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STUDY PROTOCOLS

Hypo-METRICS: Hypoglycaemia—MEasurement, ThResholds and ImpaCtS—A multi-country clinical study to define the optimal threshold and duration of sensor-detected hypoglycaemia that impact the experience of hypoglycaemia, quality of life and health economic outcomes: The study protocol

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Abstract

Introduction: Hypoglycaemia is a significant burden to people living with diabetes and an impediment to achieving optimal glycaemic outcomes. The use of continuous glucose monitoring (CGM) has improved the capacity to assess duration and level of hypoglycaemia. The personal impact of sensor-detected hypoglycaemia (SDH) is unclear. Hypo-METRICS is an observational study designed to define the threshold and duration of sensor glucose that provides the optimal sensitivity and specificity for events that people living with diabetes experience as hypoglycaemia.

Methods: We will recruit 600 participants: 350 with insulin-treated type 2 diabetes, 200 with type 1 diabetes and awareness of hypoglycaemia and 50 with type 1 diabetes and impaired awareness of hypoglycaemia who have recent experience of hypoglycaemia. Participants will wear a blinded CGM device and an actigraphy monitor to differentiate awake and sleep times for 10 weeks. Participants will be asked to complete three short surveys each day using a bespoke mobile phone app, a technique known as ecological momentary assessment. Participants will also record all episodes of self-detected hypoglycaemia on the mobile app. We will use particle Markov chain Monte Carlo optimization to identify the optimal threshold and duration of SDH that have optimum sensitivity and specificity for detecting patient-reported hypoglycaemia. Key secondary objectives include measuring the impact of symptomatic and asymptomatic SDH on daily functioning and health economic outcomes.

Ethics and dissemination: The protocol was approved by local ethical boards in all participating centres. Study results will be shared with participants, in peer-reviewed journal publications and conference presentations.

KEYWORDS

continuous glucose monitoring, hypoglycaemia, patient-reported hypoglycaemia, quality of life, sensor-detected

1 | INTRODUCTION

Hypoglycaemia has been a barrier to optimal glycaemic outcomes in people with diabetes since the discovery of insulin. The International Hypoglycaemia Study Group defines three biochemical classifications of hypoglycaemia: level 1, below ≤ 3.9 mmol/L; level 2, below ≤ 3.0 mmol/L; and level 3, severe hypoglycaemia (requiring third-party assistance)^{1,2} based on thresholds for physiological and cognitive responses. The varied impact of these levels of hypoglycaemia on different aspects of daily functioning and quality of life (QoL) in people living with diabetes is poorly understood.

In the past decade, continuous glucose monitoring (CGM) devices measuring interstitial glucose continuously are increasingly used in clinical practice and research has revealed significantly more episodes of hypoglycaemia than capillary blood glucose (CBG), with eight

times more hypoglycaemic episodes recorded on CGM than reported by people with diabetes.³ While the information provided by CGM helps people with diabetes to lower HbA1c, reduce hypoglycaemia and potentially reduce diabetes distress,⁴ there are concerns about whether all episodes of hypoglycaemia identified by sensors are clinically and personally meaningful.

Differences occur when we measure hypoglycaemia using interstitial glucose as opposed to capillary or venous glucose. Interstitial glucose measurements lag behind blood glucose levels.^{5,6} Operational issues (e.g., compression of the sensor during sleep) may create artefacts that are difficult to differentiate from true hypoglycaemia.⁶ 'Noise' in the data can cause small fluctuations around any given threshold. Furthermore, CGM provides data on the duration of episodes of hypoglycaemia, which must now be included in the definition of sensor-detected hypoglycaemia (SDH). The limitations of SDH can be confusing

and frustrating for people with diabetes, who must make sense of the data and the personal impact of each episode.⁷

A consensus statement recently defined a hypoglycaemic event using CGM as an event with sensor glucose of ≤ 3.0 mmol/L for at least 15 min.¹ This definition appears to have a high sensitivity for hypoglycaemia but a low specificity, leading to a high rate of asymptomatic episodes even in those with apparently well-preserved awareness of hypoglycaemia.⁸

Time below target glucose range (TBR) has become a key metric for assessing hypoglycaemia in clinical practice and research. While TBR is useful for considering overall hypoglycaemia exposure, it is possible that different durations and thresholds of hypoglycaemia may have different impacts. The personal impact of multiple short day-time episodes may be very different to a single prolonged overnight event although their time below range may be similar. This granularity is lost with the overarching metric of TBR, and when questionnaires with long recall periods are used to assess the personal impact. Given the high proportion of asymptomatic SDH events, it is unclear what impact these have on daily functioning and what the implications are for QoL.

