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Impact of real-time glucose monitoring using FreeStyle Libre 3 on glycaemia in type 2 diabetes managed with basal insulin plus SGLT2 inhibitor and/or GLP-1 agonist: the FreeDM2 randomised controlled trial protocol

Emma G Wilmot,[1,2] Ramzi A Ajjan,[3,4] Yee S Cheah ,[5] Pratik Choudhary,[6] Iain Cranston,[7] Rachel Ann Elliott ,[8] Mark Evans,[9,10] Ahmed Iqbal,[11,12] Shafie Kamaruddin,[13] Katharine Barnard-Kelly ,[14] Alistair Lumb ,[15,16] Thinzar Min ,[17] Patrick Moore,[18] Parth Narendran,[19] Sankalpa Neupane,[20,21] Gerry Rayman ,[22] Thozhukat Sathyapalan,[23,24] Hood Thabit,[25,26] Thomas Yates,[27,28] Lalantha Leelarathna [26,29]

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For numbered affiliations see end of article.

Correspondence to
Dr Lalantha Leelarathna; e.leelarathna@imperial.ac.uk

ABSTRACT

Introduction Effective management of type 2 diabetes mellitus (T2DM) consists of lifestyle modification and therapy optimisation. While glycaemic monitoring can be used as a tool to guide these changes, this can be challenging with self-monitoring of blood glucose (SMBG). The FreeStyle Libre 3 (FSL3) is a real-time continuous glucose monitoring (CGM) system designed to replace SMBG. The evidence for the benefit of CGM in people with T2DM on non-intensive insulin regimens is limited. This study aims primarily to assess the glycaemic impact of FSL3 in people with suboptimally controlled T2DM treated with basal-only insulin regimens plus sodium-glucose cotransporter-2 (SGLT-2) inhibitor and/or glucagon-like peptide (GLP)-1 agonist.

Methods and analysis This is an open-label, multicentre, parallel design, randomised (2:1) controlled trial. Recruitment has been offered across 24 clinical centres in the UK and nationally through self-referral. Adults with T2DM treated with basal-only insulin regimens plus SGLT-2 inhibitor and/or GLP-1 agonist and with screening HbA1c from ≥59 mmol/mol to ≤97 mmol/mol are included. Eligible participants will be randomised to either FSL3 (intervention) for 32 weeks or continuation of SMBG (control). The study is split into two phases, each of 16 weeks duration: phase 1 consisting of self-management with basal-insulin self-titration and phase 2 where additional therapies may be initiated. Control group participants may subsequently enter an optional extension phase to receive FSL3. The primary endpoint is the difference between treatment groups in mean change from baseline in HbA1c at 16 weeks. Secondary outcomes include HbA1c at 32 weeks, CGM-based metrics, therapy changes, physical activity levels and psychosocial measures. An economic evaluation for costs and patient outcomes will be undertaken.

Ethics and dissemination The study was approved by the Health Research Authority, Health and Care Research Wales and the West Midlands-Edgbaston Research Ethics Committee (reference: 23/WM/0092). Study results will be disseminated in peer-reviewed journals.

Trial registration number NCT05944432.

Secondary identifying number Identifier assigned by the sponsor: ADC-UK-PMS-22057.

Protocol version Revision D. Dated, 13 December 2024.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This randomised controlled trial has a two-phase design (self-management and therapy escalation) and will assess the impact of continuous glucose monitoring (CGM) specifically in people with type 2 diabetes mellitus treated with basal-only insulin plus SGLT-2 inhibitor and/or glucagon-like peptide (GLP)-1 or dual gastric inhibitory polypeptide/GLP-1 agonist.

⇒ A wide variety of secondary outcomes including CGM-based metrics, physical activity and psychosocial evaluation will aim to capture the impact of the intervention in a holistic manner while understanding the mechanisms behind improved outcomes.

⇒ Recruitment has been offered nationally through self-referral with the option of participants taking part in the study remotely.

⇒ The study is open-label and conducted in the UK only, which may limit the generalisability of findings to other regions of the world.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most common metabolic disorder worldwide

with its prevalence increasing rapidly.[1] A cornerstone of diabetes care is self-management consisting of individualised lifestyle modifications including diet and exercise as well as glycaemic monitoring. Additionally, optimising pharmacological therapies is key for achieving treatment goals and reducing long-term complications. Most individuals with T2DM will eventually undergo treatment intensification involving the stepwise introduction of glucose lowering medications to improve glycaemic management as measured by HbA1c.[2] Given that a high proportion of diabetes-related burden is attributed to cardiorenal complications, prescription of sodium-glucose cotransporter-2 (SGLT-2) inhibitor therapy is recommended for the majority of people living with T2DM for both improved HbA1c and cardiorenal protection.[3] In recent years, the use of glucagon-like peptide (GLP)-1 and dual gastric inhibitory polypeptide (GIP)/GLP-1 agonists has increased rapidly in accordance with the increasing evidence of associated cardiovascular and weight loss benefits.[4] Where glycaemic targets are still not achieved, treatment is further intensified through the introduction of basal insulin regimens. However, despite this intensification, a significant proportion of patients do not achieve glycaemic targets.[5]

