Clinical Study Protocol

Study Title:	**An open-label, multi-centre, randomised, parallel design study to assess the efficacy of flash glucose monitoring in adults with sub-optimally controlled type 1 diabetes**
Short Title:	**Flash-glucose monitoring in sub-optimally controlled type 1 diabetes (FLASH-UK)**
Protocol Version:	**3.0 09 March 2020**

IRAS Number: 257593

Clinical Trials.gov Number: NCT03815006 (24th January 2019)

Sponsor's Number: G64079 / B00373

Funder's Number: 18/0005836

This protocol has been written in accordance with the current ISO 14155:2011 standard and has regard for HRA guidance

KEY TRIAL CONTACTS

Chief Investigator	**Dr Lalantha Leelarathna** **University of Manchester / Manchester University NHS Foundation Trust** **Manchester Diabetes Centre, Manchester Royal Infirmary,** **Hathersage Road, Manchester M13 9WL.** **UK** **Tel: 0161 276 6709** **Fax: 0161 273 6184** **Email: Lalantha.leelarathna@mft.nhs.uk**

Principal Clinical Investigators	Dr Emma Wilmot University Hospitals of Derby and Burton NHS Foundation Trust Royal Derby Hospital, Uttoxeter Road, Derby, DE22 3NE. UK Phone: +44 1332787696 E-mail: emma.g.wilmot@gmail.com Dr Mark Evans Wellcome Trust-MRC Institute of Metabolic Science Box 289, Level 4, Addenbrooke's Hospital Hills Road, Cambridge CB2 0QQ UK Phone: +44 1223 336 994 Fax: +44 1223 330 598 E-mail: mle24@cam.ac.uk Dr Iain Cranston Academic Department of Diabetes & Endocrinology Queen Alexandra Hospital, Cosham, Portsmouth, PO6 3LY UK Phone: 02392 286044 Fax: 02392 286791 E-mail: Iain.cranston@porthosp.nhs.uk Dr Parth Narendran Institute of Immunology and Immunotherapy College of Medical and Dental Sciences University of Birmingham, Edgbaston, Birmingham B15 2TT UK Phone: 0121 414 3006 E-mail: p.narendran@bham.ac.uk Dr Sankalpa Neupane Norfolk and Norwich University Hospitals NHS Foundation Trust Colney Lane, Norwich. NR4 7UY UK Phone: 01603 286312

	Fax: 01603 288438 E-mail: sankalpa.neupane@nnuh.nhs.uk Prof Gerry Rayman Diabetes Research Office (N043) East Suffolk and North Essex NHS Foundation Trust Ipswich Hospital Heath Road Ipswich IP4 5PD E-mail: Gerry.Rayman@esneft.nhs.uk Dr Nathan Francis Wareham Surgery Streche Road Wareham BH20 4PG Phone: 01929 553444 E-mail: Nathan.francis@dorsetgp.nhs.uk; nathanfrancis@nhs.net
Other Co-Investigators	Prof Rachel Elliott (Lead Health Economist) Division of Population Health, Health Service Research & Primary Care University of Manchester Oxford Road, Manchester M13 9PL UK Phone: 0161 275 7639 E-mail: rachel.a.elliott@manchester.ac.uk Dr Hood Thabit Manchester Diabetes Centre, Manchester Royal Infirmary Manchester University NHS Foundation Trust / University of Manchester Hathersage Road, Manchester M13 9WL UK Tel: 0161 276 6709 Fax: 0161 273 6184 Email: Hood.Thabit@cmft.nhs.uk Dr Naresh Kanumilli Northenden Group Practice 489 Palatine Road Northernden Manchester M22 4DH Tel: 0161 998 3206 Email: nkanumilli@nhs.net Dr Smriti Gaur Norfolk and Norwich University Hospitals NHS Foundation Trust Colney Lane, Norwich. NR4 7UY UK E-mail: Smriti.Gaur@nnuh.nhs.uk

	Dr Rajna Golubic Wellcome Trust-MRC Institute of Metabolic Science Box 289, Level 4, Addenbrooke's Hospital Hills Road, Cambridge CB2 0QQ UK E-mail: rg380@medschl.cam.ac.uk Dr Christine Kotonya Diabetes Consultant Physician University Hospitals of Derby and Burton NHS Foundation Trust Burton Hospitals, Belvedere Road, Burton-on-Trent, DE12 0RB E-mail: christine.kotonya@nhs.net Dr Sanjeev Sharma Diabetes Research Office (N043) East Suffolk and North Essex NHS Foundation Trust Ipswich Hospital Heath Road Ipswich IP4 5PD E-mail: Sanjeev.Sharma@esneft.nhs.uk Dr Christopher Sutton (Lead Statistician and Trials Methodologist) Division of Population Health, Health Service Research & Primary Care University of Manchester Oxford Road, Manchester M13 9PL UK Phone: 0161 306 8002 Email: Chris.J.Sutton@manchester.ac.uk Prof Katharine Barnard (Health Psychologist) Barnard Health, BHR Limited 42 Kilmiston Drive Fareham, Hampshire PO16 8EG Phone: 01329511971 E-mail: katharinebarnard@bhrltd.com
Study Co-ordinator	Manchester Clinical Trials Unit (MCTU) Jean McFarlane Building University of Manchester Oxford Road, Manchester M13 9PL UK Phone: 0161 306 3199 Email: Flash-uk@manchester.ac.uk
Study Sponsor	Manchester University NHS Foundation Trust Division of Research & Innovation Manchester Royal Infirmary, Oxford Road Manchester M13 9WL

Study Funder	Diabetes UK Wells Lawrence House 126 Back Church Lane London E1 1FH

PROTOCOL SIGNATURE PAGE

The signature below documents the approval of the protocol entitled " An open-label, multi-centre, randomised, parallel design study to assess the efficacy of flash glucose monitoring in adults with sub-optimally controlled type 1 diabetes" version 3.0 dated 09.03.2020 and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, the principles of GCP and the appropriate reporting requirements.

Signature …….. Date……..

Dr Lalantha Leelarathna, Chief Investigator

SITE SIGNATURE PAGE (Birmingham, UK)

I have read the attached protocol entitled "An open-label, multi-centre, randomised, parallel design study to assess the efficacy of flash glucose monitoring in adults with sub-optimally controlled type 1 diabetes" version 3.0 dated 09.03.2020 and agree to abide by all provisions set forth therein.

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

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

Principal Clinical Investigator

Name: Dr Parth Narendran

Signature …….. Date…….

SITE SIGNATURE PAGE (Cambridge, UK)

I have read the attached protocol entitled "An open-label, multi-centre, randomised, parallel design study to assess the efficacy of flash glucose monitoring in adults with sub-optimally controlled type 1 diabetes" version 3.0 dated 09.03.2020 and agree to abide by all provisions set forth therein.

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

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

Principal Clinical Investigator

Name: Dr Mark Evans

Signature …….. Date…….

SITE SIGNATURE PAGE (Derby, UK)

I have read the attached protocol entitled "An open-label, multi-centre, randomised, parallel design study to assess the efficacy of flash glucose monitoring in adults with sub-optimally controlled type 1 diabetes" version 3.0 dated 09.03.2020 and agree to abide by all provisions set forth therein.

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

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

Principal Clinical Investigator

Name: Dr Emma Wilmot

Signature …….. Date…….

SITE SIGNATURE PAGE (Norwich, UK)

I have read the attached protocol entitled "An open-label, multi-centre, randomised, parallel design study to assess the efficacy of flash glucose monitoring in adults with sub-optimally controlled type 1 diabetes" version 3.0 dated 09.03.2020 and agree to abide by all provisions set forth therein.

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

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

Principal Clinical Investigator

Name: Dr Sankalpa Neupane

Signature …….. Date…….

SITE SIGNATURE PAGE (Portsmouth, UK)

I have read the attached protocol entitled "An open-label, multi-centre, randomised, parallel design study to assess the efficacy of flash glucose monitoring in adults with sub-optimally controlled type 1 diabetes version 3.0 dated 09.03.2020 and agree to abide by all provisions set forth therein.

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

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

Principal Clinical Investigator

Name: Dr Iain Cranston

Signature …….. Date…….

SITE SIGNATURE PAGE (Ipswich, UK)

I have read the attached protocol entitled "An open-label, multi-centre, randomised, parallel design study to assess the efficacy of flash glucose monitoring in adults with sub-optimally controlled type 1 diabetes version 3.0 dated 09.03.2020 and agree to abide by all provisions set forth therein.

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

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

Principal Clinical Investigator

Name: Prof Gerry Rayman

Signature …….. Date…….

SITE SIGNATURE PAGE (Wareham / Poole, UK)

I have read the attached protocol entitled "An open-label, multi-centre, randomised, parallel design study to assess the efficacy of flash glucose monitoring in adults with sub-optimally controlled type 1 diabetes version 3.0 dated 09.03.2020 and agree to abide by all provisions set forth therein.

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

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

Principal Clinical Investigator

Name: Dr Mark Francis

Signature …….. Date…….

PROTOCOL SIGNATURE PAGE

The signature below documents the approval of the protocol entitled "An open-label, multi-centre, randomised, parallel design study to assess the efficacy of flash glucose monitoring in adults with sub-optimally controlled type 1 diabetes" version 3.0 dated 09.03.2020 and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, the principles of GCP and the appropriate reporting requirements.

Signature …….. Date……..

Dr Chris Sutton, Lead Statistician

Table of Contents

1 List of Abbreviations and Relevant Definitions

ABCD	**Association of British Diabetologists**
ADE	**Adverse Device Effect**
ASADE	**Anticipated Serious Adverse Device Effect**
AE	**Adverse Event**
AR	**Adverse Reaction**
AUC	**Area Under the Curve**
CE	**Conformité Européenne (CE-mark)**
CEACs	**Cost-effectiveness Acceptability Curves**
CGM	**Continuous Glucose Monitoring**
CRF	**Case Report Form**
CoI	**Conflict of Interest**
CONSORT	**Consolidated Standards of Reporting Trials**
CTU	**Clinical Trials Unit**
CSII	**Continuous subcutaneous insulin infusion**
DKA	**Diabetic Ketoacidosis**
eCRF	**Electronic Case Report Form**
eGFR	**Estimated Glomerular Filtration Rate**
FDA	**US Food and Drug Administration**
FSL	**FreeStyle Libre**
FSL2	**FreeStyle Libre 2**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation**
GLP-1	**Glucagon-like peptide-1**
HbA1c	**Glycated haemoglobin (A1c)**
HCG	**Human Chorionic Gonadotropin**
HRA	**Health Research Authority**
IDMC	**Independent Data Monitoring Committee**
ITT	**Intention to Treat**
MAO	**Monoamine Oxidase**

MDI	**Multiple Daily Injection**
MHRA	**Medicine and Healthcare products Regulatory Agency**
NIMP	**Non-Investigational Medicinal Product**
PAID	**Problem Areas in Diabetes**
PIC	**Participant Identification Centre**
PPI	**Patient and Public Involvement**
PSS	**Prescribed Specialised Services**
QALYs	**Quality-Adjusted Life Years**
R & D	**Research and Development**
REC	**Research Ethics Committee**
s.c.	**Subcutaneous**
SADE	**Serious Adverse Device Effect**
SAE	**Serious Adverse Event**
SAP	**Sensor Augmented Pump Therapy**
SGLT2	**Sodium-glucose co-transporter-2**
SMBG	**Self-monitoring of blood Glucose**
T1D	**Type 1 Diabetes Mellitus**
TMG	**Trial Management Group**
TSC	**Trial Steering Committee**
USADE	**Unanticipated Serious Adverse Device Effect**

2 Study Synopsis

Title of clinical trial	An open-label, multi-centre, randomised, parallel design study to assess the efficacy of flash glucose monitoring in adults with sub-optimally controlled type 1 diabetes
Short Title	Flash-glucose monitoring in sub-optimally controlled type 1 diabetes (FLASH-UK)
Sponsor	Manchester University NHS Foundation Trust
Medical condition or disease under investigation	Type 1 diabetes
Clinical trial phase	Device Trial with CE marked Device
Purpose of clinical trial	To determine whether flash glucose monitoring with Freestyle Libre 2 (FSL2) device will improve glucose control over a 24-week period compared to self-monitoring of blood glucose in adults and adolescents (16 or older) with sub-optimally controlled type 1 diabetes.
Study objectives	The study objective is to compare flash glucose monitoring with FSL2 device vs. self-monitoring of blood glucose over 24 weeks in adults and adolescents (16 or older) with sub-optimally controlled (HbA1c 7.5% to 11%) type 1 diabetes **1.** EFFICACY: The objective is to assess the efficacy of flash glucose monitoring with FSL2 device and self-monitoring of blood glucose on glycated haemoglobin A1c (HbA1c) **2.** SAFETY: The objective is to evaluate time spent in hypoglycaemia (sensor glucose levels < 3.0 mmol/l) and episodes of severe hypoglycaemia with FSL2 and self-monitoring of blood glucose **3.** UTILITY AND ACCEPTANCE: The objective is to determine the frequency of daily scans, duration of use of FSL2 device and explore participant's expectations and experience of using FSL2 device **4.** PSYCHOSOCIAL: The objective is to evaluate participants' responses in terms of quality of life, diabetes distress, low mood, needle burden, disordered eating and diabetes treatment satisfaction **5.** COST EFFECTIVENESS: To assess the relative cost-effectiveness of the FSL2 device compared with self-monitoring in adults and adolescents (16 years or older) with sub-optimally controlled

	type 1 diabetes, from the perspective of NHS England.
Study Design	An open-label, randomised, parallel design study, for 24 weeks
Primary endpoint	The primary outcome is HbA1c at 24 weeks.
Key Secondary endpoint(s)	• Time spent in the target glucose range between 3.9 to 10.0 mmol/l (70 to 180mg/dl) based on sensor glucose levels. • Time spent below target glucose (<3.9mmol/l) (<70mg/dl) • Time spent above target glucose (10.0 mmol/l) (180 mg/dl) • Average and standard deviation glucose levels • Coefficient of variation glucose levels • The time with sensor glucose levels < 3.5 mmol/l (63 mg/dl), <3.0 (54mg/dl) and <2.8 mmol/l (50 mg/dl) • The time with sensor glucose levels in the significant hyperglycaemia (glucose levels > 16.7 mmol/l) (300mg/dl) • AUC of glucose below 3.0mmol/l (54mg/dl) • Average total daily insulin dose, basal and bolus dose • Average number of boluses of rapid acting insulin administered per day • HbA1c at 12 weeks • HbA1c ≤ 53 mmol/mol (7.0%) o at 12 weeks [yes/no] o at 24 weeks [yes/no] • HbA1c ≤ 59 mmol/mol (7.5%) o at 12 weeks [yes/no] o at 24 weeks [yes/no] • Reduction in HbA1c ≥5.5 mmol/mol (0.5%) from baseline (screening) o at 12 weeks [yes/no] o at 24 weeks [yes/no] • Reduction in HbA1c ≥ 11 mmol/mol (1.0%) from baseline (screening) o at 12 weeks [yes/no] o at 24 weeks [yes/no]

Safety Evaluation	• Frequency of severe hypoglycaemic episodes as defined by American Diabetes Association • Frequency of significant ketosis events (plasma ketones >3mmol/l) • Nature and severity of other adverse events.
Psychosocial and usability evaluation	• Evaluation of participants' responses in terms of quality of life, diabetes distress, depression, needle burden, disordered eating and diabetes treatment satisfaction using EQ-5D-5L questionnaire, Type 1 Diabetes Distress Scale (T1-DDS), Diabetes fear of injecting and self-testing (D-FISQ) questionnaire, Diabetes Eating Problem Survey (DEPS-R), Diabetes Treatment Satisfaction Questionnaire (DTSQ), Patient Health Questionnaire (PHQ-9) and The Glucose Monitoring Satisfaction Survey (GMSS). An additional questionnaire will explore participant's expectations and experience of using FSL2 device for those in the FSL2 arm
Sample size	Assuming a standard deviation of 0.8% and treatment difference of 0.4% - 128 participants (64 per each arm) with primary outcome will give 80% power to detect the difference between treatment groups at 2-sided type 1 error = 5%. Recruitment target is 180 participants (25 to 30 per centre) aiming for 150 to be randomised following the adherence run-in period, and allowing for 15% post-randomisation attrition.
Summary of eligibility criteria	Key inclusion criteria: 1. The participant is ≥16 years old 2. The participant has type 1 diabetes, as defined by WHO for at least 1 year or is confirmed C-peptide negative if duration of diabetes is < 1 years 3. Participant is treated with insulin pump or multiple daily injection for at least 12 weeks and no plans to change treatment modality during next 28 weeks 4. The participant is literate in English for safe study conduct 5. Screening HbA1c ≥ 7.5% (58.5mmol/mol) and ≤ 11% (97 mmol/mol) based on analysis from local laboratory 6. The participant is literate in English 7. The participant is willing to wear study glucose sensor and scan for glucose levels at regular intervals, 8. The participant is willing to follow study specific instructions and improve glucose control 9. Female participants of child bearing age should be on effective contraception and must

	have a negative blood or urine pregnancy test at screening. Key exclusion criteria: 1. Non-type 1 diabetes mellitus including those secondary to chronic disease 2. Any other physical disease or people with known severe mental illness (psychotic disorder, bipolar disorder, dementia, substance and alcohol dependence, learning disabilities, depression with active suicidal ideation) which are likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator 3. Untreated hypothyroidism 4. Current users of real-time glucose monitoring sensors or flash-glucose monitoring for more than 4 weeks within last 12 weeks 5. Initiation of medications/treatments known to interfere with glucose metabolism (e.g: metformin, SGLT2 inhibitors, GLP-1 agonists, Pramlinatide) within the last 6 weeks or planning to start these medications within the next 6 months (patients on stable treatment is not an exclusion) or current or planned glucocorticoid use other than inhaled/ topical use 6. Known or suspected allergy against insulin 7. Severe visual impairment 8. Complete loss of hypoglycaemia awareness 9. Significant renal impairment eGFR<30 within previous one year or on dialysis or active retinopathy (defined as presence of maculopathy or proliferative changes) as judged by the investigator 10. More than one episode of severe hypoglycaemia as defined by American Diabetes Association (30) in preceding 24 weeks
Recruitment	Participants will be recruited through diabetes clinics at participating centres. Each centre may also utilise participant identifying centres to help recruitment. Study may be advertised via social media and within GP practices that are within reasonable distance of participating centres. This will facilitate self-referral from interested candidates for screening and optimise trial recruitment across centres. 1. Manchester University Foundation Trust 2. University Hospitals of Derby and Burton NHS Foundation Trust