Increasing the precision and detection of symptomatic and asymptomatic hypoglycaemia and understanding the direct impact of these on daily functioning and QoL will enable a universal definition of SDH with known health economic outcomes. Such an evidence-based definition will help standardize hypoglycaemia outcome reporting and assist policymakers in their remuneration decisions.

The Hypo-RESOLVE programme is funded by the European Union Innovative Medicines Initiative to increase our understanding of hypoglycaemia and its personal, clinical and economic consequences.⁹ Within Hypo-RESOLVE, the Hypo-METRICS trial will provide an evidence-based definition of SDH and further our understanding of the clinical, psychological and health economic impacts of both symptomatic and asymptomatic

hypoglycaemia. While we know that symptoms of hypoglycaemia, and glucose thresholds for those symptoms, vary between individuals and within individuals, this study will identify the optimal parameters of SDH that offer the best compromise between sensitivity and specificity across a population.

2 | METHODS AND ANALYSIS

2.1 | Study design

Hypo-METRICS is a multinational, observational study. It will use blinded CGM, actigraphy, validated questionnaires (Table 1), routine clinical data and daily ecological momentary assessments (EMA) through a bespoke Hypo-METRICS app²² over a period of 10 weeks to collect data on sensor glucose levels, sleep, activity and person-reported outcomes. Recruitment commenced in October 2020 and is due to be completed by April 2022.

2.2 | Study setting

The trial will take place in specialist diabetes centres at nine sites in five countries: the United Kingdom, Denmark, the Netherlands, Austria and France.

2.3 | Participants

In all, 600 participants will be recruited;

- 200 adults living with type 1 diabetes mellitus and normal awareness of hypoglycaemia (NAH) (Gold score < 4).¹²

TABLE 1 List of questionnaires

Questionnaire	Domain assessed
1. Hypoglycaemic Fear Survey II (HFS-II) ¹⁰	Fear of hypoglycaemia
2. Modified Clarke, ¹¹ Gold Score, ¹² Hillerød method, ¹³ and Hypo-AQ ¹⁴	Awareness of hypoglycaemia
3. Hypo Cues Questionnaire ^{14,a}	Experiences with hypoglycaemia
4. SF-36 Vitality subscale only ¹⁵	Energy levels
5. PAID-20 (Problem Areas In Diabetes) ¹⁶	Diabetes distress
6. DIDP (DAWN Impact of Diabetes Profile) ¹⁷	Diabetes-specific quality of life
7. PDQ-20 (Perceived Deficit Questionnaire) ¹⁸	Perceived cognitive difficulties
8. DS-14 (Type D Scale) ^{19,b}	Type D personality trait
9. GAD-7 (General Anxiety Disorder-7) ²⁰	Anxiety symptoms
10. PHQ-9 (Patient Health Questionnaire – 9) ²¹	Depressive symptoms

^aUK sites only, to be validated.

^bCompleted at visit 1 only.

- 50 adults with type 1 diabetes mellitus and impaired awareness of hypoglycaemia (IAH) (Gold score ≥ 4).¹²
- 350 adults living with type 2 diabetes taking ≥ 1 insulin injection/day (a minimum of 25% of participants will be over 60 years of age).

Awareness of hypoglycaemia will be measured by the Gold score.¹² Key inclusion criteria for the study are being adult (aged 18–85 years), living with type 1 diabetes mellitus or type 2 diabetes mellitus, taking at least one insulin injection per day and at least one episode of hypoglycaemia in the last month. Key exclusion criteria are an eGFR of $< 30 \text{ mL/min/1.73 m}^2$ and the use of automated insulin delivery systems. A full list of inclusion and exclusion criteria is available in Table S1.

2.4 | Study procedures and follow-up

2.4.1 | Baseline assessments

Informed written consent will be obtained with time for the participant to read the participant information sheet, consent form and ask questions. Baseline data will be recorded for each participant, including a brief medical history, healthcare resource use in the previous 12 months and experience of hypoglycaemia. The participant will complete a set of baseline questionnaires (Table 1) via an online platform (Qualtrics) <https://www.qualtrics.com>.

