Dr Ian Godsland

Study Management: Narvada Jugnee

## Clinical Queries

Clinical queries should be directed to Dr 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:

Joint Research Compliance Office
Imperial College London
5th Floor Lab Block
Charing Cross Hospital
Fulham Palace Road
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**Tel:** 0203 311 0204
**Fax:** 0203 311 0203

## Funder

Dexcom

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.

# Table of Contents

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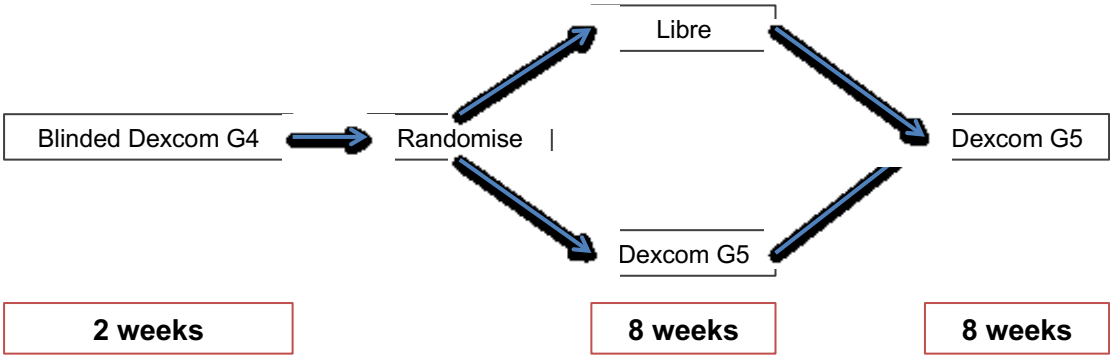
## KEYWORDS
Type 1 diabetes, continuous glucose monitoring, glucose, insulin, hypoglycaemia

# STUDY SUMMARY

| | |
|---|---|
| **TITLE** | Impact on Hypoglycaemia Awareness of Real Time CGM and Intermittent Continuous Glucose Data |
| **DESIGN** | Randomised open-label parallel group study |
| **AIMS** | This study aims to assess the impact of real-time continuous glucose monitoring and intermittently viewed continuous glucose data on frequency, duration and severity of hypoglycaemia in people with type 1 diabetes and impaired awareness of hypoglycaemia. |
| **OUTCOME MEASURES** | The primary outcome is percentage of time spent in hypoglycaemia (<3.3mmol/L, 60mg/dL) measured by a continuous glucose sensor. Secondary outcomes include other measures of hypoglycaemia, overall glucose status and patient reported quality of life. |
| **POPULATION** | Adults with type 1 diabetes and impaired hypoglycaemia awareness |
| **ELIGIBILITY** | Participants identified in type 1 diabetes clinics and by recruitment from existing databases. |
| **DURATION** | 18 weeks |

## REFERENCE DIAGRAM



# 1. INTRODUCTION

## 1.1 BACKGROUND

Type 1 diabetes (T1DM) is characterised by autoimmune destruction of the pancreatic beta cell, 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. However, 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.

Hypoglycaemia is associated with morbidity and even mortality, and places a financial burden on health systems. Severe hypoglycaemia costs £13million per year in direct NHS costs and significantly more in indirect costs to people with diabetes, their families, friends and employers. Hypoglycaemia is one of the most common metabolic complications of the treatment of type 1 diabetes. Mild hypoglycaemia results in a variety of symptoms, including tremor, hunger, and anxiety, and, as glucose concentrations fall lower patients may develop cognitive impairment. Severe hypoglycaemia, defined as hypoglycaemia requiring the assistance of another person to treat, may cause seizures, coma, or death. 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 diabetes technology.

Type 1 diabetes directly affects 300,000 people in the United Kingdom. In the UK diabetes consumes more than 10% of the National Health Service budget 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).

Diabetes technologies, such as continuous glucose monitoring and insulin pump therapy can improve overall glucose control and may reduce the frequency and severity of hypoglycaemia when used in combination with education and support for self-management. However, despite this, 72.4% of people with T1DM in England have an HbA1c over 58mmol/mol (7.5%) and 16.6% have an HbA1c over 86mmol/mol (10%). Women aged 15 to 34 have a ninefold increase in mortality risk compared with women of the same age without diabetes. Diabetes remains the leading cause of blindness, amputation and end-stage renal failure in the developed world.

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.