	3. University Hospitals Birmingham NHS Foundation Trust 4. Addenbrookes Hospital, Cambridge 5. Norfolk and Norwich University Hospital, Norwich 6. Queen Alexandra Hospital, Portsmouth 7. Ipswich Hospital, East Suffolk and North Essex NHS Foundation Trust, Ipswich 8. Wareham Surgery (Wareham) and The Adam Practice (Poole), NHS England Primary Care GP Practices Each centre will aim to recruit up to 30 participants
Maximum duration of study for a participant	30 weeks
Consent	Participants will provide written informed consent before any study procedures.
Baseline assessment	Eligible participants will undergo a baseline evaluation where blood samples for HbA1c (if not done within previous 2 weeks), renal, thyroid function (if not done in the previous one year) and serum beta HCG (pregnancy test) or urine pregnancy test in females of child-bearing potential. Questionnaires as mentioned above will also be completed.
Run-in Period	During the 2-week run-in period, blinded FSL2 will be worn by participants to ensure that participants are able to wear and tolerate subcutaneous glucose sensors, and for glucose data collections.
Randomisation	Eligible participant will be randomised using randomisation software to the use of flash glucose monitoring with FSL2 or self-monitoring of blood glucose. Randomisation, using minimisation (with a random component) will take into account among other factors, centre, baseline HbA1c, treatment modality (MDI vs. Continuous Subcutaneous insulin Infusion (CSII), previous participation of structured education course & current use of bolus calculator.
1. Flash glucose monitoring	At the start, a blood sample will be taken for the measurement of HbA1c. Training and education on the use of FSL2 will be provided by the research team. Participants will be advised to use flash glucose monitoring continuously for the next 24 weeks.
2. Self-monitoring of blood glucose	At the start, a blood sample will be taken for the measurement of HbA1c. Masked FSL2 will be applied for two weeks, during the last two weeks of control period. Education will focus on using finger-stick measurement for treatment optimisation.
End of 24 week assessments	- A blood sample will be taken for measurement of HbA1c.

	- Validated questionnaires as described before evaluating quality of life, mood, needle burden, disordered eating, diabetes distress and diabetes treatment satisfaction will be completed. Additional questionnaire for those in the FSL2 arm exploring expectations and experience of using FSL2 during the study will also be administered
Procedures for safety monitoring during trial	Standard operating procedures for reporting all adverse events will be in place.

3 Summary

FreeStyle Libre 2 (FSL2) is a novel glucose monitoring device (Flash glucose) in the form of a disc worn on the arm for 14 days and a hand-held reader which is designed to largely replace the recommended 4-10 painful finger-stick blood glucose tests required each day for the self-management of type1diabetes. The purpose of this study is to determine whether flash glucose monitoring with FSL2 device will improve HbA1c over a 24-week period compared to self-monitoring of blood glucose in adults and adolescents (16 years or older) with sub-optimally controlled (HbA1c 7.5% to 11%) type 1 diabetes.

This is an open-label, multi-centre, randomised, parallel design study, involving a 2-week run-in period, followed by a 24-week study period during which participants will use either FSL2 or continue usual finger-stick glucose monitoring in random order. A total of up to 180 participants (aiming for 150 randomised and 128 completed participants) aged 16 years and older with T1D on insulin pump therapy or multiple daily injection therapy will be recruited through diabetes clinics in participating centres.

Participants will receive appropriate training to maximise benefits of FSL2 in self-management. The primary outcome is difference in HbA1c between the two groups at 24 weeks. Secondary outcomes are time spent with glucose levels above and below target, as recorded by FSL2, and other flash glucose-based metrics. Impact on quality of life, diabetes distress, mood, needle burden, disordered eating and treatment satisfaction will also be undertaken. Relative cost-effectiveness of FSL2 device compared with self-monitoring will also be assessed from a UK NHS perspective.

4 Background

Type 1 diabetes mellitus (T1D) is characterised by an absolute deficiency of insulin caused by immunologically-mediated damage to the beta cells in the pancreas and raised blood glucose levels (1). It is one of the commonest endocrine and metabolic conditions in both children and adults. It is estimated that approximately 415 million adults (5-15% type 1 diabetes) and 520,000 children (95% type 1 diabetes) worldwide suffer from diabetes (2) . Recent reports suggest that incidence and prevalence of T1D is increasing in many countries, at least in the under 15 year age group with the predicted number of new cases of childhood diabetes in Europe increasing to 24 400 in 2020 from 15 000 in 2005 (2; 3).

Despite the availability of therapeutic options such as self-monitoring of blood glucose, structured patient education, rapid-acting insulin analogues and insulin pump therapy, glycaemic control in the majority of patients with type 1 diabetes remains suboptimal (4) and they are prone to get complications associated with poor control such as kidney failure and blindness (5). In England less than one third of patients with type 1 diabetes achieve a HbA1c level <7.5% (6) .

Studies have shown strong relationship with number of finger-stick glucose tests and HbA1c (7). However due to pain, inconvenience and accumulated trauma finger-stick glucose monitoring remains a key barrier in achieving near normal glucose levels.

4.1 Advances in glucose monitoring:

In contract to finger-stick glucose monitoring, continuous glucose monitors (CGM) can provide continuous real-time glucose information as well as glucose trend information (8). In 1999 MiniMed received FDA approval for the first retrospective continuous glucose monitor (CGM) device in the USA (9). Since then, a number of CGM options have been introduced including MiniMed iPro, Enlite 2, Enlite Enhanced, Enlite 3 (Medtronic Inc, Northridge, CA, USA), DexCom STS (Short Term Sensor), Dexcom 3, 7, Gen 4 and 5 (Dexcom Inc, San Diego, CA, USA), and Navigator I and II (Abbott Diabetes Care, Alameda, CA, USA). These devices have been evaluated in a range of studies in a variety of patient groups, using both multiple daily injections (MDI)(10; 11) and continuous subcutaneous insulin infusion (CSII)(12; 13) which have demonstrated the consistent use of CGM is associated with improvements in HbA1c and reductions in hypoglycaemia. However, widespread adoption of these

devices has been hampered by several factors including cost, accuracy of earlier devices and user acceptability.

4.2 Flash-glucose monitoring with FreeStyle Libre device:

Three years ago, in 2014 a new category of device was born: the FreeStyle Libre Flash Glucose Monitoring System (FSL) (Abbott Diabetes Care, Oxon, UK). This device is different to earlier CGM systems. Although it does produce real-time on-demand continuous glucose data, it does not alarm to alert users of rising or falling glucose levels. Hence the label: 'flash glucose monitoring'. The FSL device is a replaceable white disc, worn on the arm for 14 days. The sensor utilises wired enzyme technology (14) (osmium mediator and glucose oxidase enzyme co-immobilised on electrochemical sensor) to continuously measure interstitial glucose levels. It is factory calibrated and does not need calibration during use. Abbott provided potential users with the option of direct on-line purchase of FSL, without prior approval from health care providers. The Freestyle Libre (FSL) flash glucose monitor became available on prescription (subject to local health authority approval) in all four nations of the United Kingdom from November 2017, a watershed moment in the history of diabetes care. Freestyle Libre 2 (which is CE marked) has been produced by the manufacturer. This is identical to FSL but with the optional additional functionality of alarm alerts for users who fall outside of adequately controlled glucose levels. This model has yet to be assigned an official release date for the United Kingdom.

4.3 Evidence from randomised controlled trials:

The largest study to evaluate FSL is the IMPACT randomised controlled multicentre European trial (15). This study included 328 participants with well controlled (HbA1c <= 7.5%, 59 mmol/mol) Type 1 diabetes, a third of which used CSII therapy. FSL use was associated with improvement in a range of glucose related outcomes: a 38% reduction in time spent in hypoglycaemia (<3.9 mmol/l) with no change in total daily insulin dose. The reduction in hypoglycaemia was achieved within 2 weeks, despite no training on glucose data interpretation and no health care professional contact during this initial period, suggesting that users intuitively understood how to react to the data (Figure 1). There was an increase in glucose time in range combined with a reduction in glycaemic variability. The HbA1c was unchanged.

FSL users in the IMPACT study were scanning an average of 15 times/ day, a behaviour sustained over the 6 month follow up period. FSL utilisation was high and sustained at >90%, a reflection of the high

treatment satisfaction described. Users performed 0.5 blood glucose tests per day or one blood glucose tests every 2-5 days. Despite this, there was a reduction in hypoglycaemia, providing support for the non-adjunctive use of flash glucose monitoring, in line with the product label. It is important to highlight that those with impaired awareness of hypoglycaemia (IAH) were not included in IMPACT and the study results are not generalisable to this high-risk group, who are likely to be reliant on alarms to alert them to impending hypoglycaemia.

Reddy et al from London have assessed FSL in a randomised parallel group study compared to real time CGM (Dexcom G5) in patients with Type 1 diabetes and IAH (16). After a 2-week run in, 32 participants using intensified multiple daily injections were randomised to either Dexcom G5 CGM or FSL for 8 weeks (Preliminary analysis, conference abstract). The reduction in percentage time spent in hypoglycaemia was significantly greater in those using the Dexcom G5 compared to FSL (D=3.6, p=0.034). The difference in the reduction in the Gold score was greater with the G5 compared to FSL (D=1.1, p=0.029). The percentage of time in target was significantly greater for both devices. They concluded that real-time CGM has significantly greater benefit in those with IAH than FSL. These findings lend support to the current NICE recommendations for CGM use in Type 1 diabetes (17).

The impact of FSL was assessed in those with Type 2 diabetes on intensive insulin therapy in a large multi-centre European study of 224 participants (18). Despite less frequent senor scans than was seen in IMPACT (8 vs 15 per day), time in hypoglycaemia (<3.9mmol/l) reduced by 0.47±0.13 h/day compared with controls, representing a 43% reduction in hypoglycaemia. HbA1c was unchanged. Treatment satisfaction was higher in users and no device related serious adverse events were reported, suggesting that flash glucose monitoring also offers a suitable replacement to SMBG in those with Type 2 diabetes who are on intensive insulin therapy.

4.4 Observational studies

A range of observational studies have evaluated the FSL. Dover et al prospectively assessed the FSL in 25 participants and described improved glucose control, reduced hypoglycaemia and improved quality of life (19). The mean HbA1c of 8.0±0.14% reduced to 7.5%±0.14% after 16 weeks. Those with a baseline HbA1c >7.5% (58 mmol/mol) experienced a greater -0.59±0.15% reduction. There was a significant reduction in hypoglycaemia and diabetes distress. A key behavioural change associated with FSL use was an increase in those delivering the insulin bolus 15-20 minutes pre-meal as per recommendations. McKnight and Gibb, subsequently reported FSL use in approximately 3% of their

Type 1 diabetes clinic population in Edinburgh (20). FSL use was associated with a significant change in HbA1c versus non users (-0.2% versus +0.1%, respectively). Of those with a HbA1c >7.5% (>58mmol/mol), 32% of FSL reached target HbA1c compared to only 9.8% of non-users (p<0.001).

A study in Israel of 31 patients with poorly controlled Type 1 or Type 2 diabetes noted an HbA1c decrease of 1.33±0.29% after 8 weeks of FSL (21). For those who continued using the device (n=27), the change was maintained for 24 weeks (1.21±0.42%; p = 0.009).

Holcombe et al (conference abstract) assessed the FSL in a small group of 13 patients with Type 1 diabetes (22). Mean HbA1c reduced from 75 (9.0%) to 65 (8.1%) mmol/mol, with increased time in target (29 vs 24%) and reduced hypoglycaemia (82 vs 95 minutes). All subjects demonstrated a reduction in their PAID (Problem Areas in Diabetes) scores. Glucose monitoring increased from 3 finger-stick tests per day to 11 scans per day. They also commented in their abstract that the device facilitated virtual contact and support.

Campbell et al. evaluated the use of FSL as a replacement for SMBG in young people (4-17 years) (n=76, 58% CSII users, 46% males age 10.3±4.0 years, baseline HbA1c 7.9±1.0% (63 mmol/mol), T1D duration 5.4±3.7 years) with Type 1 diabetes in a single arm European multi-centre trial (23). After 2 weeks' baseline masked (blinded) wear, participants used FSL for 8 weeks. Time in range (70-180 mg/dL) significantly improved vs. baseline by 1.0±2.8 hours/day (mean±SD), p=0.0056. HbA1c significantly improved vs. baseline, -0.4±0.6%, p<0.0001. Scan frequency of FSL was on average 12.9 times daily, whereas SMBG tests dropped from a median of 8.0 (baseline) to 1.0/day during open use. Diabetes Treatment Satisfaction Questionnaire showed increased overall treatment satisfaction for parents (n=70), 21.7±6.6 (mean change score±SD), p<0.0001 and teens (13+years) (n=23), 18.7±5.6, p<0.0001.

These studies add to the growing clinical perception that FSL is desirable and beneficial for people living with Type 1 diabetes. This echoes the authors own clinical experience, having observed striking reductions in HbA1c with FSL use in those with very poorly controlled diabetes (HbA1c >86mmol/mol, 10%) who are doing little or no glucose monitoring. Unfortunately, these are often not patients who are included in clinical studies.

4.5 User satisfaction:

Patient feedback on FSL is generally very positive. Olafsdottir et al. explored treatment experience in 58 adults with Type 1 diabetes (24). FSL scored favourably with scores of 9/10 for 'My experience of the FSL was very positive' and 9.4/10 for 'I would like to use FSL in my daily life'. They reported it was easy to use (9.8/10), easy and trouble free insertion (9.1/10) and importantly they felt it was easy to interpret information on the FSL screen (9.6/10). Authors also compared their findings for FSL user satisfaction (overall score 8.22 to 9.8 out of 10) with their earlier studies of Dexcom G4 and Enlite sensor which used the same questions (overall score 72.5 to 90 out of 100 for Dexcom G4 and 42.1 to 86.1 out of 100 for Enlite). This may, in part, account for the >90% utilisation reported in the IMPACT study which is higher than previous CGM studies.

Ish-Shalom reported their experience in Israel with the FSL (21). All patients (n = 31) were highly satisfied and stated that they would like to use flash glucose in the future. In addition, the patients unanimously stated that it was easy to use and painless. Health care professionals reported that the data presentation, particularly the ambulatory glucose profile (AGP), was an outstanding tool, enabling better and easier control of glucose levels. (21).

Families of paediatric patients who have used the device are generally satisfied. McPhater et al contacted the families of 19 FSL users. They reported that the sensor was easy to insert and was an easier method of checking glucose than SMBG (25). The majority found the sensor lasted 14 days. Most perceived that glucose control had improved during use due to improved awareness of glucose levels, and changes in self-management behaviour, particularly around hypoglycaemia. Although trend data was useful most users did not alter self-management as a result. Confidence in nocturnal glucose control was improved. One quarter did not continue to use the sensors due to limited sensor duration and blood glucose discrepancies compared to SMBG.

Another user evaluation in the paediatric population also described high user satisfaction with the majority rating the device favourably for sensor application (84.3–92.1%),sensor wear and use (87.2–100%), comparing use to SMBG (85.4–97.5%) and the device itself (68.3–96.3%) (26) .

4.6 Real-world use of FSL:

The manufacturer has evaluated the association of the real-world scanning with FSL and glucose control measures. A large number of readers (n=50,831) with 279,446 sensors (86.4 million monitoring hours by 63.8 million scans) were analysed (27) (Figure 2). Users performed an average of 16.3 scans per day (median:14, interquartile range: 10-20). Estimated HbA1c reduced ($p<0.001$) as scan rate increased, from 8.0% (64 mmol/mol) to 6.7% (50 mmol/mol) from the lowest (mean 4.4 scans/day) to highest (mean 48.1 scans/day) groups, while time below 3.9, 3.0 and 2.5 mmol/l decreased by 15%, 40% and 49%, respectively (all $p<0.001$).