At baseline, we will collect blood samples for HbA_{1c} and creatinine and urine for albumin creatinine ratio. Data from routine care records within the last 4 weeks can be used if available. A 4-week download will be taken from each participant's routine glucose monitoring device, insulin pump and/or downloadable insulin pens. These will be anonymized, stored and recorded in the electronic case report form (eCRF).²³

Participants will be trained to use the study devices and record episodes of self-reported hypoglycaemia on the Hypo-METRICS app. For this study, we have defined patient-reported hypoglycaemia (PRH) as a symptomatic hypoglycaemic episode that resolved on ingestion of carbohydrate, or a measured glucose value $< 4 \text{ mmol/L}$.

2.5 | Study devices

2.5.1 | Continuous glucose monitoring

The Abbott Freestyle Libre 2 sensor and reader will be used for this study. The reader will be blinded using bespoke software provided by Abbott and alarms will be disabled. If the reader is out of Bluetooth range of the sensor, up to eight hours of data can be retrieved from the sensor by

scanning with the reader. Participants will be trained on insertion and removal of sensors and asked to scan at least three times a day to maintain data coverage. Data will be stored on the reader for the duration of the 10-week study and downloaded using bespoke software at visit 5.

2.5.2 | The Hypo-METRICS app

Participants will complete a check-in on the app three times per day for 10 weeks. The design and development of the Hypo-METRICS app are detailed in a prior publication.²² Briefly, the app includes:

1. 'Check-ins': Participants will complete three short sets of questions ('check-ins') in the morning, afternoon and evening. These will capture details about daily functioning across domains of sleep, mood, anxiety, fear of hypoglycaemia and hyperglycaemia, cognitive functioning, social functioning and productivity. The app will notify participants when check-ins are due. Participants will also self-report details of hypoglycaemic episodes that have occurred since the last check-in, including detection and treatment.
2. The 'Motif': This feature enables reporting of hypoglycaemic symptoms and severity in real time (Figure 1).
3. Validated questionnaires: Three validated questionnaires are also administered via the app. The first is a daily assessment of health status (EQ-5D-5L²⁴). In addition, there are weekly validated assessments of sleep²⁵ and productivity.²⁶

The Hypo-METRICS app is delivered via the software platform provided by uMotif Limited (<https://www.umorif.com/>), which participants can download to their smartphone (Figure 1).

Smartphones are provided for the duration of the study for those without a compatible device.

2.6 | Actigraphy

The FitBit Charge 4 will collect data on sleep duration,²⁷ heart rate and step count. This is worn continuously on the wrist, including at night to determine when participants were awake or asleep.

2.7 | Subsequent visits

2.7.1 | Visits 2, 3 and 4

These are brief virtual visits that will take place at weeks 2, 4 and 6. Issues with the devices will be addressed and