Self-monitoring of blood glucose (SMBG) is an important tool for people with T2DM treated with insulin; however, this is often associated with pain, inconvenience and low adherence.[6] Continuous glucose monitoring (CGM) systems are being increasingly adopted as a replacement for SMBG by offering greater convenience and insights into glucose trends.[7] They can also support lifestyle modifications by providing individualised feedback on how behaviours impact glycaemic responses.[8] The FreeStyle Libre (FSL) 3 (Abbott Diabetes Care, Witney, UK) is a CGM device worn on the posterior arm for up to 14 days. Compared with previous generations of FSL known as flash glucose monitoring systems, which required users to scan their sensor, FSL3 is a real-time CGM that communicates glucose data every minute via Bluetooth to a mobile phone app where users can view current and historic glucose trends. Additionally, users may set up optional alarms for when glucose values pass configurable high or low thresholds.

While the role of CGM is well established in T1DM,[9 10] further research is required to fully elucidate the benefits of CGM in T2DM. Previous studies have demonstrated improvements in HbA1c, CGM metrics and quality of life with CGM in T2DM treated with intensive insulin regimens.[11–14] Other studies have been performed in mixed T2DM populations; however, these are limited by single-centre design or not specifically assessing those on basal-only insulin regimens.[15–17] Much of the evidence in T2DM treated with non-intensive insulin regimens is limited to retrospective observational studies that demonstrated HbA1c reductions of 0.6–1.4%, 3–6 months following initiation of FSL.[18 19] A recent randomised controlled trial (RCT) demonstrated an adjusted difference in HbA1c of −0.4% in T2DM patients treated with basal insulin using CGM compared with continuation of SMBG after 8 months.[20] While this study included approximately 27% of participants treated with basal insulin plus SGLT-2 inhibitors and/or GLP-1 agonists, there have been no RCTs conducted to date that assess the benefit of CGM specifically in this population. This therapeutic combination represents a significant proportion of patients with T2DM, and the additional glycaemic benefit that CGM may provide over therapies which already exert significant glucose lowering effects remains to be elucidated. Furthermore, these previous studies have been unable to fully discern the mechanisms of change for the observed decreases in HbA1c. It has been hypothesised that CGM likely facilitates a reduction in HbA1c due to a combination of lifestyle changes such as increased physical activity and improved food choices as well as changes to diabetic therapy.[21 22] Interestingly, previous studies have demonstrated either no or minimal difference in insulin usage between groups[12 20 23] or a decrease in daily insulin use associated with CGM use.[15]

CGM is now universally available for people with T1DM in the UK, but recommendations for use in T2DM are more limited. Currently, CGM is only recommended for people with T2DM on intensive insulin regimens at risk of recurrent or severe hypoglycaemia, impaired hypoglycaemia awareness, an inability to perform SMBG or are required to self-measure ≥8 times per day.[24] Despite the presence of national guidelines for CGM use, inequalities in access to diabetes technology exist. Those from ethnic minorities and areas of higher deprivation are less likely to have access to CGM due to a variety of factors such as education levels, socioeconomic circumstances and variations in funding between regions.[25 26] Concurrently, T2DM is more prevalent and associated with worse outcomes in these populations that are often underrepresented in clinical trials, reducing the generalisability of results.[27 28]

Therefore, the FreeDM2 study aims to evaluate the impact of commencing FSL3 in people with T2DM treated with basal-only insulin plus SGLT-2 inhibitor and/or GLP-1 or dual GIP/GLP-1 agonist in a pragmatic manner. The clinically relevant primary endpoint of difference between treatment groups in mean change from baseline in HbA1c at 16 weeks, as well as a variety of clinical, psychosocial, usability and economic outcomes, aims to inform best clinical practice. The study is conducted in usual care settings with a visit schedule and therapy optimisation plan that mirror usual care in a UK setting. Furthermore, the study aims to facilitate the recruitment of participants from ethnic minority groups and those from areas of higher deprivation who are historically under-represented in diabetes research.