4.7 Adverse events

As one would expect, most adverse events are related to the medical grade adhesives used to secure the sensor for 14 days. Sensor-wear-related symptoms were recorded as adverse events in the IMPACT trial if the effects were severe and lasted for >7 days, or if the patient required prescription medication for the event to resolve (15). Adverse event severities were recorded on the basis of a health-care professional's assessment of mild, moderate, or severe events. IMPACT reported 13 cutaneous adverse events in 10 patients, and were categorised as mild (three cases), moderate (four cases), and severe (six cases). Seven participants withdrew from the study due to device-related adverse events or repetitive occurrences of sensor insertion-related symptoms. For participants with adverse events involving skin symptoms during this trial, symptoms (including severe) were resolved by use of barrier products (eg, Cavilon spray) or drug therapy (eg, zinc ointment, Fenistil gel, or hydrocortisone cream) as prescribed, or simply by relocating the device to another area of the skin such that the effects were maintained at a tolerable, background level (28). In other cases, although the adverse events were generally mild or moderate, the longevity of the symptoms, despite use of treatment, contributed to the participant's decision to withdraw from the trial. Investigations have since identified isobornyl acrylate as the likely agent causing contact dermatitis (29)

Since completion of the IMPACT trial, minor design changes have been made to FSL. These changes are expected to improve breathability of the skin that is in contact with the sensor and to facilitate the exclusion of moisture between the sensor–skin interface (28). During the children's study, five device related adverse events were reported in five (6%) participants, aged 6, 9, 10, 12 and 15 years: allergic reaction, blister, pink mark/scabbing and abrasion on sensor removal (n=2). Four were mild, one was moderate, all were resolved at study completion.(26)

4.8 FreeStyle Libre 2 flash-glucose monitoring system to be used in the present study

Flash-glucose monitoring system will consist of a body worn disc (about the size of £2 coin and) a hand held reader or a smart mobile phone with an app for flash glucose monitoring (Figure 1). Reader can display current glucose level as well as direction of glucose change and last 8 hours of glucose data. In contrast to the first generation FreeStyle Libre device, Libre 2 has the additional functionality of optional alarms, vibratory alerts or both when glucose levels become low and high. The "low glucose value" is factory set at 3.9 mmol/L and the "high glucose value" at 13.3 mmol/L. Users can adjust these values within a permitted range so they are tailored to their Type 1 diabetes management requirements.

Figure 1: FreeStyle Libre 2 flash glucose monitoring system (Abbott Diabetes Care, Oxon, UK):

Front & Side Profile of Sensor. The sensor probe (inserted into skin) is 0.4 mm wide and 5mm in length

4.9 Rationale for the Current Study

Use of FSL device in people with well controlled T1D has shown reduction in hypoglycemia burden. However, to date no randomised study with FSL2 has been undertaken in people with T1D and high HbA1c. Without randomised study evidence, there is a reluctance of payers to fund this device to wider group of T1D, potentially restricting its use in large number of people who could benefit. The purpose of this study is to determine whether use of flash glucose monitoring with FSL2 device will improve HbA1c over a 24-week randomised period compared to self-monitoring of blood glucose in adults with sub-optimally controlled type 1 diabetes.

5 Objectives

The study's primary objective is to compare flash glucose monitoring with Freestyle Libre 2 (FSL2) device with self-monitoring of blood glucose over 24 weeks in adults & adolescents (16 years or older) with sub-optimally controlled (HbA1c 7.5% to 11%) type 1 diabetes.

5.1 Clinical Efficacy

The objective is to assess the clinical efficacy of flash glucose monitoring with FSL2 device relative to that with self-monitoring of blood glucose on glycated haemoglobin A1c (HbA1c) (primary clinical objective) and sensor-based glucose metrics (secondary clinical objectives; e.g. time spent in target glucose range 3.9 to 10 mmol/L).

5.2 Psychosocial efficacy

Evaluation of participants' responses in terms of quality of life, diabetes related distress, diabetes treatment satisfaction, low mood, needle burden and disordered eating behaviours will be assessed using validated questionnaires.

5.3 Cost-effectiveness

The objective is to assess the relative cost-effectiveness of the FSL2 device compared with self-monitoring in adults and adolescents with sub-optimally controlled type 1 diabetes, from the perspective of NHS England

5.4 Safety

The objective is to evaluate time spent in hypoglycaemia (sensor glucose levels < 3.0 mmol/l and other sensor based biochemical hypoglycaemia) and number of episodes of severe hypoglycaemia with FSL2 and self-monitoring of blood glucose

5.5 Process Evaluation (Utility & Acceptability)

The objectives are to explore the frequency and patterns of daily scans, duration of use of FSL2 device and explore participants' expectations and experiences

6 Study Design

An open-label, multi-centre, randomised, parallel study, in adults and adolescents (16 years and older) with type 1 diabetes and sub-optimal glycaemic control (HbA1c 7.5% to 11%), either on insulin pump

treatment or multiple daily injections, contrasting flash glucose monitoring using FreeStyle Libre 2 device with traditional finger-stick glucose monitoring for 24 weeks. The study flow chart is outlined in Figure 2.

7 Study Participants

7.1 Study Population

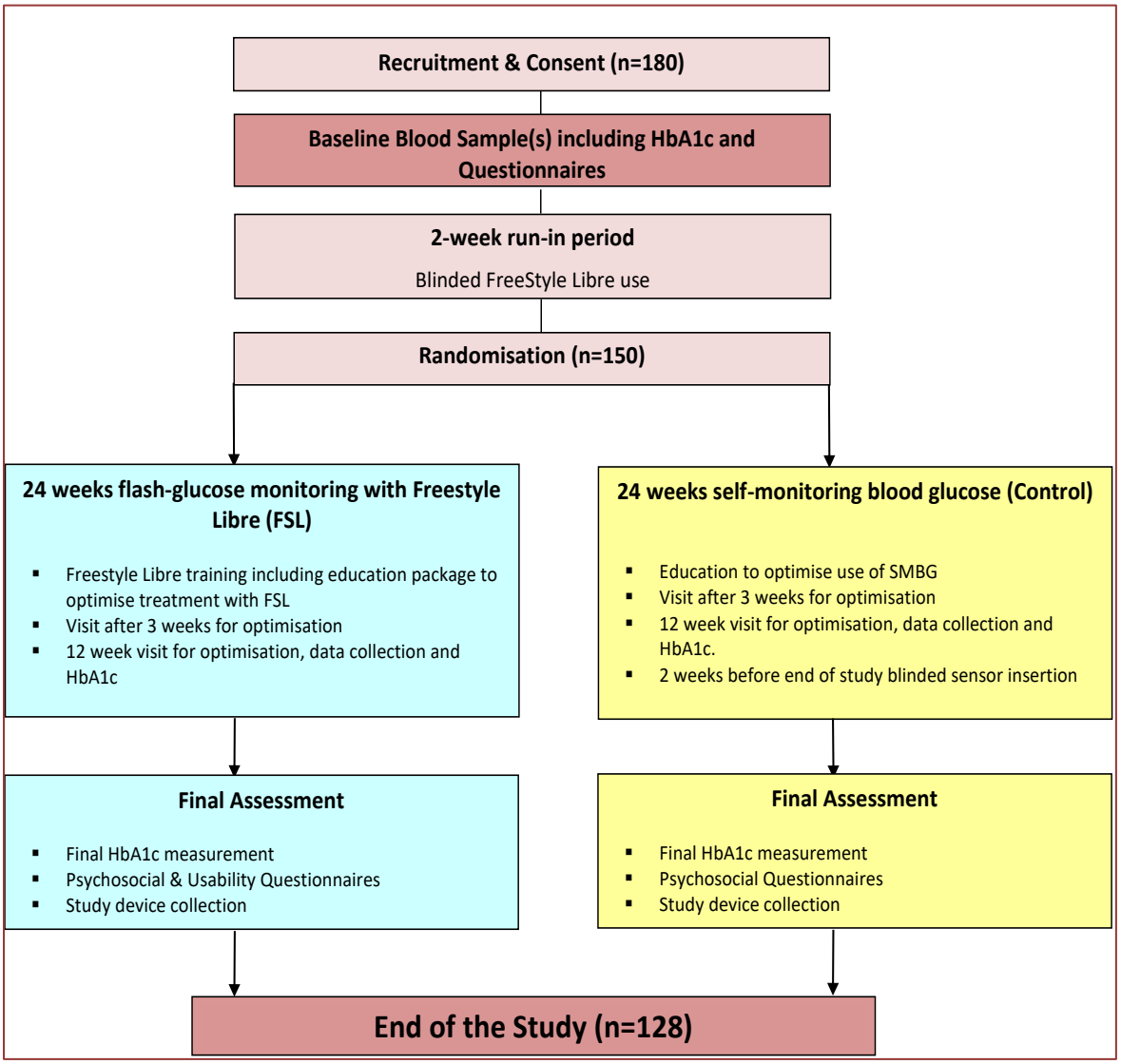
This is a UK multi-centre and recruitment will take place at the following centres:

1. Diabetes Centres within Manchester University NHS Foundation Trust
2. Diabetes Centres within University Hospitals of Derby and Burton NHS Foundation Trust
3. University Hospitals Birmingham NHS Foundation Trust, Birmingham
4. Addenbrookes Hospital, Cambridge
5. Norfolk and Norwich University Hospital, Norwich
6. Queen Alexandra Hospital, Portsmouth
7. Ipswich Hospital, East Suffolk and North Essex NHS Foundation Trust, Ipswich
8. Wareham Surgery (Wareham) and The Adam Practice (Poole), NHS England Primary Care GP Practices

Each centre will aim to recruit between 25 to 30 participants up to a total of 180 participants. Additional diabetes centres surrounding above hospitals may act as participant identification centres.

Potential participants will be identified by their treating clinicians and invited to contact the research team. They will be sent the study information leaflets and an invitation by post or in-person to join the study by the research team at least one day before the recruitment visit. The study may also be advertised via social media or posters displayed in clinic. Additionally, the study will be advertised in GP practices that are within reasonable distance of participating centres. This will facilitate self-referral from interested candidates for screening purposes and optimise trial recruitment across centres.

Figure 2. Study flow chart



7.2 Inclusion Criteria

1. The participant is ≥16 years old
2. The participant has type 1 diabetes, as defined by WHO for at least 1 year or is confirmed C-peptide negative if duration of diabetes is < 1 years

3. Participant is treated with insulin pump or multiple daily injection for at least 12 weeks and no plans to change treatment modality during next 28 weeks
4. The participant is literate in English for safe study conduct
5. Screening HbA1c ≥ 7.5% (58.5mmol/mol) and ≤ 11% (97 mmol/mol) based on analysis from local laboratory
6. The participant is willing to wear study glucose sensor and scan for glucose levels at frequent intervals
7. The participant is willing to follow study specific instructions to improve glucose control
8. Female participants of child bearing age should be on effective contraception and must have a negative blood or urine-HCG pregnancy test at screening.

7.3 Exclusion Criteria

1. Non-type 1 diabetes mellitus including those secondary to chronic disease
2. Any other physical disease or people with known severe mental illness (psychotic disorder, bipolar disorder, dementia, substance and alcohol dependence, learning disabilities, depression with active suicidal ideation) which are likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator
3. Untreated hypothyroidism
4. Current users of real-time glucose monitoring sensors or flash-glucose monitoring for more than 4 weeks within last 12 weeks
5. Initiation of medications/treatments known to interfere with glucose metabolism (e.g: metformin, SGLT2 inhibitors, GLP-1 agonists, Pramlinatide) within the last 6 weeks or planning to start these medications within the next 6 months (patients on stable treatment is not an exclusion) or current or planned glucocorticoid use other than inhaled/ topical use.
6. Known or suspected allergy against insulin
7. Severe visual impairment
8. Complete loss of hypoglycaemia awareness
9. Significant renal impairment eGFR<30 within last one year or on dialysis or active retinopathy (defined as presence of maculopathy or proliferative changes) as judged by the investigator
10. More than one episode of severe hypoglycaemia as defined by American Diabetes Association (30) in preceding 24 weeks as confirmed by clinical history or hospital notes; (severe hypoglycaemia is defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions including episodes of

hypoglycaemia severe enough to cause unconsciousness, seizures or attendance at hospital; children: severe hypoglycaemia is defined as an event associated with a seizure or loss of consciousness);

11. Total daily insulin dose ≥ 2 IU/kg/day
12. Pregnancy, planned pregnancy, or breast feeding
13. Participant is using implanted internal pace-maker
14. Participants with medically documented allergy towards the adhesive (glue) of plasters or participant is unable to tolerate tape adhesive around sensor placement area
15. Serious skin diseases (e.g. psoriasis vulgaris, bacterial skin diseases) located at places of the body, which potentially are possible to be used for localisation of the glucose sensor)
16. Participant is currently abusing illicit drugs as judged by the investigator
17. Participant is currently abusing prescription drugs as judged by the investigator
18. Participant is currently abusing alcohol as judged by the investigator
19. Participant has elective surgery planned that requires general anaesthesia during the course of the study
20. Participant has a sickle cell disease, haemoglobinopathy; or has received or plan to receive red blood cell transfusion or erythropoietin within 12 weeks prior to time of screening or during study duration
21. Participant plans to receive red blood cell transfusion or erythropoietin over the course of study participation

8 Methods under Investigation

8.1 Name and Description of the Method of Investigation

The investigational treatment the CE marked FreeStyle Libre 2 (FSL2) flash glucose monitoring device (Abbott Diabetes Care, Oxon, UK).

8.2 Intended Purpose

The intended purpose of the investigational treatment is flash-glucose monitoring intended at replacing finger-stick glucose levels.

8.3 Method of Administration

The FSL2 glucose sensor is directly attached to the patient. Each sensor is intended to last for 14 days. The component not directly attached to the patient is the handheld reader and/or mobile phone app which display current and historical glucose data (Figure).

8.4 Required Training

Prior to commencement of the study, the research team nurses/clinicians at each of the investigation centres will be trained to use the FSL2 system and its components. This will be documented on each site's training log. Prior to the use of study devices, participants will be trained to use the FSL2. Competency assessments of the participants' capability to use study devices will be made.

8.5 Precautions

During treatment with insulin there is a risk of hypoglycaemia and hyperglycaemia. Participants will be educated in minimising this risk during the study.

8.6 Accountability of the Method under Investigation

The local Investigator will provide training for the study participants and will make every effort, through regular contact, to ascertain study is conducted according to protocol. Devices will be identified using batch/lot/serial numbers and the location of investigational devices and their dates of use by participants will be documented throughout the study.

9 Study Schedule

9.1 Overview

The study will be co-ordinated from Manchester Clinical Trials Unit and performed at following sites:

1. Diabetes Centres within Manchester University Foundation Trust
2. Diabetes Centres within University Hospitals of Derby and Burton NHS Foundation Trust
3. University Hospitals Birmingham NHS Foundation Trust
4. Addenbrookes Hospital, Cambridge
5. Norfolk and Norwich University Hospital, Norwich
6. Queen Alexandra Hospital, Portsmouth
7. Ipswich Hospital, East Suffolk and North Essex NHS Foundation Trust, Ipswich
8. Wareham Surgery (Wareham) and The Adam Practice (Poole), NHS England Primary Care GP Practices

After recruitment, consent, participants will be randomised for 24-weeks home use of flash-glucose monitoring or 24-weeks use finger-stick glucose monitoring.

The study includes up to 7 visits for participants completing the study. Maximum time in study is 30 weeks. Each study visit can be scheduled with +/- 2 weeks of the planned visit date.

Table 1 outlines study activities when participant is randomised to flash glucose monitoring intervention (intervention group).

Table 2 outlines study activities when participant is randomised to finger-stick glucose monitoring (control group).

Table 1. **Schedule of study visits when participant is randomised to flash glucose monitoring intervention (intervention group).**

Visit/ contact	Description	Time since randomisation	Start relative to previous / next Visit / Activity**	Duration
Visit 1	Recruitment **& Screening** visit: Consent HbA1c, baseline bloods, questionnaires	-2 to -3 weeks	-	2 hours
Visit 2	Blinded flash glucose monitor insertion	-2 weeks	Within 1 to 2 weeks of Visit 1. Can coincide with Visit 1	0.5 hour
Visit 3	Adherence assessment & Randomisation Flash-glucose monitoring initiation - Training, education & competency assessment	0 weeks	After 2 weeks of Visit 2	2 hours
Visit 4	Review data /optimisation and use of study devices. Data download & collect participant diary	+4 weeks	After 4 weeks of Visit 3	1 hour
Visit 5	Review data /optimisation. Data download - HbA1c. - Collect participant diary	+12 weeks	After 8 weeks of Visit 4	2 hours
Visit 6	Not applicable in this arm			
Visit 7	End of Flash-glucose monitoring intervention arm - HbA1c - Questionnaires - Data download - Collect participant diary	+24 weeks	12 weeks after Visit 5	2 hours

**Each study visit can be scheduled with +/- 2 weeks of the planned visit date.

Table 2. **Schedule of study visits when participant is randomised self-monitoring of blood glucose**

Visit/ contact	Description	Time since randomisation	Start relative to previous / next Visit / Activity**	Duration
Visit 1	Recruitment & Screening visit: Consent HbA1c, baseline bloods, questionnaires	-2 to -3 weeks	-	2 hours
Visit 2	Blinded flash glucose monitor insertion	-2 weeks	Within 1 to 2 weeks of Visit 1. Can coincide with Visit 1	0.5 hour
Visit 3	Adherence assessment & Randomisation Self- monitoring of glucose initiation - Education	0 weeks	After 2 weeks of Visit 2	2 hours
Visit 4	Review data /optimisation Collect participant diary	+4 weeks	After 4 weeks of Visit 3	1 hour
Visit 5	Review data /optimisation. Data download - HbA1c - Collect participant diary	+12 weeks	After 8 weeks of Visit 5	2 hour
Visit 6	Blinded flash glucose monitor insertion (Extra visit in this arm)	+22 weeks	After 10 weeks of Visit 5	
Visit 7	End of self-monitoring intervention arm - HbA1c. - Questionnaires - Collect participant diary	+24 weeks	2 weeks after Visit 6	2 hour

**Each study visit can be scheduled with +/- 2 weeks of the planned visit date.

9.2 Visit 1: Recruitment Visit and Screening Assessment

Once the participants have agreed to participate in the study, they will be invited for the recruitment visit, and given a participant ID, when the following activities will be performed by the research team:

- written informed consent/assent
- checking inclusion and exclusion criteria
- medical and diabetes history including presence of diabetes complications and hypoglycaemia burden
- ethnicity, body weight and height measurement; calculation of BMI
- Demographic data (Date of Birth, Gender registered at birth, Full Postcode)
- record of current insulin therapy
- urine or blood pregnancy test (females of child-bearing potential)
- record of occupation and educational attainment
- any history of disordered eating or needle phobia
- previous participation in structured education, status of carb counting, use of bolus calculator

9.2.1 Screening Blood Sampling

Blood samples will be taken to measure HbA1c (measured at local laboratory if not done within last 2 weeks). Renal and Thyroid function will also be evaluated (if not done in last one year). Less than 15 ml of whole blood will be taken from each participant.