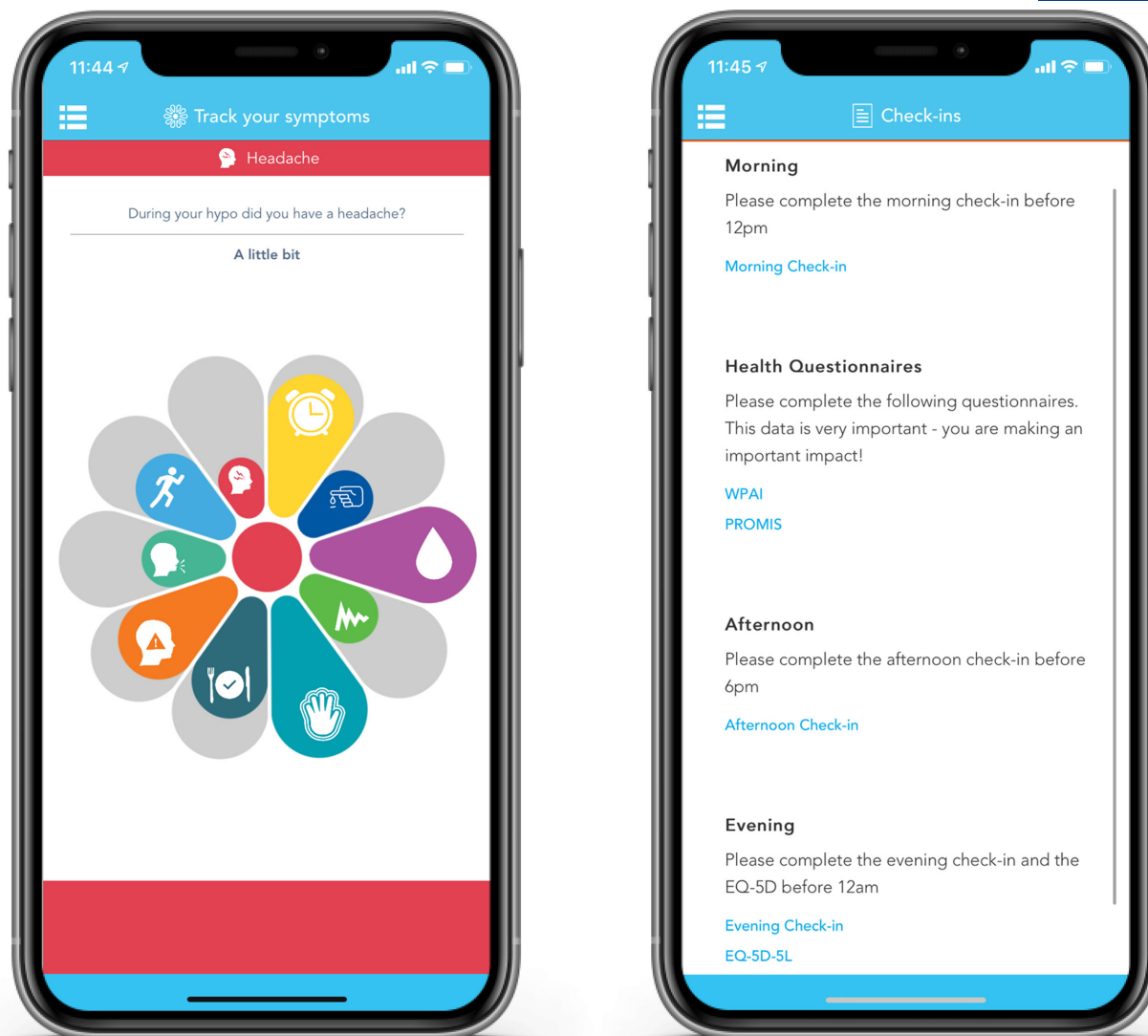


FIGURE 1 Motif and check-ins

minimum data collection will be confirmed. Details of adverse events (including severe hypoglycaemic episodes) will be recorded in the eCRF.

2.7.2 | Visit 5

This visit at week 10 will mark the end of the data recording on the study devices. At this visit, the study team will:

- Download data from the Libre 2 reader and the participants' glucose meter, insulin pump and/or connected pen.
- Download data from the Hypo-METRICS app and FitBit
- Re-administer questionnaires (Table 1)
- Collect blood samples for HbA_{1c} and random C-peptide level

- Collect data on healthcare resource utilization and severe hypoglycaemic episodes over past 10 weeks
- Participants will have the option to provide additional blood samples at this visit for biobanking and peripheral blood mononuclear cell samples.

2.7.3 | Visit 6

There will be one follow-up visit up to 52 weeks after beginning the study. Data will be collected about episodes of severe hypoglycaemia, healthcare resource utilization and major health issues that have occurred since completing the study, and a blood sample will be taken for HbA_{1c} and questionnaires will be repeated (Table 1).

2.8 | Participant timeline

The participant timeline for the study is outlined in the Table S2, with an overview in Figure 2. Due to the COVID-19 pandemic, participants can do all visits virtually.

2.9 | Patient and public involvement (PPI)

People living with diabetes have been involved throughout the development of the Hypo-METRICS study. The Hypo-RESOLVE Patient Advisory Committee has assisted us in the selection of the questionnaires and has provided feedback on the viability of study visits. Two specific PPI groups (seven people with type 1 diabetes mellitus [four women, three men, aged 19–55 years] and eight with type 2 diabetes mellitus [four women, four men, aged 59–72 years] local to King's College London

supported the development of the questions used for the Hypo-METRICS app.

2.10 | Primary and secondary objectives

2.10.1 | Primary objectives

The primary objective of this study is to define the threshold and duration of sensor glucose that provides the optimal sensitivity and specificity for events that people living with diabetes experience as hypoglycaemia.

2.10.2 | Secondary objectives

Secondary outcomes are the evaluation of the impact of symptomatic and asymptomatic SDH using the definition from the primary objective, on three key domains (Table 2).