METHODS AND ANALYSIS

Trial design

FreeDM2 is an open-label, multicentre, parallel design, superiority, pragmatic, RCT (2:1) with economic

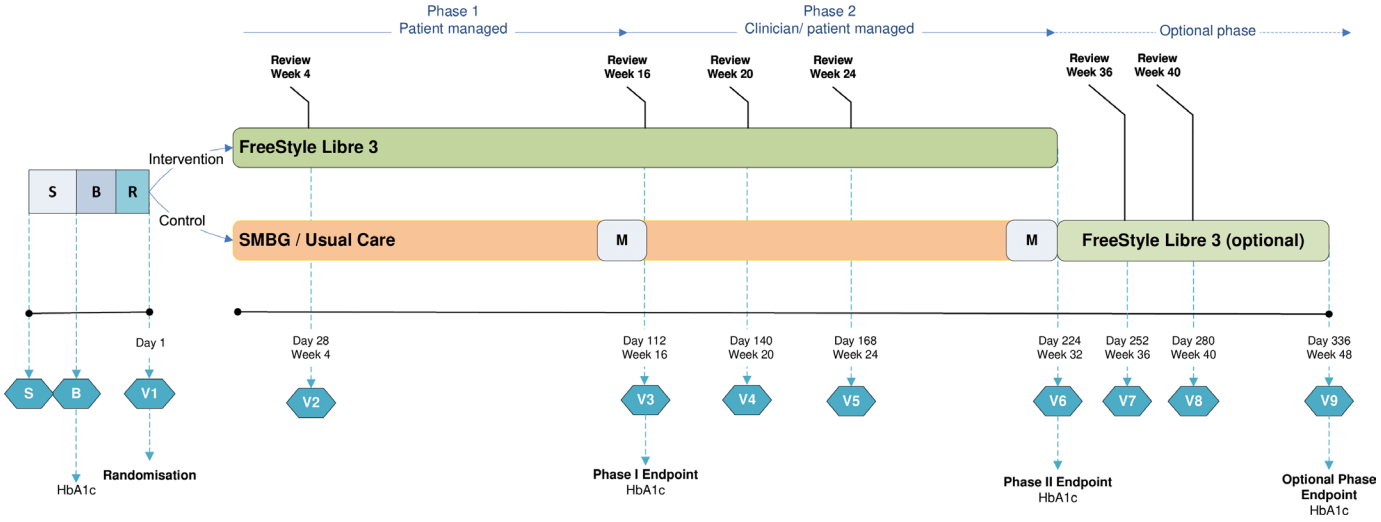

Figure 1 FreeDM2 study flow diagram. B, baseline visit; M: 14-day masked sensor wear; R, randomisation; S, screening visit; SMBG, self-monitoring blood glucose; V, visit.

evaluation (figure 1). The study is split into two phases, each of 16 weeks duration: phase 1 where participants will self-manage glucose levels through basal insulin optimisation and lifestyle change and phase 2 where clinicians will support participants to optimise existing therapy and add additional therapies as clinically appropriate and indicated. Following this, control group participants may enter into an optional extension phase. The trial recruited participants between July 2023 and January 2025. The last participant out, assuming the extension phase is entered, is expected in March 2026.

Eligibility criteria

This study has recruited adults aged ≥18 years with T2DM managed with basal-only insulin regimens plus SGLT-2 inhibitor and/or GLP-1 or dual GIP/GLP-1 agonist (with or without other oral medications) and baseline HbA1c from ≥59 mmol/mol to ≤97 mmol/mol (≥7.5% and ≤11.0%). Key inclusion and exclusion criteria are described in Box 1.

Study setting and recruitment

A three-pronged approach has been used to recruit participants. First, 24 National Health Service (NHS) sites across the UK recruited patients from their respective cohorts (online supplemental file 1). Second, clinical study sites used the services of Participant Identification Centres to identify potentially eligible participants from primary care providers. Third, recruitment was offered nationally through self-referral by advertising directly to people living with diabetes through social media, diabetes charities/organisations and a dedicated study website (https://www.freedm2.co.uk). A recruitment coordinator processed participants identified through the latter approach and signposted them to an appropriate study site. To facilitate recruitment, we have designed the study with an option for it to be performed remotely with a home healthcare service provider who will provide at-home clinical measurements, phlebotomy and online upload of glucose data. Participants will be reimbursed for travel costs and inconvenience fees. This recruitment approach aims to ensure that participants living in areas of higher deprivation are not limited by barriers to trial participation such as poorer healthcare infrastructure and access to travel. Where feasible, recruitment will actively seek individuals from ethnic minority backgrounds and areas of higher deprivation to aim for approximately 25% representation from each group in the overall study population. This would achieve a participation-to-prevalence ratio of 0.83 for deprivation indices 1–3 and 0.89 for ethnic minority backgrounds.