9.2.2 Questionnaires at Screening

Evaluation of participants' responses in terms of quality of life, diabetes distress, needle burden, disordered eating, depression and diabetes treatment satisfaction using EQ-5DL-5L questionnaire, Type 1 Diabetes Distress Scale (DDS), Diabetes fear of injecting and self-testing (D-FISQ) questionnaire, Diabetes Eating Problem Survey (DEPS-R), Diabetes Treatment Satisfaction Questionnaire (DTSQ), Patient Health Questionnaire (PHQ-9) and The Glucose Monitoring Satisfaction Survey (GMSS). Hypoglycaemia burden will be assessed using Clarke questionnaire and Gold score.

9.3 Visit 2: Insertion of blinded glucose monitoring device

Purpose of visit 2 is to insert a blinded glucose monitor (FreeStyle Libre Pro device). Participant will be provided with instructions about using this device for next 2 weeks. Visit 2 may be combined with visit 1.

9.4 Visit 3: Adherence assessment, randomisation and start of study treatment

During Visit 3, participant's adherence / tolerance of using the flash-CGM over preceding 14 days will be assessed. To proceed with the study participant should have worn the blinded glucose monitoring device for at least 10 days' during last 14 days of run-in period. If the participant fails to demonstrate adherence or develops any significant allergy or intolerance to the glucose sensor, the study will be terminated and participant will be removed from the study. If the sensor records less than 10 days' worth of data due to a problem with the sensor itself (premature sensor failure) rather than a participant related issue, a new sensor should be inserted to get a minimum of total 10 days' worth of data. In cases in which there is a premature sensor failure, participant randomisation should only proceed once a minimum total of 10 days data has been downloaded.

9.4.1 Randomisation scheme

Randomisation to one of the two intervention arms (24-weeks use of flash-glucose monitoring or 24 weeks use of conventional finger-stick glucose monitoring) will use the minimisation method, with a random element to improve allocation concealment. We will minimise over the following factors: study centre (Birmingham; Cambridge; Derby; Manchester; Norwich; Portsmouth), baseline HbA1c (7.5%-9.0%; >9.0%-11%), treatment modality (Multiple daily injections (MDI); Continuous Subcutaneous insulin Infusion (CSII)), prior participation in structured education course (yes; no) and current use of bolus calculator (yes; no).

9.4.2 Method of implementing the allocation

Participants not removed from the study due to non-adherence or significant allergy or intolerance to the glucose sensor will be randomised during visit 3 using the web-based randomisation platform SealedEnvelope.com. The responsibility for randomising participants into the trial lies with the Principal Investigator and staff at sites. Access to the randomisation system will be limited to the core study team members at each trial site. The delegation log at each trial site should clearly identify which roles and/or individuals are delegated to perform the randomisation procedure on the SealedEnvelope.com web platform. Individuals undertaking the randomisation will be required to enter the patient's initials, month/year of birth, date of randomisation, site and confirmation of eligibility criteria into the SealedEnvelope.com secure website, before being permitted to randomised participants. The system will need to record the unique trial ID which will be assigned to each participant during screening (Visit 1) and should be used on all trial documentation (CRF, SAE forms etc.). This ID will be sequential across all NHS sites and will consist of a three digit site reference followed by the sequential across site ID. Following randomisation an email confirmation with the

allocated randomised treatment and trial ID will be disseminated to the trial site staff and key CTU personnel, automatically via the randomisation system. A copy of this confirmation should be filed in the participant's study notes. An emergency contact card should be pre-populated will the trial ID. Further details of the randomisation process will be provided in a user manual.

9.4.3 Initiation of study treatment

Body weight measurement will be made. Participants will be provided with necessary training on use of study devices according to randomisation. Participants will also be provided with a paper diary to collect information about insulin doses and carbohydrate intake in last 5 days before study visits 4, 5 and 7 (Appendix 13).

9.4.4 Training session (Appendix 9)

Participants randomised to the flash-glucose monitoring arm will receive education and training about insertion and initiation of the sensor as well as how to use flash-glucose monitoring data for treatment optimisation. They will be encouraged to download data at home to identify pattern recognition. This session will be conducted by a professional diabetes educator or a member of the study team. Education will be tailored to meet the needs of the individual.

Participants randomised to conventional finger-stick glucose monitoring arm will be encouraged to use finger-stick glucose levels to optimise treatment and will receive education about insulin dose adjustments using finger-stick glucose levels. The study will try to mimic real-life conditions by continuing participant's pre-study diabetes treatment unchanged and finger-stick glucose testing frequency as determined by the participant as required. Participants in both arms will also receive training on sick day rules and dealing with hypo and hyperglycaemia.

Participants assigned to either arm will receive an information leaflet following the training session. The information provided will be tailored to suit the trial arm for which they will be assigned to. The leaflet provided to those who will be randomised to the Flash Glucose Monitoring arm will include sign-posting to educational videos provided by the Association of British Clinical Diabetologists (ABCD) (https://abcd.care/dtn/education).

9.5 Visit 4: (+4 weeks since randomisation): Review data and treatment optimisation

Purpose of this visit is to review data from Flash-glucose monitoring and finger-stick glucose monitoring to further optimise treatment. Study devices will be downloaded. Information about insulin doses and any adverse events will be collected.

9.6 Visit 5: (+12 weeks since randomisation): Review data and treatment optimisation

Purpose of this visit is to review data from Flash-glucose monitoring and finger-stick glucose monitoring to further optimise treatment. Study devices will be downloaded. Information about insulin doses, participant diaries and any adverse events will be collected. Blood sample will be collected for HbA1c.

9.7 Visit 6: (+22 weeks since randomisation): Finger-stick glucose monitoring arm only

Participants randomised to finger-stick glucose monitoring arm will have an extra visit 10 weeks after visit 5 to insert a blinded glucose sensor for data capture.

9.8 Visit 7: (+24 weeks since randomisation): End of randomised study treatment

The participant will be invited to attend the research centre approximately 12 weeks after Visit 5. This would be the end of 24 weeks randomised study period. All study devices will be downloaded. Insulin usage data will be recorded and diaries collected. The participant will have a blood test for the HbA1c. Body weight measurement will be made. Participant will be asked to complete questionnaires evaluating diabetes related quality of life, diabetes distress and diabetes treatment satisfaction. In addition, participants in the FSL2 arm will be asked to complete a questionnaire exploring expectations and experience of using FSL2 during the study.

9.9 Participant Withdrawal Criteria

The following pre-randomisation withdrawal criteria will apply:

1. Participant is unable to demonstrate safe use of flash-glucose monitoring during run-in period as judged by the investigator
2. Participant develops significant allergy to sensor plaster

The following pre- and post-randomisation withdrawal criteria will apply:

3. Participant may terminate participation in the study at any time without necessarily giving a reason and without any personal disadvantage
4. Significant protocol violation or non-adherence

5. Decision by the investigator or the sponsor that termination is in the Participant's best medical interest
6. Participant becomes pregnant during the study period
7. Allergic reaction to insulin
8. Allergic reaction to glucose sensor
9. If patient cannot be contacted over a period of 4 weeks then the participant will be considered lost to follow up

Participants who are withdrawn for reasons stated in (4), (5), (7), and (8) may be invited to provide the blood sample for the assessment of HbA1c and complete the self-report questionnaires at the end of the planned study intervention period.

9.10 Study Stopping Criteria

The study may be stopped if three consecutive participants withdraw on safety grounds or on the advice of an Independent Data Monitoring Committee (IDMC)

9.11 End of Trial

For regulatory purposes, the end of trial will occur at each study site when the last participant has undergone their final assessment and the data has been collected. The declaration of end of trial form will be submitted to regulatory authorities. The Manchester CTU will notify the REC and the HRA at the end of a clinical trial (when all participating sites have completed final participant assessments) within 90 days of its completion. Following this, Manchester CTU will advise sites on the process for closing the trial at site.

9.12 Support telephone line

There will be a telephone helpline to the local research teams for participants in case of any technical device or problems related to diabetes management such as hypo- or hyperglycaemia during normal working hours. Outside working hours participants will be advised to contact usual out hours NHS support services.

9.13 Participant reimbursement

The study will provide the FSL2 device and related consumables. Participant will continue their usual glucose meter, and glucose test strips. Reasonable travel expenses will also be reimbursed. After completing the study, participants will not keep the study devices. They will revert to their conventional finger-stick glucose monitoring.

10 Endpoints

10.1 Primary Endpoint

The primary outcome (endpoint) is HbA1c at 24 weeks.

10.2 Secondary Endpoints

10.2.1 HbA1c based

- HbA1c at 12 weeks
- HbA1c ≤ 53 mmol/mol (7.0%)
    - at 12 weeks [yes/no]
    - at 24 weeks [yes/no]
- HbA1c ≤ 59 mmol/mol (7.5%)
    - at 12 weeks [yes/no]
    - at 24 weeks [yes/no]
- Reduction in HbA1c ≥5.5 mmol/mol (0.5%) from baseline (screening)
    - at 12 weeks [yes/no]
    - at 24 weeks [yes/no]
- Reduction in HbA1c ≥ 11 mmol/mol (1.0%) from baseline (screening)
    - at 12 weeks [yes/no]
    - at 24 weeks [yes/no]

10.2.2 Sensor based:

- Time spent in the target glucose range between 3.9 to 10.0 mmol/l (70 to 180mg/dl).
- Time spent below target glucose (<3.9mmol/l) (<70mg/dl)
- Time spent above target glucose (10.0 mmol/l) (180 mg/dl)
- Average glucose levels
- Standard deviation glucose levels
- Coefficient of variation glucose levels
- The time with sensor glucose levels:
    - < 3.5 mmol/l (63 mg/dl)
    - < 3.0 mmol/l (54mg/dl)
    - < 2.8 mmol/l (50 mg/dl)

- The time with sensor glucose levels in the significant hyperglycaemia (glucose levels > 16.7 mmol/l) (300mg/dl)
- AUC of glucose below 3.0mmol/l (54mg/dl)

All the sensor based metrics will also be analysed separately for daytime (7:00-23:00 hours) and night-time (23:00-7:00 hours) in addition to overall period.

10.2.3 Non- sensor based secondary clinical:

- Daily average total insulin dose
- Daily average basal insulin dose
- Daily average bolus dose
- Average number of boluses of rapid acting insulin per day
- Frequency of severe hypoglycaemic episodes as defined by American Diabetes Association
- Frequency of significant ketosis events (plasma ketones >3mmol/l)
- Nature and severity of other adverse events.

10.2.4 Non-sensor based secondary patient-reported (psychosocial):

- Type 1 Diabetes Distress Scale (T1-DDS)
- Quality of Life (EQ-5D-5L)
- Patient Health Questionnaire (PHQ-9)
- Diabetes fear of injecting and self-testing questionnaire (D-FISQ)
- The revised Diabetes Eating Problem Survey (DEPS-R)

10.2.5 Process evaluation (utility and acceptability)

- FSL2 device utilization data, including: average number of scans per day (7:00-23:00 hours), per night (23:00-7:00 hours) and over the full 24-hour period; average number of days of usage per week
- Number of finger-stick glucose level tests per day
- Diabetes Treatment Satisfaction Questionnaire (DTSQ)
- Glucose Monitoring Satisfaction Survey (GMSS)

11 Assessment and Reporting of Adverse Events

11.1 Definitions

11.1.1 Reportable Adverse Events

A reportable Adverse Event is any untoward medical occurrence that meets criteria for a serious adverse event or any unanticipated medical occurrence in a study participant that is study or device-related. Device deficiencies that could have led to a serious adverse device effect will also be reported.

11.1.2 Adverse Events

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in a participant who has received an investigational device, whether or not related to the investigational medical device. This definition included events related to the device under investigation or the comparator or to the study procedures. For users or other persons, this definition is restricted to events related to the investigational device.

11.1.3 Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition also includes any event resulting from use error or from intentional misuse of the device under investigation.

11.1.4 Serious Adverse Event

A serious adverse event (SAE) is an adverse event that:

- led to a death
- led to a serious deterioration in the health of the participant, that either resulted in:
    - a life threatening illness or injury
    - a permanent impairment of a body structure or function
    - in-patient hospitalisation or prolonged hospitalisation
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- led to foetal distress, foetal death or a congenital abnormality or birth defect

A planned hospitalization for pre-existing condition, or a procedure required by the study protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

More than one of the above criteria can be applicable to one event. Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant 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. Medical judgement should be exercised in deciding whether an adverse event or reaction is serious in other situations.

Important adverse events or reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

11.1.5 Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

11.1.6 Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the device manual.

This includes unanticipated procedure related serious adverse events; that is, serious adverse events occurring during the study procedure that are unrelated to any malfunction or misuse of the investigational medical device.

An Anticipated Serious Adverse Device Effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the protocol.

11.1.7 Device Deficiencies

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labelling. A device deficiency may lead to an Adverse Device Effect or Serious Adverse Device Effect.

11.1.8 Adverse Event Intensity

Intensity	Definition
Mild	Patient is aware of signs and symptoms but they are easily tolerated
Moderate	Signs / symptoms cause sufficient discomfort to interfere with usual activities

Severe	Patient is incapable to work or perform usual activities

NB. The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as ‘serious’, which is based on patient/event outcome or action criteria (see definition 11.1.4). For example, itching for several days may be rated as severe, but may not be clinically serious.

11.1.9 Adverse Event Causality

Intensity	**Definition**
Not assessable	A report suggesting an adverse event, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship, which makes a causal relationship improbable, and in which other drugs/treatments, chemicals or underlying disease(s) provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment/use of investigational treatment/device, but which also could be explained by concomitant diseases or other drugs/treatments or chemicals.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment/use of medical method/device, unlikely to be attributable to concomitant disease(s) or other drugs/treatments or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
Definite/certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to study treatment/use of medical method/device and which cannot be explained by concomitant disease(s), other drugs/treatments or chemicals. The response to withdrawal of the treatment (dechallenge) should be clinically plausible. The event must be unambiguous, either pharmacologically or as phenomenon, using satisfactory rechallenge procedures if necessary.

(Reference: WHO-UMC Causality Categories)

11.2 Recording and Reporting of Adverse Events, Serious Adverse Events and Device Deficiencies

11.2.1 Monitoring Period of Adverse Events

The period during which adverse events will be reported is defined as the period from the beginning of the study (obtaining informed consent) until 3 weeks after the end of their study participation. Adverse events that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected. The follow up of AEs may therefore extend after the end of the clinical investigation; however no new AEs will be reported after the trial reporting period.

11.2.2 Recording and Reporting of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the participant, and appropriate medical intervention will be taken. The investigator will elicit reports of adverse events from the participant at each visit and complete adverse event forms. All AEs, including those the participant reports spontaneously, those the investigators observe, and those the participant reports in response to questions will be recorded on electronic AE forms at each site within 30 days of discovering the event.

The study investigator will assess the relationship of any adverse event to be device-related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device or study procedures. The individual investigator at each site will be responsible for managing all adverse events according to local protocols, and decide if reporting is required.

11.2.3 Severe Hypoglycaemia

Severe hypoglycaemia will be defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopaenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Severe hypoglycaemia will be regarded as a foreseeable adverse event and an adverse event form will be completed. Severe hypoglycaemia is not necessarily a serious adverse event and hence may not

require immediate reporting to the Sponsor. Non-severe hypoglycaemia will not be reported or considered an adverse event.

11.2.4 Reporting of Serious Adverse Events and Serious Adverse Device Effects

When reporting adverse events, all pertinent data protection legislation must be adhered to.

The serious adverse event report should contain the following information*:

1. Study identifier (Sponsor Reference)
2. Participant's unique study number, Initials and Trial Arm Assignment
3. Date of birth
4. Event description
5. Start date of event and whether initial / follow-up report.
6. Laboratory tests used and medical interventions used to treat the SAE
7. Planned actions relating to the event, including whether the study device was discontinued
8. Statement on the patient's current state of health
9. Reason for seriousness (i.e. death, life threatening, hospitalisation, disability/incapacity or other)
10. Evaluation of causality (including grade of relatedness) with the following (more than one may apply):
    a. the investigational treatment/medical device
    b. the clinical study/a study specific procedure
    c. other: e. g. concomitant treatment, underlying disease
11. Principal and Chief Investigator's assessment declaration with record of the reporter's name, date and signature

*In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as soon as this becomes available.

The relationship of the SAE to the investigational treatment / medical device should be assessed by the delegated members of the research team, as should the anticipated or unanticipated nature of any SAEs and SADEs.

All SAEs whether or not deemed investigational method/device related and whether anticipated or unanticipated must be reported to the Sponsor by email within 24 hours (one working day) of the Investigator learning of its occurrence.