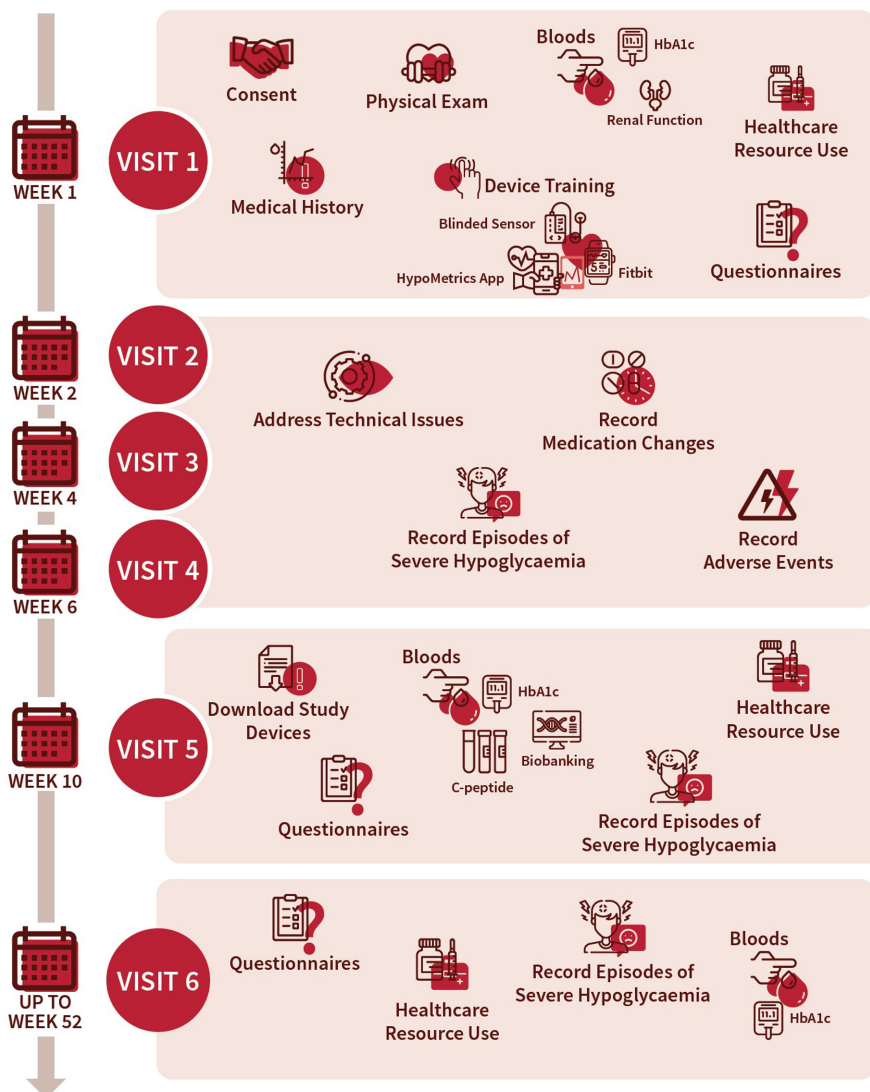


FIGURE 2 Participant timeline for the study

TABLE 2 Table of objectives

Primary objective
1. To define the threshold glucose value and duration of sensor glucose that provides the optimal sensitivity and specificity for events that people living with diabetes experience as hypoglycaemia.
Secondary objectives
Biochemical
1.1. To assess the effect of the following factors on sensitivity and specificity of the newly defined SDH:
1.1.1. Type of diabetes (type 1 diabetes mellitus or type 2 diabetes mellitus)
1.1.2 Sleep status (asleep or awake)
1.1.3 Usual method of glucose monitoring (CBG vs Flash vs CGM)
1.1.4 Rate of SDH during the study
1.1.5 Glycaemic Variables (HbA _{1c} , Time in & below range, mean glucose)
1.2 Compare the rates of hypoglycaemia as defined by our new definition vs ATTD consensus definition in independent datasets.
1.3 To investigate the following baseline factors as predictors of SDH and PRH:
1.3.1 Biochemical factors
1.3.2 Psychological factors (see Table 1)
1.3.3 Socio-demographic factors
1.4 To compare the rates of SDH and PRH in those using CBG vs Flash/CGM
1.5 To assess the impact of the rate of SDH on rates of PRH and severe hypoglycaemia
Daily functioning and psychological factors
2.1 To conduct psychometric analyses to explore reliability and validity of the Hypo-METRICS app.
2.2 To explore the impact of symptomatic and asymptomatic SDH on domains of daily functioning (measured with the Hypo-METRICS app).
2.3 To investigate whether the impact (from 2.2) of changes depends on diabetes type, sleep status, hypoglycaemic awareness status and after adjustments for relevant variables.
2.4 To explore the cumulative effect and duration of effect of SDH on daily functioning.
Health economic
3.1 To calculate the country-specific quality adjusted life year (QALY) associated with SDH.
3.2 To calculate the effect of SDH on work and productivity.
3.3 To explore the relationship of SDH with healthcare utilization.
3.4 To determine the parameters of SDH that best identify 1.5-h loss of effective work/ activity and a reduction of 0.07 QALYs.