Interventions

FSL3 (intervention group)

The intervention is the CE-marked FSL3 system (Abbott Diabetes Care, Witney, UK), which consists of an arm-worn sensor that communicates glucose data to a user's mobile phone app. Participants without a compatible phone will be provided with a study phone for the duration of the study. Glucose data will be automatically uploaded from the app to LibreView (a cloud-based diabetes management software) which can be accessed by users and healthcare professionals (HCPs). Participants randomised to this intervention will receive appropriate training on system use as per product labelling and be encouraged to perform their own retrospective data reviews for glucose pattern recognition. During phase 1, intervention participants will be encouraged to wear sensors continuously and be advised to self-manage their diabetes using sensor glucose readings. Participants will receive guidance on basal insulin self-titration to minimise hypoglycaemia and hyperglycaemia (online supplemental file 2). During phase 2, participants will also review their glucose data and HbA1c results with an HCP at specified visits using LibreView, and additional new therapies may be introduced in keeping with local and national guidance.[24]

Box 1 Key inclusion and exclusion criteria

Inclusion criteria

⇒ Aged 18 years or over.
⇒ Diagnosed with type 2 diabetes mellitus (T2DM) for ≥1 year prior to enrolment.
⇒ T2DM treated with a basal insulin injection regimen and SGLT2 inhibitor (unless SGLT2 inhibitor therapy is contraindicated or has been previously not tolerated) and/or GLP-1 or dual GIP/GLP-1 agonist, with or without other oral antihyperglycaemic therapy at enrolment.
⇒ Current diabetic treatment regimen established and stable (with no clinically significant interruption* to GLP-1 or dual GIP/GLP-1 supply, if used) for ≥3 months prior to study enrolment.
⇒ Screening HbA1c from ≥59 mmol/mol to ≤97 mmol/mol (≥7.5% and ≤11.0%) within the last 28 days.
⇒ The participant is willing to wear the glucose sensor and follow study-specific instructions for improving glucose control at enrolment.

Exclusion criteria

⇒ Any diagnosis of diabetes other than T2DM including those secondary to chronic disease.
⇒ Any other concomitant disease or condition that may compromise patient safety, interfere with normal study conduct or result in interpretation, such as unstable coronary heart disease, learning disabilities, severe mental illness (such as psychotic disorder, bipolar disorder, dementia, substance/ alcohol dependence or depression with active suicidal ideation), eating disorders or any other uncontrolled medical condition.
⇒ Currently using any form of continuous glucose monitoring (including professional use) or has done so for ≥10 days within the previous 3 months.
⇒ In the investigator's opinion, intensification of glucose therapy is not suitable for the participant.
⇒ Participant is prescribed prandial or premixed (biphasic) insulin or a mixed therapy combination with basal insulin (eg, insulin degludec and liraglutide (Xultophy)) at enrolment.
⇒ Currently prescribed or anticipated short-term use of glucocorticoid therapy (oral, intra-articular, intramuscular or intravenous) for any acute condition.
⇒ Currently participating in another study that could affect glucose measurements or glucose management.
⇒ Currently receiving dialysis or estimated glomerular filtration rate <30 mL/min/1.73 m^2, measured within the previous 12 months or receives dialysis during the study.
⇒ A female participant who is pregnant, planning pregnancy within the next 12 months, becomes pregnant during the study or is breastfeeding.
⇒ Has planned major medical intervention expected to significantly alter red cell lifespan or a history of blood transfusion in the last 3 months.
⇒ Bariatric surgical procedure within the past 12 months or is planning/scheduled for bariatric surgery within the study duration.

*Clinically significant interruption defined as >2 weeks without GLP-1 supply/use. GLP, glucagon-like peptide; GIP, gastric inhibitory polypeptide.

SMBG (control group)

Participants randomised to the control group are expected to continue glucose monitoring with their current SMBG device. The frequency of SMBG testing (through either a diary or meter upload) will be discussed and recorded at visits with a HCP. During phase 1, participants will be expected to continue their usual practices for glucose self-management. Participants will receive guidance on basal insulin self-titration (online supplemental file 3) and may adjust their dose(s) to address any hypoglycaemia or hyperglycaemia. During phase 2, participants will review their SMBG data and HbA1c results with an HCP as per usual site practices, and additional new therapies may be introduced in keeping with local and national guidance.[24]