Specific reporting instructions:

SAEs should be reported to the sponsor via Manchester Clinical Trials Unit (CTU). E-mail address specifically for SAE reporting is saereport_manctu@manchester.ac.uk. If record of receipt is not provided by the mCTU within 2 working days then there should be subsequent follow-up by the site PI.

A written report must follow within five working days and is to include a full description of the event and sequelae, in the format detailed on the Serious Adverse Event reporting form.

Manchester CTU will notify the Research Ethics Committee (REC) of any USADE in line with pertinent legal requirements. Manchester CTU will inform the Sponsor about all reports sent to the reporting organisation including follow-up information and answers by the reporting organisation. Manchester CTU is responsible for informing other site principal investigators and the CI of all SAEs.

The main REC will be notified of all USADEs within 7 days if they resulted in death or categorised as life-threatening and 15 days for all other USADEs following the occurrence of the event.

11.2.5 Recording and Reporting of Device Deficiencies

All device deficiencies will be documented throughout the study. The investigator at each site will be responsible for managing all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect.

All device deficiencies that might have led to a serious adverse device effect(s) if: suitable action had not been taken; intervention had not been made; or if circumstances had been less fortunate, must be reported to the CTU /Sponsor as for SAEs/SADEs.

11.2.6 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI / Manchester CTU shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant HRA REC of the measures taken and the circumstances giving rise to those measures. The study sponsor

will also be notified. A substantial amendment to the protocol and any relevant study documentation (e.g. PIS, CRF) will be applied.

11.2.7 Healthcare Arrangements and Compensation for Adverse Events

Healthcare arrangements for participants who suffer an adverse event as a result of participating in the study may include advice from clinical members of the study team or the patient's treating diabetes team, or use of emergency health services.

The standard National Health Service insurance and indemnity will apply to this study. If an adverse event occurs, there are no special compensation arrangements unless this was due to the negligence of one of the clinical investigators. In this case participants may have grounds for legal action for compensation. The normal national complaints mechanism will be available and NHS insurance and indemnity only covers negligent harm. There is no provision for non-negligent harm as a result of participating in the study.

11.3 Expected Adverse Events, Risks and Benefits

11.3.1 Risks and expected adverse events

Known risks represent hazardous situations which may result in anticipated adverse events. In the following text, where appropriate, the term "risk" and "anticipated adverse events" are used interchangeably without affecting meaning.

11.3.2 Hypoglycaemia and Hyperglycaemia

Participants with type 1 diabetes have a pre-existing risk for hypoglycaemia and hyperglycaemia. Potential risks are:

- Risk of mild to moderate hypoglycaemia and associated symptoms such as sweating, trembling, difficulty thinking and dizziness. There is also a rare risk of severe hypoglycaemia when conscious level is altered, needing help from a third party to correct the hypoglycaemia. These risks are pre-existent in any patient with type 1 diabetes and the study objective is to develop systems to minimise these risks
- Risk of possible mild to moderate hyperglycaemia similar to the risk that a participant with type 1 diabetic experiences on a daily basis
- Risk of hyperglycaemia leading to diabetic ketoacidosis (DKA). This risk is pre-existent in any patient with type 1 diabetes.

11.3.3 Blood Sampling

Participants will be required to have three blood tests (venepuncture) during the whole study. Venepuncture is required annually as part of the annual review for people with diabetes, and in some instances venepuncture is required every 3 to 6 months for assessment of HbA1c. Potential risks include:

- Slight discomfort or bruising at the site (common)
- Excess bleeding at the site (unlikely)
- Infection at the site (rare)

Local anaesthetic cream or spray may be used to minimise the discomfort.

11.3.4 Finger-prick Blood Glucose Measurements

Finger-prick tests may produce pain and/or bruising at the site.

11.3.5 Insulin Pump Therapy

Some participants in this study are already using an insulin pump. Potential risks associated with insulin pump therapy include:

- Slight discomfort at the time of insertion of the insulin delivery cannula (common)
- Slight bruising at the site of insertion (common)
- Bleeding at insertion site (rare)
- Infection at the site of insertion (rare)
- Allergy to the insulin delivery cannula or adhesive (rare)
- Infusion set and cannula occlusions (rare)
- Insulin pump malfunction and mechanical problems (rare)
- Allergy to insulin (very rare)
- Lipodystrophy / lipoatrophy (very rare)

11.3.6 Flash Glucose Monitoring

Potential risks associated with flash glucose monitoring:

- Slight discomfort at the time of insertion of CGM (common)
- Slight bruising at the site of insertion (unlikely)
- Bleeding at insertion site (rare)
- Infection at the site of insertion (rare)

- Allergic reaction to the CGM sensor material (rare)

If a skin reaction is classified as severe (the observation is noticeable and bothersome to participant and may indicate infection or risk of infection or potentially life-threatening allergic reaction), an adverse event form will be completed.

11.3.7 Questionnaires

As part of the study, participants will complete questionnaires which include questions about their private attitudes, feelings and behaviour related to diabetes. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these reactions are uncommon.

11.4 Benefits

It is expected that use of flash glucose monitoring will lead to improvements in HbA1c and play an important role in the management of type 1 diabetes. Therefore, the results of this study are likely to be beneficial for participants with diabetes.

It is possible that participants will not directly benefit from being a part of this study. However, it is also possible that the blood sugar information from the CGM devices will be useful for participants' diabetes self-management.

11.5 Independent Data Monitoring Committee (IDMC)

The IDMC (see 17.1) will be informed of all serious adverse events and any unanticipated adverse device effects that occur during the study and will review compiled adverse event data at periodic intervals.

12 Data Collection

12.1 Procedures

12.1.1 Height and Weight

These will be recorded at the study initiation visit at screening using equipment available at each clinic.

12.1.2 Subcutaneous Glucose Monitoring

At least 10 days of blinded continuous glucose (Freestyle Libre Pro) data will be collected prior to the randomisation with the aim of gaining knowledge of the specific participant's glucose control characteristics at screening and assessing adherence before the beginning of any intervention arm. Participants in the intervention arm will be encouraged to upload freestyle libre 2 data at regular intervals.

12.1.3 Insulin Pump Data

Data from participants on insulin pump therapy will be downloaded periodically during each intervention.

12.2 Questionnaires

12.2.1 Questionnaires

Quantitative data on health-related quality of life, diabetes distress, needle burden, disordered eating, depression and diabetes treatment satisfaction will be assessed using validated questionnaires. Participants will complete the questionnaires at screening and at the end of the study intervention. All results will be evaluated at the end of the study.

List of questionnaires are:

1. EQ-5D-5L questionnaire (Appendix 1)
2. The Glucose Monitoring Satisfaction Survey (GMSS) (Appendix 2).
3. Patient Health Questionnaire (PHQ-9) (Appendix 3)
4. Diabetes Treatment Satisfaction Questionnaire (DTSQ) (Appendix 4)
5. Diabetes fear of injecting and self-testing questionnaire (D-FISQ) (Appendix 5)
6. Diabetes Eating Problem Survey (DEPS-R) (Appendix 6)
7. Type 1 Diabetes Distress Scale (DDS) (Appendix 7)
8. The Clarke questionnaire and Gold score. (Appendix 8)
9. Additional non-validated questionnaires for subset of participants in the FSL2 arm (Appendix 10 and 11) and clinical investigators (Appendix 12) exploring expectations and experience of using FSL2 during the study

12.3 Laboratory Methods

12.3.1 Screening Sample

Renal and thyroid function will be measured locally if not done within the previous one year.

12.3.2 HbA1c

Blood samples for the measurement of HbA1c levels will be taken at three different time points: screening, 12 weeks and at the end of study intervention at 24 weeks. All HbA1c will be measured locally.

12.4 Total Blood Loss

The total blood loss will be approximately 30 ml (Approximately 10 ml on three occasions)

13 Study Materials and Products

13.1 Flash Glucose Monitor

Freestyle Libre 2 (Abbott Diabetes Care, Oxon, UK) flash-glucose monitor will be used in the intervention arm.

13.2 Standard Blood Glucose Meters

Participants in the control arm will be using their usual finger-stick glucose monitor throughout the study.

13.3 Insulin pumps

Participants already on insulin pump therapy will continue their usual insulin pump throughout the study.

13.4 Insulin

Participants will continue their usual insulin therapy throughout the study.

14 Statistics and Data Analysis

14.1 Sample size

The sample size calculation (128 evaluable cases from 150 randomised 1:1, up to 180 recruited to allow for any dropouts pre-randomisation) was premised on a between trial arm t-test for follow-up HbA1c values (2-tail alpha = 0.05, power = 0.80 when the true mean difference is 0.4% and the SD is 0.8% i.e. Standardised Effect Size [SES] = 0.5). There is expected to be a moderate-to-large correlation between baseline and follow-up HbA1c values, so the planned use of ANCOVA (see 14.2 and 14.3) will in fact have greater power (assuming other inputs unchanged).

We chose delta (MCID) of 0.4% as this is consistent with other relevant trials (REPOSE (31) used 0.5%, DIAMOND (10) used 0.4% and GOLD (11) used 0.3%, for delta at the design stage), although there is no consensus as to which of these values is most appropriate. We also considered findings from other RCTs (DIAMOND (10) 0.6%, GOLD (11) 0.43%, as detailed in our application) and a recent meta-analysis of trials and longitudinal observational studies (32) which have suggested that an effect of the order of 0.43%-0.7% might be expected, somewhat greater than the potential range for delta of 0.3%-0.5%, and therefore chose to power the proposed trial on a delta of 0.4%, deeming that this was the most

efficient approach without potentially over-powering the trial (an interim analysis is not possible given the length of follow-up relative to the recruitment period).

The assumed SD was informed by published results from the DIAMOND (10) and GOLD (11) trials, although the eligible baseline HbA1c values for these trials were 7.5 to 10.0% and >=7.5%, respectively, which each differ somewhat from the 7.5% to 11.0% range intended for this trial (it is likely that the SD will be lower with a narrower eligibility range, suggesting that our SD may lie between the 0.8 reported for DIAMOND (10) and the 0.9 implied for GOLD (11)). Increasing SD and baseline/follow-up correlation (rho) act in opposite directions on power for a given sample size – the table below illustrates reasonable power for a range of plausible values.

Power for an ANCOVA with 128 evaluable cases (150 randomised 1:1):

	rho			
SES = delta/SD	0	0.3	0.5	0.7
0.44 (e.g. 0.4/0.9)	0.70	0.73	0.81	0.93
0.50 (e.g. 0.4/0.8)	0.80	0.84	0.90	0.98

As can be seen in the table above, if the correlation (rho) between baseline and 6-month HbA1c values is at least 0.5 (consistent with a scatterplot provided in the DIAMOND (10) paper), power will be at least 90% for a SES of 0.5, but will still detect a SES of 0.44 (e.g. SD 0.9 rather than 0.8) with at least 81% power. We therefore believe that our choice of 128 participants with evaluable HbA1c at the 6-month time-point is optimal.

14.2 Statistical Analysis Plan (SAP)

All analyses will be conducted following the intention to treat (ITT) principle where all randomised participants are analysed in their allocated treatment group whether or not they receive their randomised treatment. All baseline, 12-week and 24-week outcome data will be presented descriptively, both overall and within treatment group, using mean (SD), median (IQR) or frequency (percentage), as appropriate. All statistical tests will use a 2-sided significance level of 5% (unless otherwise specified). All confidence intervals presented will be 95% and two sided.

A full, detailed SAP will be approved by the TSC (following drafting and review by the TMG, TSC and IDMC) before the first substantive statistical analysis. All statistical analyses will be performed using Stata (StataCorp, College Station TX, USA).

14.2.1 Primary Outcome

The primary outcome analysis will evaluate between group differences in HbA1c levels at the end of the 24-week treatment period. An analysis of covariance (ANCOVA) model will be used, with 24-week HbA1c as the outcome and trial arm effect as the focus, and with adjustment for baseline HbA1c and the other baseline variables included in the minimisation allocation algorithm as covariates. We have allowed for up to 15% attrition by 24 weeks in our sample size calculation; should we have more than 10% missing HbA1c at 24 weeks (or more than a 10% difference between missing data percentages in the two arms) we will use multiple imputation will be used in order to implement a more complete ITT analysis of the substantive ANCOVA model (otherwise this will be performed as a sensitivity analysis, with a complete case analysis used as the primary analysis). The imputation model will include baseline and 12-week

HbA1c, all the baseline variables used in the allocation algorithm and any other recorded variables found to be predictive of missing the 24-week outcome in exploratory analyses.

14.2.2 Secondary Outcomes

HbA1c based

For the HbA1c 12-week outcome, an ANCOVA model will be used, with trial arm effect as the focus, and with adjustment for baseline HbA1c and the other baseline variables included in the minimisation allocation algorithm as covariates.

For the HbA1c-based [yes/no] variables, logistic regression models will be used. For each model, trial arm effect will be the focus, with adjustment for the baseline variables included in the minimisation allocation algorithm (including baseline HbA1c category) as covariates.

Sensor-based

The respective sensor-based measures obtained during the last 2 weeks of the 24-week randomised interventions contrasting the flash-glucose against the SMBG will be compared using independent-samples statistical techniques. For any non-normally distributed (substantially skewed) measures, transformation or nonparametric analyses will be used. Where possible, analysis will be adjusted for baseline sensor values obtained during blinded run-in period and the baseline variables included in

the minimisation allocation algorithm. Analysis will also be repeated for day and night-time period (the interval from 7.00 to 23:00 defines day-time period; 23:00 to 07:00 am defines the night-time period).

Non-sensor based clinical

For the insulin dose data, independent-samples statistical techniques will again be used. For any non-normally distributed (substantially skewed) measures, transformation or nonparametric analyses will be used. Analysis will be adjusted for the baseline value of the outcome measure and the baseline variables included in the minimisation allocation algorithm.

Safety data, including severe hypoglycaemia events and ketone-positive hyperglycaemia, will be tabulated for all participants, including drop-outs and withdrawals, irrespective of whether CGM data are available and irrespective of whether closed-loop was operational. Severe hypoglycaemic events and ketone-positive hyperglycaemia will be tabulated in each treatment group, which will be compared using repeated measures logistic regression (generalised estimating equations). For purposes of analysis, a severe hypoglycaemic event will be defined as an event requiring assistance of another person actively to administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopaenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Non-sensor based patient-reported (psychosocial)

ANCOVA will also be used for the psychosocial outcome data evaluation, with trial arm effect as the focus, adjusting for baseline level of the outcome and the other baseline variables included in the minimisation allocation algorithm as covariates.

14.2.3 Subgroup analysis

Planned subgroup analysis will be applied for the primary outcome measure and will include:

- Those with baseline HbA1c 7.5%-9.0% and >9.0%-11%
- Treatment modality: Multiple daily injections (MDI) vs Continuous Subcutaneous Insulin Infusion (CSII)

- Prior participation in structured education course (yes; no)
- Different age groups, 16 <30, 30 to <45, 45 to <60 and >=60 years at enrolment
- Education < Bachelor's degree, >= Bachelor's degree
- Hypoglycaemia Unawareness (Clarke score >3)

14.2.4 Interim analysis

No interim analysis will be performed.

14.3 Economic analysis

The economic evaluation will determine the difference in costs and outcomes generated by the FSL2 device compared with self-monitoring. The economic evaluation will be conducted prospectively alongside the randomised controlled trial from the perspective of NHS/Prescribed Specialised Services (PSS) following standard quality design and reporting criteria (33). During the study we will collect information about healthcare (NHS) resource use up to 24 weeks after commencement of randomised study period. These will include events such as A&E attendance (ambulance or walk-in), Readmissions or admissions to other hospitals, Outpatient attendance, GP surgery attendance (GP or nurse) / telephone contact/home visit, Paramedic calls and attendances

A within-trial cost-utility analysis will compare differences in total costs and differences in quality of life using QALYs derived from the EQ-5D-5L. QALYs will be calculated by attaching available utility weights to the health states generated from the EQ5D-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 generated for each person in the FSL2 device and self-monitoring arms from a combination of trial-based resource use with published unit costs, allowing comparison in terms of costs to NHS and PSS. The unit costs of resource use will be taken from publicly available sources including current editions of NHS reference costs and the Unit Costs of Health & Social Care (34-35). Costs will be compared between the two groups using a bootstrapped regression model (as the data are likely to be skewed).

Modelling the potential effect of the intervention on costs and outcomes beyond the trial period will provide a better idea of overall impact as the benefits of controlling HbA1c are likely to be seen after the endpoint of the trial. Therefore, we will carry out an economic evaluation informed by modelling to estimate longer-term benefits and NHS/PSS costs.

A commercially available cost-effectiveness model, the IMS Centre for Outcomes Research and Effectiveness diabetes model version 8.5 (IMS Health, Danbury, CT, USA), will be used for this economic evaluation. This model is an internet-based, interactive simulation model that predicts the long-term health outcomes and costs associated with the management of T1DM and type 2 diabetes. The model consists of 15 submodels designed to simulate diabetes-related complications, non-specific mortality and costs over time. As the model simulates individuals over time, it updates risk factors and complications to account for disease progression. It also incorporates the costs and effects of hypoglycaemia, so is particularly well-suited to this study. Two major validation papers on the IMS CDM have been published to date. (36-37)The IMS Core Diabetes Model has also been used in a UK-based recent health technology assessment of CGM commissioned by NICE.(38)

Given the degree of validation of the model, and in order to be in line with the updated T1DM NICE guideline NG17 which used this model, (17) It was considered important not to use an alternative model or develop a de novo cost effectiveness model for this evaluation. We will use input parameters based on the RCT. This will allow us to properly reflect our population (i.e. adults and adolescents with T1DM with poorly controlled HbA1c) and their specific risk factors, including age, sex, duration of diabetes and baseline HbA1c. We will use the results of the trial comparisons of change in HbA1c levels and the rates of severe hypoglycaemic events to model the treatment effects.