2.11 | Sample size

Sample size calculations were performed for the primary objective for hypoglycaemia aware type 1 diabetes

mellitus and type 2 diabetes mellitus participants separately, with the statistical power of $\gamma = 80\%$ and the significance level of $\alpha = 0.05$. The sample size was calculated for the negative binomial regression, as this regression directly models the effect of SDH rate on the rate of PRH events which is the main response in the primary objective. Using published data, we estimated rates of SDH and PRH to be 4.8 and 1.3 events/patient-week, respectively, in type 1 diabetes mellitus⁸ and 1.9 and 0.3 events/patient-week in type 2 diabetes mellitus.^{3,28} Employing these parameters, the minimum required number of type 1 diabetes mellitus and type 2 diabetes mellitus participants was calculated as 180 and 321, respectively. We adjusted for 10% dropout, aiming to recruit to 200 type 1 diabetes mellitus with NAH and 350 type 2 diabetes mellitus. Participants with IAH will not be included in the primary analysis.

2.12 | Statistical methods

2.12.1 | Primary objective

The primary objective of the study is to define the threshold and duration of sensor glucose that provides the optimal sensitivity and specificity for events that people living with diabetes experience as hypoglycaemia

The definition of SDH has two parameters: a glucose threshold (h) and a minimum duration (t) below that threshold, as illustrated in [Figure 3](#).

PRH will be obtained from the Hypo-METRICS app. We will exclude events where the reported glucose was >5.6 mmol/L or the participant reported that they 'prevented' hypoglycaemia. We will apply ranges for threshold between 5.6 and 2.2 mmol/L and for duration between 5 and 300 min, values considered of potential clinical relevance. We will use the lowest glucose within ± 1 h of the reported time for the analysis, to allow for any inaccuracy of the time stamp reported by the participant on the app. We will use particle Markov chain Monte Carlo optimisation to identify the optimal threshold and duration of

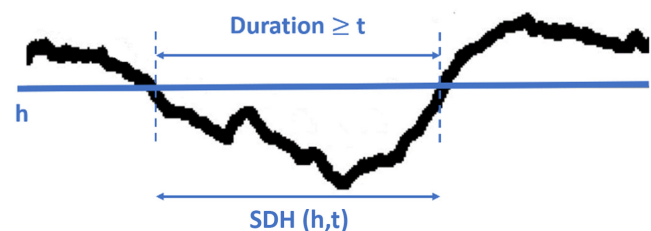


FIGURE 3 A SDH defined by a threshold, h , and a minimum duration, t , under the threshold

SDH that makes the best trade-off between the sensitivity and specificity for detecting PRH²⁹. The sensitivity is calculated as the number of true positives over the total number of PRHs, where a true positive is a PRH which is matched to a SDH. A SDH which is not matched to a PRH, is a false positive. By dividing the number of false positives by the total number of SDH events, the precision is calculated by subtracting this fraction from one. This allows the calculation of the F_β score, measuring the effectiveness of the SDH to detect PRH, using the formula below:

$$F_\beta = (1 + \beta^2) \cdot (\text{Precision} \cdot \text{sensitivity}) / (\beta^2 \text{Precision} + \text{Sensitivity})$$

When β is >1 , sensitivity is prioritized and when β is <1 precision is prioritized. Thus, the optimal parameters for SDH are the threshold and duration that have the highest F_β score (or detection performance for PRH). The statistical analysis plan has been tested in various simulations reported in Mahmoudi et al.²⁹ Optimal parameters for each participant will be calculated, and then we will generate an overall optimal definition that combine data from all participants and weight for individual events of SDH and PRH.

For CGM data gaps shorter than 30min, we will use linear interpolation to fill gaps. Where gaps are >30 min, those data will not be used. Where the total data of CGM or EMA provided is $<70\%$ of the 10 weeks of data, those subjects will be excluded from the primary analysis to prevent bias in reporting (Figure 4).

2.13 | Secondary analyses

Once the primary objective is complete, the new definition will be used to analyse the secondary objectives. The secondary objectives in Table 2 will be examined in an independent fashion in each domain.