Participant timeline and data collection

A summary of key activities for study participants at each visit is summarised in online supplemental file 4. Visits may either be conducted in person at study sites or remotely. Prior to participation, prospective participants will be provided with a participant information sheet and an informed consent form available in five additional languages (online supplemental files 5 and 6). Following informed consent and successful screening, all participants will wear a masked FSL3 sensor and masked accelerometer for 14 days during the baseline phase. Patients who have ≥70% of FSL3 sensor data captured over 14 days will progress to randomisation. The study is subsequently split into two phases consisting of 2×16-week periods. During phase 1, consisting of visits 1 and 2, no new pharmacological therapies will be introduced unless deemed clinically essential for participant safety so the impact of the intervention on participant-driven behavioural changes can be assessed. Intervention group participants will receive training and be commenced on unmasked FSL3 use at visit 1. Participants will perform a self-review of glucose data. In the final 2 weeks of phase 1, control group participants will wear a masked FSL3 device to collect data for secondary outcomes. All participants will also wear a masked wrist-worn accelerometer during the final 2 weeks of phase 1.

During phase 2, consisting of visits 3–6, participants will undergo clinical reviews of sensor or SMBG data with an HCP. If indicated and in line with NICE and local prescribing guidelines, additional therapies may be introduced. For the final 2 weeks of phase 2, control group participants will wear the masked FSL3 device for 2 weeks to collect data for secondary outcomes. All participants will also wear a masked wrist-worn accelerometer during this period. Control group participants have the option to advance into an extension phase, consisting of visits 7–9, where they will be able to use the FSL3 system. During this phase, therapy adjustments may again be introduced if clinically indicated. Laboratory HbA1c samples will be collected at baseline and in an unblinded manner at visits 3, 6 and 9 (visit 9, extension phase only). Questionnaires including patient reported outcome measures (PROMs) will be conducted at baseline and visits 3 and 6. Participants will report symptomatic hypoglycaemia events through a questionnaire issued via mobile phone around periods of masked sensor wear. A subgroup of participants will partake in a qualitative interview at baseline

and visit 6. Changes to medication and adverse event data will be collected throughout the study period.

Masked CGM

FSL3 will be worn in a masked manner by all participants at baseline and by control group participants 2 weeks prior to visits 3 and 6. During these periods, participants will be provided with an FSL3 sensor accompanied by a handheld FSL3 reader configured in a 'masked mode'. In this configuration, sensor glucose data will not be visible to participants or HCPs. Data from such sensors will be extracted with the aid of the study sponsor following sensor wear.

Randomisation

At visit 1, participants will be allocated in a 2:1 ratio to the intervention group or the control group using permuted block randomisation stratified by study site produced by a computer pseudorandom number generator. This will ensure the number of patients allocated to each group at each site is approximately in the intended ratio, while maintaining random allocation. Study staff will review the participant's eligibility and adequate baseline data capture of ≥70% prior to randomisation.[29] Allocation concealment will be preserved until visit 1 by using varying block size and centralised randomisation with the OpenClinica Randomize module (OpenClinica, Massachusetts, USA).

Blinding (masking)

This is an open-label trial where it is not possible to blind participants or HCPs to the receipt or wear experience of the intervention.

Sample size calculation

The target effect size (minimally clinically important HbA1c difference) of 0.35% was chosen as this equates to approximately a 4% (1 hour) increase in time in target range (TIR) which represents a clinically meaningful difference for a treatment group according to consensus guidelines.[29 30] This difference is also consistent with other relevant trials (0.4% in MOBILE and 0.35% in REPLACE).[11 20] To achieve 80% power using an analysis of covariance for 16-week HbA1c values (2-tail 5% alpha power =0.80, effect size =0.35%, correlation between baseline and follow-up =0.51, SD=1.0%),[31], 216 participants with primary outcome data are required. This is inflated to a target of 270 being randomised (assuming maximum 20% attrition) and approximately 415 being recruited (to allow for prerandomisation losses).

Outcomes

The FreeDM2 study will use a variety of clinical, psychosocial, usability and economic outcomes to gain a holistic understanding of the effect of the intervention. The primary endpoint is the difference between treatment groups in mean change from baseline in HbA1c at 16 weeks (phase 1 endpoint).

Prespecified secondary outcomes are detailed in online supplemental file 7 and further information about a dedicated health economic evaluation is provided later. The first ranked key secondary endpoint is the difference between treatment groups in mean change from baseline in HbA1c at 32 weeks (phase 2 endpoint). Key sensor-based outcomes will rely on the international consensus guidelines assessed at baseline, 16 weeks and 32 weeks, including TIR (3.9–10.0 mmol/L), time in tight range (3.9–7.8 mmol/L), time above range (>10.0 mmol/L and >13.9 mmol/L) and time below range (TBR) (< 3.9 mmol/L and < 3.0 mmol/L) as well as composite outcomes which combine these metrics.[29 30] CGM-based hypoglycaemic events will be defined as ≥15 min and ≥120 min duration with glucose <3.9 mmol/L. Hyperglycaemic events will be defined as ≥120 min (extended) duration with glucose >13.9 mmol/L. All sensor-based metrics will be analysed separately for daytime (06:00–00:00) and night-time (00:00–06:00) hours in addition to the whole 24-hour period. Other clinical outcomes include changes to non-insulin glucose-lowering medications, insulin regimens and doses. Physical activity measured by masked accelerometers and change in weight will also be assessed. Safety outcomes include the frequency of severe hypoglycaemic episodes,[32] symptomatic hypoglycaemic events recorded by the participant, significant ketosis events (plasma ketones >3 mmol/L) and the nature and severity of other adverse events. In addition, sensor-based metrics such as TBR also capture the safety of the study intervention.