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. These will be taken from published sources. Health benefits will be expressed in terms of life-years and QALYs gained. If more than one complication occurs at a time, a multiplicative approach will be applied.

14.3.1 Incremental economic analysis for both economic evaluations

Incremental cost-effectiveness ratios will be calculated in the event of the intervention having higher costs and better outcomes (based on QALYs and trial primary outcome). The base case analysis will express costs incurred in terms of QALY gain. Uncertainty will be addressed by generating cost-effectiveness planes from bootstrapped resamples. Cost-effectiveness acceptability curves (CEACs) will be constructed to show the probability that the intervention is cost-effective for different QALY thresholds. Incremental economic analysis using IMS CORE model will require the model's time horizon to be set to 80 years. All costs and effects will be discounted by 3.5%.

14.4 Process Evaluation Analysis

The process evaluation will be undertaken 'to explain discrepancies between expected and observed outcomes, to understand how context influences outcomes, and to provide insights to aid implementation'. Specifically, we will investigate whether: (1) treatment is consistent with the behaviour change theories, which underpin it and (2) contextual factors have affected implementation. Process evaluation will use a pipeline logic model, showing causal links between resources, activities and outcomes, integrating the National Institute for Health Behaviour Change Consortium's (NIHBCC's) approach to treatment fidelity (39) and a modified version of Linnan and Steckler's framework for process evaluation.(40) We will describe context qualitatively and take a mixed methods approach to characterising recruitment, reach, dose delivered/received and fidelity, with triangulation between data sources.(41) Free text response questionnaires will be completed by intervention designers, health professionals and trial participants (Appendices 10, 11 and 12), and analyses combined with trial data, including FSL2 device utilization and glucose finger-stick usage data, (DTSQs), Glucose Monitoring Satisfaction Survey (GMSS) which will be analysed descriptively (including the use of appropriate graphical representation), within arms where appropriate, will be synthesised and findings triangulated appropriately.

15 Case Report Forms

The Case Report Form (CRF) is the printed, optical, or electronic document designed to record all the protocol required information to be reported to the Chief Investigator for each study participant. CRFs will be completed in accordance with GCP and ISO 15197;2013 Guidelines and conform to the Manchester CTU SOPs.

Electronic CRFs (eCRFs) will be created for the study using the REDCap Cloud electronic data capture system (https://www.redcapcloud.com/) and these will follow the visit schedule outlined in this protocol. The REDCap Cloud system provides an edit feature that records the identity of the person making the change and retains a record of the before and after values of the data field(s) in question. In addition, all eCRF changes require electronic review and signoff by the investigator associated with the visit and only those who are signatories of the Manchester CTU site delegation log will be able to enter participant data. Paper based CRFs will be used for SAE reporting although information will also be recorded in REDCap Cloud. Standardised questionnaires will be completed on paper form with a record of their completion being provided electronically in REDCap Cloud. An export of the eCRF will be provided to sites so local workbooks can be utilised to ensure all participant data is effectively recorded, as some information may be obtained retrospectively (e.g. test result obtained following participant visit). Site workbooks will also act as another level of source documentation that could be used alongside patient records for monitoring purposes.

The site PI will be responsible for ensuring the accuracy, completeness, legibility and timely provision of the data recorded in the electronic CRFs that is provided to the Manchester CTU.

Sites must retain all original reports, traces and images from trial investigations, measures and assessments. Sites should keep sufficient information for all participants to enable records to be linked (e.g. CRFs, hospital records and samples) for the purposes of site monitoring and auditing. Any data recorded directly in the CRF that will not be verifiable from other sources are considered to be source data.

If any amendments to the protocol or other study documents are made, CRFs will be reviewed to determine if an amendment to these forms is also necessary.

16 Data Management

Confidentiality of participant data shall be observed at all times during the study. Personal details for each participant taking part in the research 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 of the investigation centres. These details will not be revealed at any other stage during the study, and all results will remain anonymous. The study identification number will be used on the case report forms and on all the blood and serum samples that are collected throughout the study. Names and full addresses will not be used. The full postcode of each participant will be recorded as part of demographic information collection as this will be required to ascertain whether deprivation has an impact on device usage. Collected samples will be stored securely and locked away. Only researchers directly involved in the study will have access to the samples.

Electronic data will be stored on password-protected computers. All paper records will be kept in locked filing cabinets, in a secure office at each of the investigation centres. Only members of the research team and collaborating institutions will have password access to the anonymised electronic data. Only members of the research teams will have access to the filing cabinet. Paper copies of the data will be stored for 15 years.

Direct access to the source data will be provided for monitoring, audits, REC review during and after the study. The fully anonymised data may be shared with third parties (EU or non-EU based) for the purposes of advancing management and treatment of diabetes.

Appropriate procedures agreed by the Manchester Clinical Trials Unit, Chief Investigator and Clinical Principal Investigators will be put in place for data review, database cleaning and issuing and resolving data queries.

17 Study Management

17.1 Independent Data Monitoring Committee (IDMC)

An IDMC will comprise a chairperson, a clinical expert and an independent statistician. The IDMC will be informed of all serious adverse events and any unanticipated adverse device effects/events that occur during the study. The IDMC will review compiled adverse event data at periodic intervals. The IDMC will report to the Study Management Committee any safety concerns and recommendations for suspension or early termination of the investigation.

17.2 Trial Steering Committee (TSC)

Trial Steering Committee with an independent chair will be appointed. Membership of the TSC will include two service users, independent health economist, two to three members of the study team

including chief investigator (CI) (Only CI voting), independent statistician and independent clinical psychologist. Other members of the study team and representatives from Manchester CTU and sponsor may also attend TSC meetings but will not have voting rights.

17.3 Trial Management Group (TMG)

Trial management group consisting of the Chief Investigator, Principal Clinical Investigators, Study Coordinators, and Study Data Manager will meet quarterly to discuss the operational aspects of the study.

17.4 Study Monitoring

A detailed risk assessment completed by the Sponsor and the Manchester CTU will inform the development of a Project Delivery Plan. This will be developed by the Manchester CTU trial team and will require CI / sponsor approval. The procedures, source data transfer modalities and anticipated frequency for monitoring will be documented in the Project Delivery Plan. Both a copy of the risk assessment and the project delivery plan will be stored in the TMF. Manchester CTU study monitors will be fully independent of both the Sponsor and Site Principal Investigators.

Authorised representatives of Sponsor, regulatory authority, or an Ethics Committee may perform audits or inspections at the recruiting centres, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the approved protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained.

18 Responsibilities

18.1 Chief Investigator

The Chief Investigator (CI) is the person with overall responsibility for the research and all ethics and HRA applications will be submitted by the CI. The CI is accountable for the conduct of the study and will ensure that all study personnel are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments and procedures and their study related duties.

The CI should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant study-related duties.

18.2 Principal Clinical Investigators

The Principal Clinical Investigators at each investigation centre will be responsible for the day-to-day conduct of the clinical aspects of the study.

18.3 Study Coordinators

Manchester CTU will provide overall co-ordination and project management for the trial, including planning investigator meetings, site initiation and routine monitoring visits. Additionally, local study coordinators will provide day-to-day support for the sites.

19 Ethics

The study will be conducted in accordance with the Declaration of Helsinki Ethical Principles for Medical Research involving Human Subjects (October 2000).

19.1 Research Ethics Committee and HRA approval

Prior to commencement of the study, the protocol, any amendments, participant information and informed consent forms, any other written information to be provided to the participant, participant recruitment procedures, current investigator CVs, and any other documents as required by the Research Ethics Committee / HRA will be submitted. Written approval will be obtained from the REC / HRA prior to the commencement of the study. Any additional requirements imposed by the REC shall be followed.

19.2 Informed Consent of Study Participants

In obtaining and documenting informed consent, the investigator will comply with the applicable regulatory requirements and will adhere to GCP standards and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the start of the study, the Investigator will obtain favourable ethical opinion of the written informed consent form, assent form and any other written information to be provided to participants.

Potential participants will be given full verbal and written information regarding the objectives and procedures of the study and the possible risks involved. The study team will avoid any coercion or undue improper inducement of the patient to participate and potential participants will be given

ample time to consider participation in the study. Potential participants will be informed about their right to withdraw from the study at any time.

The participant and/or their legal representative will be informed in a timely manner should any new information become available during the course of the study that may affect their well-being, safety and willingness to participate in the study.

Written consent will be obtained from participants according to REC requirements. The signed informed consent forms will be photocopied, originals filed in the Investigator's Site File, and a copy placed in the patient's notes and a copy given to the participants.

20 Amendments to the Protocol

Any substantial amendments to the protocol and other documents shall be notified to, and approved by, the Research Ethics Committee and sponsor, prior to implementation as per nationally agreed guidelines.

21 Deviations from the Protocol

Deviations from the protocol should not occur without prior approval of the REC or sponsor except under emergency circumstances, to protect the rights, safety and well-being of participants. If deviations do occur, they will be documented, stating the reason and the date, the action taken, and the impact for the participant and for the study. The documentation will be kept in the Investigator's Site File. Deviations will be logged electronically and will require chief investigator or local principal investigator acknowledgement and sign-off.

Deviations affecting the participant's rights, safety and well-being or the scientific integrity of the study will be reported to the REC and sponsor as soon as possible/ in a timely manner, following nationally-agreed guidelines.

22 Timetable

Inclusion of the first participant in the study is planned to take place in September 2019, with an enrolment period of up to 30 weeks. The expected completion of the last participant is March 2020 and the planned completion of the Clinical Study Report is June 2021.

23 Reports and Publications

Data will be submitted for publication in internationally peer-reviewed scientific journals; members of the investigator group will all be co-authors. The privacy of each participant and confidentiality of their information shall be preserved in reports and publication of data.

24 Retention of Study Documentation

Participant notes must be kept for the maximum time period as permitted by each individual site. Other source documents and the Investigator's Site File must be retained for at least 15 years, in line with the Data Protection Act 2018. The Principal Investigator will archive the documentation pertaining to the study after completion or discontinuation of the study.

25 Indemnity Statements

The clinical investigators are indemnified to cover negligent harm to patients participating in the study by their membership of medical defence organisations.

26 Appendices

26.1 Appendix 1: EQ-5D-5L questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

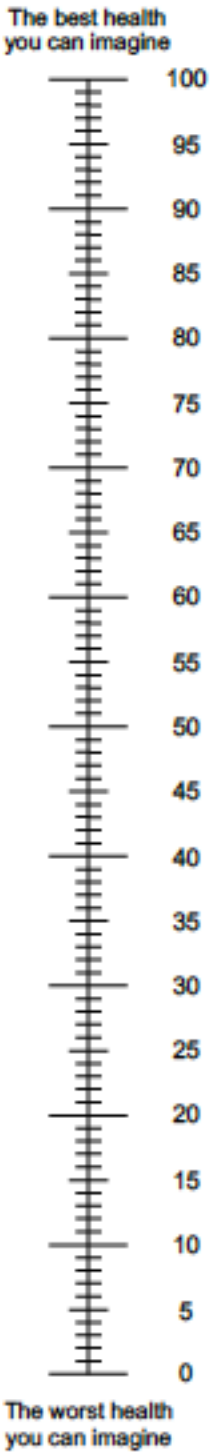
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



26.2 Appendix 2: Glucose Monitoring Satisfaction Survey

The Glucose Monitoring Satisfaction Survey (GMSS)

Version: Type 1 Diabetes

We are interested in your thoughts and feelings regarding your current glucose monitor.

For each item below, circle the number that best indicates how much you agree or disagree with each statement as it pertains to your current monitor. Some patients use more than one monitor. Please consider the monitor you use the most or consider to be your primary monitor when answering these questions.

	My current monitor:	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1	Helps me feel more satisfied with how things are going with my diabetes.	1	2	3	4	5
2	Makes me think about diabetes more than I want to.	1	2	3	4	5
3	Takes too much time to use.	1	2	3	4	5
4	Doesn't seem to be as accurate as I would like it to be.	1	2	3	4	5
5	Makes me worry a lot.	1	2	3	4	5
6	Is too much of a hassle to use.	1	2	3	4	5
7	Gives me numbers that I don't entirely trust.	1	2	3	4	5
8	Helps me feel less restricted by diabetes.	1	2	3	4	5
9	Makes me feel more frustrated with my diabetes.	1	2	3	4	5

10	Helps me be more spontaneous in my life.	1	2	3	4	5
11	Causes too many skin irritations or bruises.	1	2	3	4	5
12	Often gives me results that don't make sense.	1	2	3	4	5
13	Makes me feel more down and depressed.	1	2	3	4	5
14	Helps me be more open to new experiences in life.	1	2	3	4	5
15	Is too painful to use.	1	2	3	4	5

Scoring instructions:

The GMS for Type 1 Diabetes contains four subscales as well as a total score. Each can be obtained by calculating the mean item response score for the groups of items below.

Openness (higher scores indicate greater openness):	Items 1, 8, 10, 14
Emotional Burden (higher scores indicate greater burden):	Items 2, 5, 9, 13
Behavioral Burden (higher scores indicate greater burden):	Items 3, 6, 11, 15
Trust (higher scores indicate greater trust):	Reverse code items 4, 7, 12
Total scale (higher scores indicate greater satisfaction):	Mean of items 1-15 (reverse code items: 2-7, 9, 11-13, and 15)

26.3 Appendix 3: Patient Health Questionnaire 9

Fill in the boxes with pen or pencil to mark your answers.

A. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all 0	Several days 1	More than half the days 2	Nearly every day 3
1. Little interest or pleasure in doing things	❑	❑	❑	❑
2. Feeling down, depressed, or hopeless	❑	❑	❑	❑
3. Trouble falling/staying asleep, sleeping too much	❑	❑	❑	❑
4. Feeling tired or having little energy	❑	❑	❑	❑
5. Poor appetite or overeating	❑	❑	❑	❑
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down.	❑	❑	❑	❑
7. Trouble concentrating on things, such as reading the newspaper or watching television.	❑	❑	❑	❑
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual.	❑	❑	❑	❑
9. Thoughts that you would be better off dead or of hurting yourself in some way.	❑	❑	❑	❑
Total Score _____ =	_____+	_____+	_____+	_____

B. If you have been bothered by any of the 9 problems listed above, please answer the following:

How difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat Difficult	Very Difficult	Extremely Difficult
❑	❑	❑	❑

This health survey was adapted from the PRIME-MD® Patient Health Questionnaire © 1999, Pfizer Inc. Reproduced with permission. For research information, contact Dr. Robert L. Spitzer at rls8@columbia.edu.

26.4 Appendix 4: Diabetes Treatment Satisfaction

Diabetes Treatment Satisfaction Questionnaire: DTSQs

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

most of the time	6	5	4	3	2	1	0	none of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

most of the time	6	5	4	3	2	1	0	none of the time

4. How convenient have you been finding your treatment to be recently?

very convenient	6	5	4	3	2	1	0	very inconvenient

5. How flexible have you been finding your treatment to be recently?

very flexible	6	5	4	3	2	1	0	very inflexible

6. How satisfied are you with your understanding of your diabetes?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

8. How satisfied would you be to continue with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

Please make sure that you have circled one number on each of the scales.

26.5 Appendix 5: Diabetes fear of injecting and self-testing (D-FISQ) questionnaire

SELF-INJECTING OF INSULIN

		(almost) never	some-times	often	(almost) always
When I have to inject myself:					
1.	I become restless	0	0	0	0
2.	I feel tense	0	0	0	0
3.	I feel afraid	0	0	0	0
4.	I worry about it	0	0	0	0
5.	I feel nervous	0	0	0	0
6.	I brood about it	0	0	0	0

SELF-TESTING OF BLOOD GLUCOSE

		(almost) never	some-times	often	(almost) always
When I have to prick my finger:					
7.	I become restless	0	0	0	0
8.	I try to avoid it	0	0	0	0
9.	I feel tense	0	0	0	0
10.	I feel afraid	0	0	0	0
11.	I worry about it	0	0	0	0
12.	I feel nervous	0	0	0	0
13.	I brood about it	0	0	0	0
14.	I try to postpone it	0	0	0	0
15.	I get angry	0	0	0	0

26.6 Appendix 6: Diabetes Eating Problem Survey

DIABETES EATING PROBLEM SURVEY – REVISED (DEPS-R)

Living with diabetes can sometimes be difficult, particularly regarding eating and diabetes management. Listed below are a variety of attitudes and behaviors regarding diabetes management. For each statement, choose the ONE answer that indicates how often this is true for you during the PAST MONTH.