The Dexcom G4 and G5 systems are CE marked real-time continuous glucose sensor systems which provide dynamic glucose information to people with type 1 diabetes, or their carers. These glucose data are updated every 5 minutes. Sensors are used for 7 days before replacement. The G4 system sensor requires calibration to capillary blood glucose values twice a day and verification with a capillary blood glucose test before treating diabetes based on sensor reported data. The Dexcom G5 can be used non-adjunctively (does not require pre-treatment verification with capillary blood glucose before diabetes treatment decisions). The G5 system does require twice a day calibration with capillary blood glucose.

The Libre intermittent glucose monitoring system provides up to 8 hours of retrospective continuous glucose monitoring data to users when the monitor is waved in proximity with the sensor. In contrast to real-time CGM the Libre system sensor is used for 14 days and is non-adjunctive.

### 1.2 RATIONALE FOR CURRENT STUDY

This clinical study proposes to assess the impact of Libre on frequency, duration and severity of hypoglycaemia, compared with non-adjunctive use of the Dexcom G5 real-time CGM and will focus on people with impaired awareness of hypoglycaemia.

Hypothesis: Libre intermittent CGM has an equivalent impact on hypoglycaemia to real-time CGM.

## 2. STUDY OBJECTIVES

***Primary outcome:*** % time spent in hypoglycaemia (<3.3mmol/L, 60mg/dL)

***Secondary outcome:*** % time spent in hypoglycaemia (<2.8mmol/L, 50mg/dL)
% 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 (requiring third party assistance to treat)
MAD%
Glucose variability
HbA1c
Sensor usage (compliance)
Sensor life and % of sensor failure
% of reported sensor readings compared to total possible readings
Change in insulin dosage
Diabetes treatment satisfaction
CGM usability
Diabetes quality of life
Fear of hypoglycaemia
Healthcare professional qualitative feedback

## 3. STUDY DESIGN

Randomised parallel group trial over 18 weeks in 40 adult participants with type 1 diabetes and impaired hypoglycaemia awareness

## 4. PARTICIPANT ENTRY

### 4.1 PRE-REGISTRATION EVALUATIONS

HbA1c
Serum C-peptide
Plasma glucose
Gold score

### 4.2 INCLUSION CRITERIA

Adults over 18 years of age
Type 1 diabetes confirmed on the basis of clinical features and a fasting c-peptide <200 pmol/L
Severe hypoglycaemic event in the last 12 months requiring third party assistance OR a Gold Score ≥ 4
Type 1 diabetes for greater than 3 years
On an intensified multiple dose insulin injection regimen for > 6 months (MDI)
Previous type 1 diabetes structured education (either group or 1:1)

### 4.3 EXCLUSION CRITERIA

Use of CGM or Libre device within the last 6 months (except short periods of diagnostic blinded use under clinic supervision)
Use of regular paracetamol
Pregnant or planning pregnancy
Breastfeeding
Enrolled in other clinical trials, except at the discretion of the chief investigator
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 London - Hampstead where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie 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 Dr 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

**Screening**
Following informed consent study participants will give a full medical history, and medication history and will undergo a physical examination and ECG. Fasting blood tests will be sent to assess HbA1c, plasma glucose, urea and electrolytes, 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. A Gold Score questionnaire will be completed. If participants meet the inclusion criteria they will complete a structured participant interview and Quality of Life Questionnaires. A type 1 diabetes structured education refresher will be delivered according to the study curriculum and data from the preceding 4 weeks will be downloaded from the participants capillary blood glucose monitor using the Diasend software.

**Run-in**
Participants will then commence a 2 week run-in phase using the Dexcom G4 sensor with a blinded receiver which stores glucose data but does not make it available to the participant. During the run-in phase participants will wear a Dexcom G4 continuous glucose sensor in the

anterior abdominal wall. The sensor detects glucose in the interstitial fluid and is calibrated to capillary blood glucose values taken a minimum of twice daily. Sensors last seven days and participants will be instructed on how to remove a sensor and implant a new one. This run-in will provide baseline data on glucose control including frequency and severity of hypoglycaemia and information on subject's compliance with frequency of CGM use.

**Randomisation**
Participants will then receive standardised CGM education for the Dexcom and Abbott devices from study staff and will be randomised to Libre or the Dexcom G5 system with receiver. All education will be delivered by the research nurse from a predefined curriculum and will be supported by independent written materials. Both the Libre and G5 systems will be used non-adjunctively (without capillary blood glucose verification before making a treatment decision, in accordance with product licences) but 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 will use the G5 sensor with the accompanying receiver and will change sensor every seven days (or sooner in the event of sensor failure). Real-time glucose data will be available to participants. Participants will use the Libre sensor with the accompanying receiver and will change the sensor after 14 days (or sooner in the event of sensor failure). Participants will be enabled to use the Libre monitor to assess glucose value and trend as often as they choose.