2.14 | Biochemical outcome analysis

By dividing our dataset into validation and test data, we will test the sensitivity and specificity of our definition of SDH in type 1 diabetes mellitus and type 2 diabetes mellitus, sleep status, method of glucose monitoring and based on rate of SDH during the study. We will then compare the rate of SDH using our new definition to the consensus definition from the ATTD.² We will use independent datasets from the wider Hypo-RESOLVE group to measure the rate of SDH using both definitions. We will also analyse the rates of SDH and PRH in those using CGM vs those use CBG during the 10 weeks of the study and the impact of different biopsychosocial variables on rates of SDH and PRH.

2.15 | Daily functioning and psychological factors analysis

Key among our secondary objectives is exploring the impact of symptomatic and asymptomatic SDH on domains

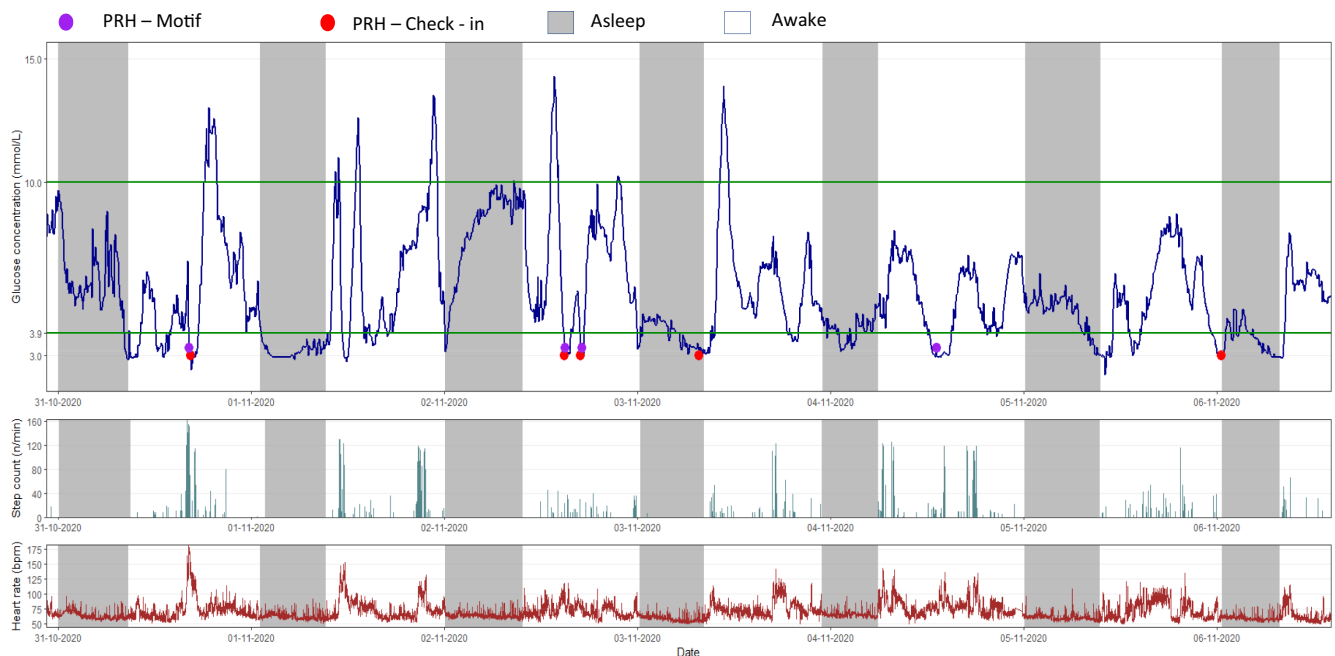


FIGURE 4 Data visualization; Sensor glucose with step count and heart rate over time

of daily functioning (measured with the Hypo-METRICS app), which have been validated, as described by Søholm et al.²² Using the definition from our primary objective and data collected from the Hypo-METRICS app and the blinded CGM, we will compare daily functioning between days with and without symptomatic and asymptomatic hypoglycaemia. We will also explore whether the impact changes depending on diabetes type, sleep status, hypoglycaemia awareness and after adjustments for related variables. Finally, we will explore the cumulative effect and duration of effect of SDH on psychological factors (see Table 1) at follow-up.

2.16 | Health economic analysis

We will calculate utility scores from the EQ-5D-5L responses using country-specific tariffs^(30–35) and data recorded in the Hypo-METRICS app and eCRF. For countries with no tariff, we will use the UK tariff. We will calculate QALYs from the utility scores using the area under the curve method. We will calculate the total number of working hours lost either due to absenteeism or low productivity using the work productivity and activity impairment questionnaire. We will use panel data methods to estimate the effect of SDH on working hours lost and QALYs in each week. We will adjust for age, gender, severe hypoglycaemic episodes, diabetes-related complications and study site. We will conduct exploratory analyses on healthcare resource use to see whether SDH over a 10-week period is associated with changes in medication, visits to family doctors/general practitioners and hospital visits both over the 10-week and 52-week period.