	Never	Rarely	Some-times	Often	Usually	Always
1. Losing weight is an important goal to me.	⓪	①	②	③	④	⑤
2. I skip meals and/or snacks.	⓪	①	②	③	④	⑤
3. Other people have told me that my eating is out of control.	⓪	①	②	③	④	⑤
4. When I overeat, I don't take enough insulin to cover the food.	⓪	①	②	③	④	⑤
5. I eat more when I am alone than when I am with others.	⓪	①	②	③	④	⑤
6. I feel that it's difficult to lose weight and control my diabetes at the same time.	⓪	①	②	③	④	⑤
7. I avoid checking my blood sugar when I feel like it is out of range.	⓪	①	②	③	④	⑤
8. I make myself vomit.	⓪	①	②	③	④	⑤
9. I try to keep my blood sugar high so that I will lose weight.	⓪	①	②	③	④	⑤
10. I try to eat to the point of spilling ketones in my urine.	⓪	①	②	③	④	⑤
11. I feel fat when I take all of my insulin.	⓪	①	②	③	④	⑤
12. Other people tell me to take better care of my diabetes.	⓪	①	②	③	④	⑤
13. After I overeat, I skip my next insulin dose.	⓪	①	②	③	④	⑤
14. I feel that my eating is out of control.	⓪	①	②	③	④	⑤
15. I alternate between eating very little and eating huge amounts.	⓪	①	②	③	④	⑤
16. I would rather be thin than have good control of my diabetes.	⓪	①	②	③	④	⑤

26.7 Appendix 7: Type 1 Diabetes Distress Survey

T1-DDS

Instructions

Living with type 1 diabetes can be tough. Listed below are a variety of distressing things that many people with type 1 diabetes experience. Thinking back **over the past month**, please indicate the degree to which each of the following may have been a problem for you by circling the appropriate number. For example, if you feel that a particular item was not a problem for you over the past month, you would circle "1". If it was very tough for you over the past month, you might circle "6".

		Not a problem	A slight problem	A moderate problem	A somewhat serious problem	A serious problem	A very serious problem
1	Feeling that I am not as skilled at managing diabetes as I should be.	1	2	3	4	5	6
2	Feeling that I don't eat as carefully as I probably should.	1	2	3	4	5	6
3	Feeling that I don't notice the warning signs of hypoglycemia as well as I used to.	1	2	3	4	5	6
4	Feeling that people treat me differently when they find out I have diabetes.	1	2	3	4	5	6
5	Feeling discouraged when I see high blood glucose numbers that I can't explain.	1	2	3	4	5	6
6	Feeling that my family and friends make a bigger deal out of diabetes than they should.	1	2	3	4	5	6
7	Feeling that I can't tell my diabetes doctor what is really on my mind.	1	2	3	4	5	6
8	Feeling that I am not taking as much insulin as I should.	1	2	3	4	5	6
9	Feeling that there is too much diabetes equipment and stuff I must always have with me.	1	2	3	4	5	6
10	Feeling like I have to hide my diabetes from other people.	1	2	3	4	5	6
11	Feeling that my friends and family worry more about hypoglycemia than I want them to.	1	2	3	4	5	6
12	Feeling that I don't check my blood glucose level as often as I probably should.	1	2	3	4	5	6
13	Feeling worried that I will develop serious long-term complications, no matter how hard I try.	1	2	3	4	5	6

		Not a problem	A slight problem	A moderate problem	A somewhat serious problem	A serious problem	A very serious problem
14	Feeling that I don't get help I really need from my diabetes doctor about managing diabetes.	1	2	3	4	5	6
15	Feeling frightened that I could have a serious hypoglycemic event when I'm asleep.	1	2	3	4	5	6
16	Feeling that thoughts about food and eating control my life.	1	2	3	4	5	6
17	Feeling that my friends or family treat me as if I were more fragile or sicker than I really am.	1	2	3	4	5	6
18	Feeling that my diabetes doctor doesn't really understand what it's like to have diabetes.	1	2	3	4	5	6
19	Feeling concerned that diabetes may make me less attractive to employers.	1	2	3	4	5	6
20	Feeling that my friends or family act like "diabetes police" (bother me too much).	1	2	3	4	5	6
21	Feeling that I've got to be perfect with my diabetes management.	1	2	3	4	5	6
22	Feeling frightened that I could have a serious hypoglycemic event while driving.	1	2	3	4	5	6
23	Feeling that my eating is out of control.	1	2	3	4	5	6
24	Feeling that people will think less of me if they knew I had diabetes.	1	2	3	4	5	6
25	Feeling that no matter how hard I try with my diabetes, it will never be good enough.	1	2	3	4	5	6
26	Feeling that my diabetes doctor doesn't know enough about diabetes and diabetes care.	1	2	3	4	5	6
27	Feeling that I can't ever be safe from the possibility of a serious hypoglycemic event.	1	2	3	4	5	6
28	Feeling that I don't give my diabetes as much attention as I probably should.	1	2	3	4	5	6

26.8 Appendix 8: Clarke Questionnaire and Gold Score

Please answer each question by ticking the appropriate answer. A single answer must be given to each question.

1	Check the category that best describes you O I always have symptoms when my blood sugar is low [A] O I sometimes have symptoms when my blood sugar is low [R] O I no longer have symptoms when my blood sugar is low [R]
2	Have you lost some of the symptoms that used to occur when your blood sugar was low? O Yes [R] O No [A]
3	In the past six months, how often have you had moderate hypoglycaemia episodes? (episodes where you might feel confused, disoriented or lethargic and were unable to treat yourself) O Never [A] O Once or twice [R] O Every other month [R] O Once a month [R] O More than once a month [R]
4	In the past year, how often have you had severe hypoglycaemic episodes? (episodes where you were unconscious or had a seizure or needed glucagon or intravenous glucose? O Never [A] O 1 time [R] O 2 times [R] O 3 times [R] O 4 times [R] O 5 times [R] O 6 times [R] O 7 times [R] O 8 times [R] O 9 times [R] O 10 times [R] O 11 times [R] O 12 times or more [R]

5	How often in the last month have you had readings <70 mg/dL (3.9mmol/L) **with** symptoms? O Never O 1 to 3 times O 1 time / week O 2 to 3 times / week O 4 to 5 times / week O Almost daily No rating for this question
6	How often in the last month have you had readings <70 mg/dL (3.9mmol/L) **without** symptoms? O Never O 1 to 3 times O 1 time / week [A] if answer to Q6 ≤ Q5 O 2 to 3 times / week O 4 to 5 times / week [R] if answer to Q6 > Q5 O Almost daily
7	How low does your blood sugar need to go before you feel symptoms? O 60 - 69 mg/dL (3.4 - 3.9 mmol/L) [A] O 50 - 59 mg/dL (2.8 - 3.3mmol/L) [A] O 40 - 49 mg/dL (2.2 - 2.7 mmol/L) [R] O < 40 mg/dL (2.2 mmol/L) [R]
8	To what extent can you tell by your symptoms that your blood sugar is low? O Never [R] O Rarely [R] O Sometimes [R] O Often [A] O Always [A]

Total Clarke Score :.....

Gold score :

2. Do you know when your hypos are commencing? Please circle a number:

	Always aware						Never aware
Awareness	1	2	3	4	5	6	7

26.9 Appendix 9: Outline of educational curriculum: FLASH-UK study

During the trial each participant will attend 3 visits for therapy optimisation.

- Visit 3: at randomisation with ~1 hour for education/optimisation
- Visit 4: 4 weeks after randomisation - ~40 minutes for education/optimisation
- Visit 5: 12 weeks after randomisation - ~1 hour for education/optimisation
-

The principles of therapy optimisation are broadly similar between the fingerstick glucose testing group and the Flash monitoring group and are based on Dose Adjustment for Normal Eating (DAFNE) principles.

Each individual participant will have their needs assessed by an experienced diabetes educator. They will work with the individual to optimise insulin therapy based on available glucose data (SMBG or flash glucose).

Areas covered at each visit will include participant goals and any barriers and their personal action plan. Insulin dosing will be reviewed: basal, bolus, correction, calculation of doses. All participants will be encouraged to review their data between study visits to identify patterns and make alterations to their therapy as needed. All participants will be given information about currently available online diabetes education support tools (Bertie online and DTN-UK flash glucose monitoring education platform).
Throughout the trial all participants will be encouraged to follow the management principles:
General advice

1. Check your glucose regularly, particularly before each meal and before bed
2. Aim for a flat stable glucose overnight, most nights (ask for support if this is difficult)
3. Try to give mealtime insulin 15-20 minutes pre-meal
4. If the insulin:carbohydrate ratio is correct your glucose should return to target after 4-5 hours of a meal bolus
5. If your correction ratio is correct, your glucose should return to target 4-5 hours after a correction dose
6. Hypo management: If < 3.5 mmol/L: treat with 15-20g rapid-acting carbohydrate; if below target but ≥ 3.5 mmol/L: eat 10g carbohydrate.
7. Try to find time to regularly review your data and think what changes may be needed to improve glucose control

Control arm:

Participants randomised to conventional finger-stick glucose monitoring arm will be encouraged to use finger-stick glucose levels to optimise treatment and will receive education about insulin dose adjustments using finger-stick glucose levels. The study will try to mimic real-life conditions by continuing participants pre-study diabetes treatment and insulin dose adjustment will be based on finger-stick glucose testing in the control arm and flash glucose monitoring in the intervention arm. Participants will be provided with a paper diary to collect information about insulin doses and carbohydrate intake.

Intervention arm:

Participants randomised to flash-glucose monitoring arm will receive education and training about insertion and initiation of the sensor as well as how to use flash-glucose monitoring data for treatment optimisation. The education sessions will be conducted by a professional diabetes educator or a member of the study team. Education will be tailored to meet the needs of the individual.

Advice specific to flash glucose arm

1. Scan as much as possible, aiming >15/day
2. Work towards increasing % time in range (3.9-10mmol/l). If you are struggling to improve time in range, ask your team for support
3. Aim to keep hypos (<3.9mmol/l) below 10%, ideally <5%
4. If glucose below 7 and falling, stop and consider the need or additional carbohydrate to help avoid hypoglycaemia
5. Do a blood glucose if the FreeStyle Libre 2 suggests you are hypo (<3.9mmol/l)
6. If < 3.5 mmol/L: treat with 15-20g rapid-acting carbohydrate; if below target but ≥ 3.5 mmol/L: eat 10g carbohydrate.
7. Avoid insulin stacking: avoid the temptation to give correction doses within 3 hours of a meal bolus unless willing and able to scan every 20-30 minutes for the next few hours to avoid hypoglycaemia
8. Remember the libre 2 reading lags behind blood glucose by 5-10 minutes
9. Blood glucose above 5mmol/l is legally required for driving
10. Use of alarm features of FSL 2

26.10 Appendix 10: Assessing expectations and experience of using Freestyle Libre 2 during FLASH-UK Clinical Trial

1. Why did you choose to go into the trial?

2. What would you say your expectations were before you entered the trial?
   Was there anything that you particularly hoped for?
   Was there anything you were concerned about?

3. Thinking outside of glycaemic control for a minute, did you think the Libre 2 would have any impact on your quality of life? If so, in what way? How did that work out now that you are at the end of the trial?

4. Thinking now about using the Libre 2 system for the last few months:
   Was there anything in particular that you found positive about using the Libre 2 system? If so, please state.

5. 'What was your experience of the alarms on the Libre 2 system? [prompt for further detail e.g.: positive, negative, intrusive, unhelpful , helpful, reassuring, worrying]

6. If you were asked to describe your experience of using the Libre 2 system to a friend, what would you say about it?

7. Were there occasions when you found yourself 'flashing' more than others? If so, please state. What prompted you to flash more often? How did this make you feel?

8. Did having the flexibility to flash rather than finger prick impact the way you view your control over diabetes and its management? If so, how was that?

9. Thinking along the same lines, did having access to the trend data impact the way you view your control over diabetes and its management? If so, how?

10. Was there anything in particular that you didn't like or found frustrating about using the Libre 2 system? What was that?

11. If you were asked to recommend the Libre 2 system, what would you say?

12. Thinking about your experience of using the Libre 2 system, is there anything you would change about it? If yes, what is that?

13. If given the choice, would you wish to continue using the system? Why is that?

26.11 Appendix 11: Process Evaluation, Topic guide: Participants

Notes: This topic guide is a flexible tool and may be revised as new areas of interest arise during the process of data collection. The wording of questions is for guidance only and can be varied to suit the natural style of the interviewer and the level of understanding of the participant.

Questions

1. How did you find the libre 2 study?
   - Was there anything in particular that you liked about it?
   - Was there anything in particular that you didn't like about it?
   - How many visits did you attend?
   - Did you feel you got any benefit from the study?
   - Were there any downsides?
   - Did the study meet your needs?

2. Was it easy to fit the study demands into your usual routine?
3. Would you have preferred fewer study visits?
4. How did you hear about this study?
   - How did you feel about being approached to participate in the study?
   - How did you feel about a computer deciding whether you were going to get the libre 2 or not?

5. We asked you to fill in some questionnaires at the beginning of the study and again recently.
   - What did you think about the number of questions you were asked?
   - Did you have any trouble answering any of the questions?
   - We use those questions to find out whether how you are feeling. Did you feel any of the questions were more important than others?

Thank you for your time

26.12 Appendix 12: Process Evaluation, Topic guide: Health Professionals and Triallists

Notes: The detailed version of the topic guide will be tailored by the research team following the intervention development. This topic guide is a flexible tool and may also be revised as new areas of interest arise during the process of data collection. The wording of questions is for guidance only and can be varied to suit the natural style of the interviewer and the level of understanding of the participant.

For Study Healthcare Professionals:

First, a few questions about the Libre 2 intervention and the service in which you work

Coherence (meaning and sense-making by professionals):

- Is the intervention easy to describe when you're talking to patients and professionals?
- Is it clearly distinct from other interventions?
- Does it have a clear purpose for patients and professionals?
- Do you think patients and professionals have a shared sense of its purpose?
- What benefits do you think the intervention will bring; to whom?
- Are these benefits likely to be valued?
- Does the intervention fit with the overall goals and activity of your organisation?

Cognitive participation (commitment and engagement by professionals)

- Do patients and professionals think the Libre 2 is a good device?
- Do they see the point of the libre 2 device as part of routine care?
- Are patients and professionals prepared to invest time, energy and work into it?

Collective action (the work professionals and patients do to make the intervention function)

- How has the libre 2 affected your work;
- What effect has it had on your consultations and communication with patients and carers?
- Does it impact on the way that health professionals in the unit relate to each other?
- How compatible is the trial with existing work practices?
- Does it seem to be the right thing to be doing?
- It is perceived as valid…. as useful?
- Who needs to be involved in its use?
- Does rolling out the libre 2 mean health professionals learning new skills or doing things differently?
- Do all individuals involved in using libre 2 have the right set of skills?
- What impact does the libre 2 have on:
    - the division of labour in your unit
    - resources
    - responsibility between different professional groups?
- Does a rigorous protocol for libre 2 challenge professional autonomy over working practices?
- Does the libre 2 impact on case load and allocation of work?
- Who has the power to make the libre 2 part of routine care?

- Do you think the system wants the libre 2 to be part of routine care?
- Do we need to and, if so, how can we divert resources to libre 2 prescribing?

Reflexive Monitoring (professionals reflect on or appraise the intervention)

- How are users likely to perceive the device once they've been using it for a while?
- Is it likely to be perceived as advantageous for patients or staff?
- Will it be clear what effects the device has had?
- Can patients and professionals contribute feedback about study procedures?
- Can the intervention procedures be adapted/improved on the basis of experience?

- "Thank you, is there anything else you want to say about the libre 2 research?"

For Triallists:

Now, a few questions about the trial and its procedures:

Any general comments about the trial?

Coherence (meaning and sense-making by professionals):

- Is the trial easy to describe when you're talking to patients and professionals?
- Is it clearly distinct from other trials?
- Does it have a clear purpose for patients and professionals?
- Do you think patients and professionals have a shared sense of its purpose?
- What benefits do you think the trial will bring; to whom?
- Are these benefits likely to be valued by professionals and patients who might take part in the main trial?
- Does the trial fit with the overall goals and activity of your organisation?

Cognitive participation (commitment and engagement by professionals)

- Do patients and professionals think the trial is a good idea?
- Do they see the point of the trial easily?
- Are they prepared to invest time, energy and work in it?

Collective action (the work professionals and patients do to make the trial function)

- How do the trial procedures affect your work; do they promote or impede it?
- What effect has the trial had on your consultations?
- Does participation in the trial require extensive training for staff involved?
- How compatible is the trial with existing work practices?
- What impact does it have on division of labour, resources, power, and responsibility between
- different professional groups?

Reflexive Monitoring (professionals reflect on or appraise the trial)

- How are users likely to perceive the trial once it's been on-going for a while?
- Is it likely to be perceived as advantageous for patients or staff?
- Will it be clear what effects the study has had?

- Can users/staff contribute feedback about study procedures?
- Can the study procedures be adapted/ improved on the basis of experience?

26.13 Appendix 13: FLASH-UK study: Participant Diary

To be completed starting five days before visits 4, 5 and 7:

	Rapid acting insulin dose (Novorapid, Humalog, Apidra, Fiasp etc) (meal dose+ correction)				Long acting Insulin (Lantus, Levemir, Toujeo, Tresiba etc)	
Date	Breakfast	Lunch	Evening meal	Corrections or snacks (add total)	Morning	Evening

Additional Notes:

26.14 Appendix 14: Participant Information Leaflet Freestyle Libre 2 Treatment Arm

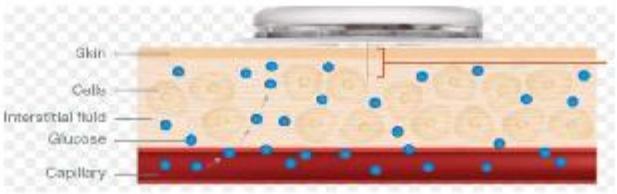
Flash-glucose monitoring in sub-optimally controlled Type 1 diabetes; IRAS ID: 25793

Getting the most from Flash Glucose Monitoring

This information leaflet aims to help you get the most out of using your flash glucose monitoring device i.e. the Freestyle Libre 2© sensor. In addition we also encourage you to watch the videos available at https://abcd.care/dtn/education (see page 8 below)

Glucose measured

Your Libre 2 sensor, a flash glucose monitoring system, sits just under the skin and measures the glucose in the fluid around the cells (interstitial fluid) and will be referred to as the "sensor glucose". The glucose measured by the sensor is always "behind" what the blood glucose is measuring; usually around 5-10 minutes.