**Follow-Up**
There will be a telephone visit 2 weeks after randomisation with a short, structured interview focusing on the function of the technology and any difficulties with use.

Participants will attend the clinical research facility 4 weeks after randomisation and data will be downloaded from their CGM device and self-monitoring using the Diasend software. At 8 and 16 weeks after randomisation participants will attend the clinical research facility and will have a blood test for HbA1c. They will additionally complete a Gold Score questionnaire, repeat the Quality of Life questionnaires, undergo a semi-structured interview conducted by the research team and data will be downloaded from their CGM device and capillary blood glucose monitor.

After 8 weeks all participants will be offered the opportunity to continue with the Dexcom G5 system for a further 8 week period. The G5 system in the follow-on may be used with the Dexcom receiver or Apple iOS smartphone application and will focus on usability, psychosocial outcomes and qualitative interviews. Participants will change the G5 sensor every seven days (or sooner in the event of sensor failure).

The participants will be provided with a contact number for technical support but insulin titration decisions will be made by the participant.

Quality of life, CGM-related treatment satisfaction and fear of hypoglycaemia data will be collected by mixed quantitative and qualitative methodologies. Validated (Problem Area in Diabetes (PAID),,Glucose Monitoring System Satisfaction Survey (GMSS), Hypoglycaemia Fear Survey-II(FHS-II)) and non-validated questionnaires will be used and scripted interviews with participants will be undertaken by the research team to assess the impact of the technology on everyday living with type 1 diabetes. Gold questionnaire will be used to assess impact on hypoglycaemia awareness.

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 depending during

the telephone visit depending on participant preference. High glucose alerts may be personalised.

The study will be completed at the end of the 8 week open label period.

# 7. STATISTICS AND DATA ANALYSIS

With 40 participants, we can demonstrate as significant at 80% power a mean difference in time in hypoglycaemia between Libre and G5 of 0.45 standard deviations. Any smaller difference will be distinguished as signifying no significant difference between Libre and CGM. To allow for a 10-15% drop out, 45 participants will be recruited. Randomisation will be stratified by HbA1c quartiles (5-6%, 6.1-7.0%, 7.1-8.0% and 8.1-9%). Randomisation will be done using sealedenvelope.com.

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

Analysis will be by 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 Kruskall Wallis test.

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 Chief Investigator has obtained approval from the London Hampstead Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D and MHRA approval letter before accepting participants into the study. 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.

### 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, Dr 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.

## 10. REFERENCES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3. Lawton J, Rankin D, Elliott J, Heller SR, Rogers HA, de ZN et al. Experiences, views, and support needs of family members of people with hypoglycemia unawareness: interview study. Diabetes Care. 2014; 37(1):109-115
4. Heller SR, Cryer PE. Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. Diabetes. 1991; 40(2):223-226
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7. Cranston I, Lomas J, Maran A, Macdonald I, Amiel SA. Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. Lancet. 1994; 344(8918):283-287

8. Cryer PE. Severe hypoglycemia predicts mortality in diabetes. Diabetes Care. 2012; 35(9):1814-1816

**APPENDICES**

- Summary of investigations, treatment and assessments
- Dexcom G4/ G5 instructions for use
- Abbott Libre instructions for use
- Validated questionnaires
  - PAID
  - Gold
  - CGMSS
  - HFS-II
- CGM questionnaire

## Appendix 1. Summary of investigations, treatment and assessments

| | Screening | Randomisation | 2 weeks | 4 weeks | 8 weeks | 16 weeks |
|---|---|---|---|---|---|---|
| History | x | | | | | |
| Medication history | x | | | | | |
| ECG | x | | | | | |
| Physical examination | x | | | | | |
| Urine pregnancy test | x | | | | | |
| HbA1c | x | | | | x | x |
| Glucose | x | | | | | |
| Urea/ electrolytes | x | | | | | |
| TFT | x | | | | | |
| 9am cortisol | x | | | | | |
| Coeliac screen | x | | | | | |
| C-peptide | x | | | | | |
| Gold Score | x | | | | x | x |
| Participant interview | | x | | | x | x |
| QoL Questionnaires | | x | | | x | x |
| Diabetes Education | | x | | | | |
| CGM education | | x | | | | |
| Meter download | | x | | x | x | x |
| Telephone consultation | | | x | | | |
| CGM download | | | | x | x | x |
| Research clinic visit | x | x | | x | x | x |