2.17 | Data collection

We have created an eCRF using REDCap, which is GDPR and HIPPA compliant.²³ Data collected during all study visits will be entered directly into REDCap with source data, such as CGM and CBG downloads, uploaded as .csv files into this database. Questionnaires will be completed on Qualtrics and exported as .csv files into REDCap.

All data collected through uMotif, Qualtrics, REDCap and FitBit will be collected using a unique patient identifier.

2.18 | Monitoring

Regular monitoring will be performed according to the trial-specific Monitoring Plan. The monitors will verify

that the clinical trial is conducted, and data are generated, documented and reported in compliance with the protocol, UK good clinical practice guidelines and the applicable regulatory requirements.

2.19 | Ethics

Ethical approval to conduct the study has been granted in the UK by Oxford B Research Ethics Committee, in the Netherlands by CMO Region Arnhem-Nijmegen, in Austria by Ethikkommission der Medizinischen Universität Graz, in Denmark by Videnskabssetisk Komite for Region Hovedstaden and in France by the Comite Die Protection Des Personnes SUD Mediterranee IV.

The trial registration number is NCT04304963.

2.20 | Dissemination

We will report the results of the trial to the participants through written and verbal reports, at national and international conferences and in peer-reviewed scientific journals.

AUTHORS' CONTRIBUTIONS

PD revised and adapted the protocol, is responsible for the operations of the study, and wrote and revised the paper. NZ wrote the first draft of the protocol, contributed to the design of the study and the development of the Hypo-METRICS app, led the PPI and PAC reviews of the protocol, contributed to writing and revising the paper, and is the trial manager. UF was involved in the development of the Hypo-METRICS app, contributed to writing of passages and reviewed the paper for content. JS reviewed the draft protocol for critical content and approved the final version. PC contributed to the design of the study and the development of the Hypo-METRICS app, led the PPI and PAC reviews of the protocol, supported the writing of the paper, reviewed drafts and is the trial PI.

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CONFLICT OF INTEREST

SAA has served on advisory boards for NovoNordisk and Medtronic and has spoken at an educational symposium sponsored by Sanofi. MLE has served on advisory boards and/or received lecture fees and/or research support from NovoNordisk, Eli Lilly, AstraZeneca, Medtronic, Dexcom, Ypsomed, Abbott Diabetes Care, Roche, NGM Pharma, Zucara, Pila Pharma. UPB has served on advisory boards and has received lecture fees from Sanofi and Novo Nordisk. JKM is a member in the advisory board of Boehringer Ingelheim, Eli Lilly, Medtronic, NovoNordisk AS, Prediktor A/S, Roche Diabetes Care, Sanofi-Aventis and received speaker honoraria from Abbott Diabetes Care, Astra Zeneca, Dexcom, Eli Lilly, Medtronic, MSD, NovoNordisk AS, Roche Diabetes Care, Sanofi, Servier and Takeda. ER has served as a consultant/advisor for Abbott, Air Liquide SI, Astra-Zeneca, Boehringer-Ingelheim, Dexcom, Eli-Lilly, Hillo, Insulet, Medirio, Novo-Nordisk, Roche, Sanofi-Aventis, Tandem, and received research support from Dexcom and Tandem. JS has served on advisory boards for Janssen, Medtronic, Roche Diabetes Care and Sanofi Diabetes; her research group (Australian Centre for Behavioural Research in Diabetes [ACBRD]) has received honoraria for this advisory board participation and has also received unrestricted educational grants and in-kind support from Abbott Diabetes Care, AstraZeneca, Medtronic, Roche Diabetes Care and Sanofi Diabetes. JS has also received sponsorship to attend educational meetings from Medtronic, Roche Diabetes Care, and Sanofi Diabetes, and consultancy income or speaker fees from Abbott Diabetes Care, AstraZeneca, Medtronic, Novo Nordisk, Roche Diabetes Care and Sanofi Diabetes. PC has received personal fees Abbott Diabetes Care, Insulet, Dexcom, Novo Nordisk, AstraZeneca, Medtronic, Roche Diabetes Care and Sanofi Diabetes. Research funding support from Abbott Diabetes Care, Medtronic and Novo Nordisk.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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