Two qualitative interviews will be performed in a sample of intervention and control participants at baseline and 32 weeks to further understand the impact of the intervention on participants' expectations, experience, decision making and behaviour. The sample will be selected by a health psychologist in a non-random manner to be representative of the study population based on age, sex, ethnicity, deprivation index and duration of diabetes. All participants will complete questionnaires including PROMs at baseline, 16 weeks and 32 weeks to assess factors important to quality of life, diabetes distress, treatment satisfaction and sleep quality. These will include the EuroQol 5-Dimension 5-level (EQ-5D-5L) questionnaire,[33] Glucose Monitoring Satisfaction Survey,[34] UK Diabetes and Diet Questionnaire,[35] Hypoglycaemia Confidence Scale,[36] Hypo-fear survey (HFS-II, worry scale only)[37] and two sleep satisfaction questions (online supplemental file 8).

Laboratory analysis

A blood sample (venous or capillary) will be taken for HbA1c at screening to check eligibility against the inclusion criteria. If a result from an HbA1c test performed within the preceding 28 days is already recorded in the participant's medical notes, this may be used in lieu of a screening blood sample. All participants will have a blood test for HbA1c, lipids and renal function at baseline, day 112 (week 16) and day 224 (week 32) (additional testing for liver function and thyroid function tests will be performed at baseline). Further samples for HbA1c

will be obtained for control participants only on day 336 (week 48) if participating in the extension phase. A urine sample will be sent at baseline for albumin-to-creatinine ratio testing, or alternatively, a result measured within the preceding 12 months may be used. Evaluation of samples will be performed by a central laboratory using samples taken by study personnel at sites or collected at home using validated kits.

Accelerometer data analysis

Following wear periods, participants will return masked accelerometers to the study team. Accelerometer data will be retrieved via an upload utility and processed by staff blinded to allocation group using the open-source R-package GGIR with outcomes generated using standard operating procedures developed by the National Institute for Health Research Leicester Biomedical Research Centre.[38] Metrics that describe the pattern of physical behaviours across the 24-hour day will be extracted, including: sleep duration, sleep efficiency, sleep midpoint variability, physical activity volume (including average acceleration and steps/day), physical activity intensity distribution (intensity gradient), time spent inactive, in light-intensity physical activity and in moderate-to-vigorous-intensity physical activity and the proportion meeting national physical activity guidelines.[39]

Data management

An electronic data capture system using electronic informed consent forms, electronic case report forms and electronic questionnaires will be used to collect participant data. Participant confidentiality shall be observed during the study and in accordance with the General Data Protection Regulation. Personal details for each participant taking part in the study and linking them to a unique identification number will be held locally on a study screening log in the investigator site file at each site. All participant-related reports and communications transferred to the central laboratory or study sponsor will identify participants by the assigned participant identification number only. Only members of the research team, collaborating institutions and the study sponsor will have access to the anonymised electronic data. Standard procedures agreed by the joint chief investigators and study sponsor are in place for data review, cleaning and resolving data queries.

Analysis

Statistical methods

The primary estimand is the difference between treatment groups in mean change from baseline in HbA1c at 16 weeks in the modified intention to treat population, regardless of the intercurrent events of trial product discontinuation and use of ancillary medication.[40] The population is participants meeting the eligibility criteria at enrolment while alive, not pregnant nor on dialysis. The secondary estimand is the difference between treatment groups in mean change from baseline in HbA1c at 16 weeks in all randomised participants under the assumption that all participants had adhered to treatment (trial product) for the entire planned duration of the trial.

The primary outcome analysis will evaluate between-group differences in HbA1c levels at the end of the 16-week treatment period. A linear mixed model will be used, with follow-up HbA1c as the outcome, trial arm effect as the focus, adjustment for baseline HbA1c as a covariate and site as a random effect. If more than 10% HbA1c data are missing at follow-up (or a >10% difference between missing data percentages in the two arms), multiple imputation will be used in order to implement a more complete analysis for the primary estimand (otherwise this will be performed as a sensitivity analysis, with a complete-case analysis used as the primary analysis) and for the secondary estimand. The imputation model will include baseline and 16-week and 32-week HbA1c, sex, age, baseline BMI, duration of diabetes, quintile of deprivation index, study centre and treatment group. Sensitivity analyses will be performed to examine the robustness of how missing data are handled, including a scenario with imputation per the opposite group. Quantitative secondary outcomes will also be analysed using linear mixed models, and binary secondary outcomes will be analysed using mixed logistic regression. In each case, the analysis will be adjusted for the baseline value of the outcome, and site will be included as a random effect. Safety data will be reported descriptively as frequencies and percentages (%) and compared between intervention arms.

Planned subgroups analyses will be conducted according to baseline HbA1c; age group; duration of diabetes; baseline BMI; baseline SGLT2 inhibitor, GLP-1 agonist use; education; deprivation index quintile; ethnic group; baseline TIR (online supplemental file 9). Further sensitivity and/or subgroup analyses will be performed as appropriate. All statistical tests will use a two-sided significance level of 5% without multiple testing correction. All CIs will be presented at a level of 95% and will be two-sided. All statistical analyses will be performed using SAS V.9.4 (or higher). The protocol and statistical analysis plan were reviewed by an independent statistician (Alessandro Leidi, Director, Statistical Services Centre Ltd, Reading, UK).

Economic analysis

An economic analysis will be performed to demonstrate the difference in costs and outcomes generated by use of the FSL3 system compared with SMBG. The economic evaluation will be prospective, in parallel with the randomised phases of the study and from the perspective of NHS/personalised social services (PSS) following standard quality design and reporting criteria.[41] A within-trial cost-utility analysis will compare differences in total costs and differences in quality of life using quality-adjusted life years (QALYs) derived from the EQ-5D-5L.[33] The QALY calculation will be performed by attaching utility weights to health states generated from the EQ-5D-5L, using area

under the curve methods with an assumption of a linear change between time points, controlling for baseline. Person-level costs will be created for each participant by combining trial-based resource use and published unit costs, which will offer an evaluation of NHS and PSS costs.[41 42] A bootstrapped regression model will be used to analyse costs for the two study arms as the data are likely to be skewed. EQ-5D-5L data collected at baseline and 16-week and 32-week follow-up will be used to estimate health status, assuming a linear relationship between the time points (area under the curve method). The base-case analysis will use a 5L to 3L crosswalk algorithm using the UK reference table.[43]

To gain an understanding of the long-term effects of the intervention, the effects beyond the trial period will also be modelled. The IQVIA Center for Outcomes Research and Effectiveness Diabetes Model V.10 (IMS Health, Danbury, Connecticut, USA) consists of 15 submodels designed to simulate diabetes-related complications, non-specific mortality and costs over time while accounting for disease progression.[44 45] The results from baseline data (online supplemental file 10) and primary endpoints from the study will be used to model treatment effects to ensure representation of the study population. The direct costs that will be included in the model are for: management (for primary prevention of complications); diabetes-related complications; the treatment of diabetes (this also includes the cost of the interventions) and other hospital costs. Health benefits will be expressed in terms of life-years and QALYs gained.

Changes to the protocol

During 2023, a National Patient Safety Alert was issued in the UK which limited the prescription of GLP-1 agonists due to a global shortage of these drugs.[46] Revision B of this protocol contained an amendment to exclude patients prescribed GLP-1 agonists. Following an update to this alert in January 2024, after recruitment had commenced, certain limitations on prescribing were lifted and the protocol was updated to reinclude patients prescribed GLP-1 agonists (revision C). The current revision of the protocol (revision D) was made due to recruitment challenges which made the original sample size requirement unobtainable in a reasonable timeframe. The primary endpoint was changed from a dual endpoint to a single endpoint, thus reducing the sample size while maintaining the power to detect the same clinically relevant difference in HbA1c.

Trial monitoring and management

Trial Steering Committee

A trial steering committee (TSC) with an independent chair has been appointed. Members of the TSC will include two independent service users (patients), an independent health economist, the joint chief investigators (included in voting decisions with one vote), an independent statistician, an independent clinical psychologist and one representative of the study sponsor (excluded from voting decisions). Other members of the study team and/or representatives from the study sites or the sponsor may attend TSC meetings but will not have voting rights.

Study monitoring

A detailed study risk assessment was completed by the sponsor. The procedures, source data transfer modalities and anticipated frequency for monitoring are documented in the monitoring plan. Copies of the risk assessment and the monitoring plan will be stored in the trial master file. Study monitoring is conducted by the sponsor, in accordance with their standard operating procedures. Authorised representatives of the sponsor or an ethics committee may perform audits or inspections at the recruiting centres, including source data verification.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Limitations

Given the nature of the intervention, this study is open-label which may render certain findings susceptible to bias. Since the study is conducted in the UK, its findings may not be generalisable to all regions of the world due to varying patient demographics and clinical practices. Despite efforts to include participants from ethnic minority backgrounds and areas of higher deprivation, barriers to access diabetes technology and participate in trials persist, which may prevent achieving the intended participation-to-prevalence ratios. This study was affected by global shortages in the supply of GLP-1 agonists, necessitating amendments to the protocol that excluded and then reincluded patients prescribed GLP-1 agonists based on national availability. It was essential to modify the primary outcome due to slower than expected recruitment. While the study population represents a significant proportion of individuals living with diabetes, further investigation is warranted to evaluate the benefit of CGM in adults with T2DM who are managed without insulin and/or other medication combinations.

Conclusion

The FreeDM2 study will provide information on the efficacy of real-time CGM using FSL3 on changes in HbA1c among adults with T2DM managed with basal insulin along with an SGLT2 inhibitor and/or GLP-1 or dual GIP/GLP-1 agonist. This represents a significant proportion of individuals living with type 2 diabetes, many of whom do not reach glycaemic targets. A key strength of this study lies in its objective to understand the mechanisms by which CGM influences change in glycaemia. The two-phase design will capture both actions taken by participants and HCPs, while a comprehensive range of secondary outcomes will evaluate the impact of CGM in a holistic manner. Given that current prescribing guidelines for CGM in T2DM are limited, the findings from this study will ultimately inform evidence-based clinical practice.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the Declaration of Helsinki Ethical Principles for Medical Research involving Human Subjects. Ethical approval was obtained from the Health Research Authority, Health and Care Research Wales and the West Midlands Edgbaston Research Ethics Committee with reference number 23/WM/0092. All participants will be provided with oral and written information about the trial, including the most common adverse events and the procedures involved in the study before obtaining written informed consent. Any further substantial/non-substantial amendments will be managed by the sponsor, and substantial amendments will be notified to the Ethics Committee. Study results will be communicated to trial participants and disseminated through conference presentations and peer-reviewed publications. The data sharing plan is available in online supplemental file 11.

Author affiliations
[1]University of Nottingham, Nottingham, UK
[2]University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK
[3]Leeds Institute for Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
[4]Leeds Teaching Hospitals NHS Trust, Leeds, UK
[5]King's College Hospital NHS Foundation Trust, London, UK
[6]University Hospitals of Leicester NHS Trust, Leicester, UK
[7]Portsmouth Hospitals University NHS Trust, Portsmouth, UK
[8]Manchester Centre for Health Economics, The University of Manchester, Manchester, UK
[9]Institute of Metabolic Science, University of Cambridge, Cambridge, UK
[10]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[11]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[12]The University of Sheffield, Sheffield, UK
[13]County Durham and Darlington NHS Foundation Trust, Darlington, UK
[14]Barnard Health, BHR Limited, Portsmouth, UK
[15]Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[16]NIHR Oxford Biomedical Research Centre, Oxford, UK
[17]Swansea Bay University Health Board, Port Talbot, UK
[18]The Adam Practice, Poole, UK
[19]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[20]Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK
[21]University of East Anglia Norwich Medical School, Norwich, UK
[22]The Ipswich Diabetes Centre and Research Unit, East Suffolk and North Essex NHS Foundation Trust, Colchester, UK
[23]Hull University Teaching Hospitals NHS Trust, Hull, UK
[24]Hull York Medical School, Hull, UK
[25]The University of Manchester, Manchester, UK
[26]Manchester University NHS Foundation Trust, Manchester, UK
[27]Diabetes Research Centre, University of Leicester, Leicester, UK
[28]NIHR Leicester Biomedical Research Centre, University Hospitals of Leicester NHS Trust, Leicester, UK
[29]Imperial College London and Imperial College Healthcare NHS Trust, London, UK

X Rachel Ann Elliott @RachelElliott67

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ORCID iDs
Yee S Cheah http://orcid.org/0009-0009-1948-1960
Rachel Ann Elliott http://orcid.org/0000-0002-3650-0168
Katharine Barnard-Kelly http://orcid.org/0000-0002-3888-3123
Alistair Lumb http://orcid.org/0000-0001-7041-9534
Thinzar Min http://orcid.org/0000-0003-4467-3840
Gerry Rayman http://orcid.org/0000-0003-3331-7015
Lalantha Leelarathna http://orcid.org/0000-0001-9602-1962

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