Please Note: your sensor glucose measurement will rarely be the same as your blood glucose measurement. This doesn't mean your sensor is inaccurate; it reflects that they are measuring different things.

Glucose information

The sensor glucose is displayed in 3 ways:

- What the glucose is now (within last 5-10 minutes)
- Which way it is heading (arrows depicting steady / rising / falling levels)
- Glucose history as it sits within your target glucose range for the last 8 hours

Libre 2 handset

When is it best to scan?

An advantage of wearing the Libre sensor is that it fills in the gaps of glucose information between meals and overnight without having to do lots of extra finger stick checks.

Aim to scan your sensor like you would have normally tested your blood glucose levels:

- ✓ After getting out of bed each morning, to check fasting glucose
- ✓ Before each meal
- ✓ 2hrs after a meal (to determine post meal glucose profile)
- ✓ Before, during and after physical activity
- ✓ Before going to sleep, to check low glucose won't be an issue
- ✓ If you feel that you are going hypo or high glucose reading

Using your Libre sensor data

- Some people can find all this extra data a little overwhelming, especially at the beginning. If this is the case please talk to your team. It might be worth getting used to wearing the sensor and seeing the additional data for a week or so before starting to respond to it.
- Be prepared to see glucose readings out of target.
- It is important not to over-react to higher readings by giving more insulin after a meal as this can cause more erratic glucose levels which are harder to keep in target.

When to do glucose finger stick checks

Your sensor can replace many finger stick glucose checks but there are times it is recommended that a finger stick check is made:

- ✓ To confirm you are hypo and monitor recovery from a hypo
- ✓ If the sensor reading doesn't match how you feel or the glucose you were expecting to see

There are times when the Libre glucose data may be less reliable and you might want to do some additional finger stick checks to confirm the glucose level

- ✓ During first 24 hours of new sensor

✓ During times of rapidly changing glucose levels

Recording data

A glucose entry is created every time the sensor is swiped with your reader.

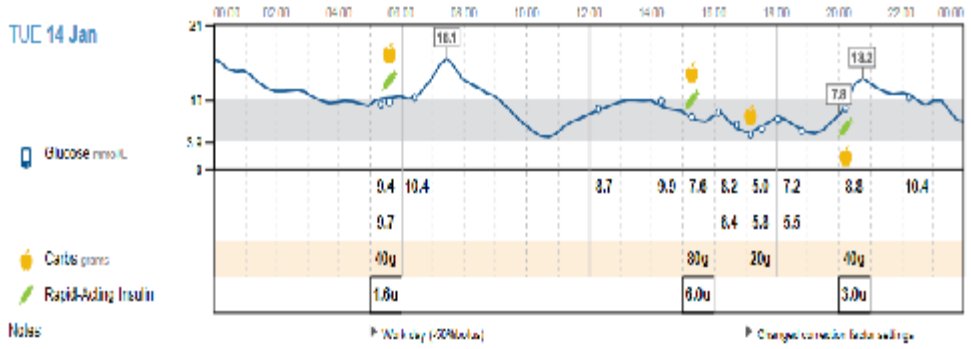
Using Libre sensor data reflectively

Libre View reports your sensor glucose data in a number of ways to help reflect on patterns:
Daily Log / Weekly Summary / Glucose Pattern Insights

- ✓ You can look to see where glucose is mostly in target and showing what is working well
- ✓ Steady / gentle changes in glucose tends to indicate carbohydrate choices, insulin to carbohydrate ratio and timing of insulin bolus worked well
- ✓ You can identify where the glucose is out of target and reflect on what might need changing.

Consider:

- Type and amount of carbohydrate eaten
- Timing of insulin bolus
- Insulin to carbohydrate ratio
- Activity post meal
- Basal review overnight



Time in range

This is another way of looking at overall glucose control that gives a better indication of how your glucoses are sitting. The goals to aim for:

- ✓ 70% or more time in range 3.9-10.0mmol/l **(GREEN)**

- ✓ Less than 25% above 10.0 mmol/l **(YELLOW)**
- ✓ Less than 4% below 3.9 mmol/l **(RED)**

What do the trend arrows mean?

Directional Arrows	Over past 20 minutes the glucose has been	If glucose trend continues how will glucose change?	
		In 10 minutes	In 30 minutes
↑	Rising quickly	Rising by more than 1.0mmol/l	Rising by 3.0 mmols/l
↗	Rising	Rising by 0.6-1.0 mmol/l	Rising by 1.8-3.0 mmols/l
→	Stable or changing slowly	Change by less than 0.6 mmol/l	Change by less than 1.8 mmols/l
↘	Falling	Falling by 0.6-1.0 mmols/l	Falling by 1.8-3.0 mmols/l
↓	Falling Quickly	Falling by more than 1.0 mmol/l	Falling by 3.0 mmols/l

Using Libre sensor data in real time

There are times when using the sensor glucose information at the time of seeing it can be helpful

- ✓ Checking if you are safe to drive ("*above 5 to drive*")
- ✓ If your sensor glucose is showing a glucose at the lower end of the target range with arrows down you might want to take action to avoid a hypo such as bring a meal forward or take a small amount of carbohydrate (remembering 10g carbohydrate will raise glucose by 2-3 mmols/l) see hypo section below

  It is worth noting that sensors can measure your glucose to be lower than they actually are when at the lower end of the glucose range. If there is any sense that your sensor is reading on the low side it is worth checking your glucose with a finger stick measurement to confirm you need to take action.

- ✓ If your sensor glucose is reading above or at the upper end of target with arrows up (AND it is more than 4 hours since you last gave insulin) you might want to consider a correction. If your sensor glucose is at the upper end of target or above with arrows down you can leave it and monitor to see if it returns to range.
- ✓ If your sensor glucose is reading above the glucose target range with arrows up – avoid correcting unless 4 hours after a previous insulin dose (unless you are unwell or showing ketones then follow Sick Day Rules)

Avoiding hypoglycaemia

Being able to check your glucoses more frequently and using the directional arrows on your Libre can be especially helpful to avoid hypos.

Important: Libre sensors can read lower at the lower end of the glucose range so it is important to confirm a hypo with a finger stick measurement

Directional Arrows	Over past 20 minutes the glucose has been	If Trend continues how will glucose change?	
		In 10 minutes	In 30 minutes
↘	Falling	Falling by 0.6-1.0 mmols/l	Falling by 1.8-3.0 mmols/l
↓	Falling Quickly	Falling by more than 1.0 mmol/l	Falling by 3.0 mmols/l

- 5-10g carbohydrates can raise glucose by 1-3 mmols/l and may be enough to prevent a hypo
- Always use finger stick measurements to monitor your recovery from a hypo
- Remember your sensor glucose is 5-10 minutes behind what your blood glucose is measuring and can show a low reading even when your blood glucose is back in range.
- Using sensor glucose to monitor recovery from hypoglycaemia usually results in over treatment of hypoglycaemia.

Glucose Alarms

One of the unique features of the Libre 2 is the ability to set alarms. Please see the separate document about setting alarms on the Libre.

Guidance on meal bolus adjustment based on rate of change arrow (DirecNet Method)

***Please remember that these dose adjustments are only a starting point and may need to be adjusted to suit individuals*

Directional Arrows	Over past 20 minutes the glucose has been	If glucose trend continues how will glucose change?		Action needed
		In 10 minutes	In 30 minutes	
↑	Rising quickly	Rising by more than 1.0 mmol/l	Rising by 3.0 mmols/l	Add 20% of meal time dose as extra
↗	Rising	Rising by 0.6-1.0 mmol/l	Rising by 1.8-3.0 mmols/l	Add 10% of meal time dose as extra
→	Stable or changing slowly	Change by less than 0.6 mmol/l	Change by less than 1.8 mmols/l	Give usual meal time dose
↘	Falling	Falling by 0.6-1.0 mmols/l	Falling by 1.8-3.0 mmols/l	Take 10% off meal time dose
↓	Falling Quickly	Falling by more than 1.0 mmol/l	Falling by 3.0 mmols/l	Take 20% off meal time dose

How to check your bolus dose is correct?

If glucose reading is 3.0 mmol/l higher at 2hrs post meal than pre meal, consider:

- ✓ Is your carbohydrate counting accurate?
- ✓ Has the meal insulin been delivered 15-20 minutes before (*exception is Fiasp – just before)
- ✓ Have you missed an injection?
- ✓ Are injection sites in good health (i.e. no signs of 'lumpy sites')?
- ✓ Have you exercised?

Corrections

The Libre sensor will enable you to view glucose levels between meals. The temptation will be to correct post meal glucose 'spikes'.

- **Avoid correction doses between meals (remembering the active insulin time of your meal bolus).** If glucose levels are often 'spiking' consider how you can optimise your meal bolus insulin (i.e bolus timing, carbohydrate accuracy, type of carbohydrate)
- Only correct between a meal if you have forgotten to give your meal insulin

Flash-glucose monitoring in sub-optimally controlled Type 1 diabetes; IRAS ID: 25793

Further information:

We strongly encourage you to watch the following videos available at https://abcd.care/dtn/education

Which modules are available?

1. **Introduction** – Dr Emma Wilmot, Derby Watch now (4:14)
2. **Mike's experience of FreeStyle Libre** – Mike Kendall, DTN-UK representative Watch now (15:34)
3. **Getting started with FreeStyle Libre** – Dr Peter Hammond, Harrogate Watch now (11:58)
4. **Interpreting daily traces** - Geraldine Gallen, DSN, London Watch now (19:48)
5. **Basal insulin** - Dr Emma Wilmot, Derby
   - with insulin pens Watch now (7:54)
   - with insulin pumps (online only) Watch now (8:26)
6. **Carbohydrates** – Nicola Taylor, Dietitian, Derby
   - Introduction Watch now (11:59)
   - Fats and Protein and the Freestyle Libre (online only) Watch now (15:10)
7. **Bolus insulin** – Dr Jackie Elliott, Sheffield
   - with insulin pens Watch now (13:10)
   - with insulin pumps (online only) Watch now (13:03)
8. **Reviewing my data: what does it all mean?** – Dr Fraser Gibb, Edinburgh Watch now (11:27)
9. **The diabetes rollercoaster** – Dr Emma Wilmot & Nick Rycroft, Derby Watch now (11:34)
10. **Exercise strategies** – Dr Parth Narendran, Birmingham & Dr Rob Andrews, Exeter Watch now (25:06)
11. **Hypoglycaemia** - Dr Pratik Choudhary, London Watch now (19:15)
12. **Understanding arrows** – Dr Pratik Choudhary, London Watch now (25:57)
13. **Glycaemic Variability** – Dr Iain Cranston, Portsmouth Watch now (21:00)

26.15 Appendix 15: Participant Information Leaflet Self-Monitoring Blood Glucose Control Arm

Flash-glucose monitoring in sub-optimally controlled Type 1 diabetes; IRAS ID: 25793

Getting the most from blood glucose monitoring

This information leaflet aims to help you get the most out of the flash study visits.

Glucose monitoring

- ✓ Check your glucose regularly, particularly before each meal and before bed
- ✓ Try to work towards the following glucose targets:
  - **5-7mmol/l fasting**
  - **4-7mmol/l pre meal**

Carbohydrate counting

- ✓ If the insulin:carbohydrate ratio is correct your glucose should return to target after 4-5 hours of a meal bolus.
- ✓ You may already have an established insulin: carbohydrate ratio (e.g. 1:1 or 1unit:10g) which you can check works.
- ✓ If you are not currently counting carbohydrates but would like to learn, the diabetes team will work with you on this.
- ✓ Rapid acting insulin takes time to work. Try to take your mealtime rapid acting insulin 15-20 minutes pre-meal.

Correction Factor

- ✓ If your correction ratio is correct, your glucose should return to target 4-5 hours after a correction dose of rapid acting insulin.
- ✓ For instance, some may find 1 unit of insulin reduces the glucose by 3mmol/l.
- ✓ If the correction factor is about right then the glucose should arrive at the target glucose 4-5 hours after a correction dose of rapid acting insulin is given.

- ✓ If your correction factor is not working for you, work with your team to adjust the ratio.

Overnight

- ✓ Aim for a flat stable glucose overnight, most nights (ask for support if this is difficult)
- ✓ In the event of unexplained overnight hypos, reduce the overnight basal insulin the following night.
- ✓ If the glucose levels consistently rise overnight, increase the basal.
- ✓ If overnight glucose persistently fall overnight, then reduce the basal.

Dietary intake

- ✓ Aim to accurately count carbohydrates.
- ✓ Aim to cover all carbohydrate intake with rapid acting insulin where possible.

Hypoglycaemia

- ✓ Hypo management: If < 3.5 mmol/L: treat with 15-20g rapid-acting carbohydrate.
- ✓ If below target but ≥ 3.5 mmol/L: eat 10g carbohydrate.

Reviewing your data

- ✓ Try to find time to regularly review your data and think about what changes may be needed to improve glucose control.
- ✓ There is an online programme called Bertie Online which covers all aspects of diabetes management. It can be accessed for free at: https://www.bertieonline.org.uk/

Online support

- ✓ There is an online programme called Bertie Online which covers all aspects of diabetes management. It can be accessed for free at: https://www.bertieonline.org.uk/

References

1. Daneman D: Type 1 diabetes. Lancet 2006;367:847-858

2. International Diabetes Federation, The Diabetes Atlas, Seventh Edition. Brussels:2015. http://www.diabetesatlas.org/, 2015

3. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G, Group ES: Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet 2009;373:2027-2033

4. McKnight JA, Wild SH, Lamb MJ, Cooper MN, Jones TW, Davis EA, Hofer S, Fritsch M, Schober E, Svensson J, Almdal T, Young R, Warner JT, Delemer B, Souchon PF, Holl RW, Karges W, Kieninger DM, Tigas S, Bargiota A, Sampanis C, Cherubini V, Gesuita R, Strele I, Pildava S, Coppell KJ, Magee G, Cooper JG, Dinneen SF, Eeg-Olofsson K, Svensson AM, Gudbjornsdottir S, Veeze H, Aanstoot HJ, Khalangot M, Tamborlane WV, Miller KM: Glycaemic control of Type 1 diabetes in clinical practice early in the 21st century: an international comparison. Diabet Med 2015;32:1036-1050

5. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B, Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643-2653

6. NHS Digital: National Diabetes Audit - 2015-2016: Report 1, Care Processes and Treatment Targets. http://digitalnhsuk/catalogue/PUB23241 2017;

7. Miller KM, Beck RW, Bergenstal RM, Goland RS, Haller MJ, McGill JB, Rodriguez H, Simmons JH, Hirsch IB, Network TDEC: Evidence of a Strong Association Between Frequency of Self-Monitoring of Blood Glucose and Hemoglobin A1c Levels in T1D Exchange Clinic Registry Participants. Diabetes Care 2013;36:2009-2014

8. Hovorka R: Continuous glucose monitoring and closed-loop systems. Diabet Med 2006;23:1-12

9. Bode BW, Sabbah H, Davidson PC: What's ahead in glucose monitoring? New techniques hold promise for improved ease and accuracy. Postgrad Med 2001;109:41-44, 47-49

10. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, Kollman C, Kruger D, McGill JB, Polonsky W, Toschi E, Wolpert H, Price D, Group DS: Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA 2017;317:371-378

11. Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, Schwarz E, Olafsdottir AF, Frid A, Wedel H, Ahlen E, Nystrom T, Hellman J: Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial. JAMA 2017;317:379-387

12. Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Hirsch IB, Huang ES, Kollman C, Kowalski AJ, Laffel L, Lawrence JM, Lee J, Mauras N, O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer S, Wilson DM, Wolpert H, Wysocki T, Xing D, Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group: Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464-1476

13. Bergenstal R, Tamborlane W, Ahmann A, Buse J, Dailey G, Davis S, Joyce C, Peoples T, Perkins B, Welsh J, Willi S, Wood M, The STAR 3 Study Group: Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1 Diabetes. N Engl J Med 2010;

14. Danne T, de Valk HW, Kracht T, Walte K, Geldmacher R, Sölter L, von dem Berge W, Welsh ZK, Bugler JR, Lange K, Kordonouri O: Reducing glycaemic variability in type 1 diabetes self-management with a continuous glucose monitoring system based on wired enzyme technology. Diabetologia 2009;52:1496-1503

15. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R: Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 2016;388:2254-2263

16. Reddy M, Jugnee N, Spanudakis E, Oliver N: Impact on hypoglycaemia awareness of real time continuous glucose monitoring and intermittent continuous glucose data (I HART CGM). Diabetic Med 2017;34:29-29

17. National Institute for Health and Care Excellence: Type 1 diabetes in adults: diagnosis and management. In *https://wwwniceorguk/guidance/ng17*, 2015

18. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G: Use of Flash Glucose-Sensing Technology for 12 months as a Replacement for Blood Glucose Monitoring in Insulin-treated Type 2 Diabetes. Diabetes therapy : research, treatment and education of diabetes and related disorders 2017;8:573-586

19. Dover AR, Stimson RH, Zammitt NN, Gibb FW: Flash Glucose Monitoring Improves Outcomes in a Type 1 Diabetes Clinic. J Diabetes Sci Technol 2017;11:442-443

20. McKnight JA, Gibb FW: Flash Glucose Monitoring is associated with improved glycaemic control but use is largely limited to more affluent people in a UK diabetes centre. Diabet Med 2017;34:732

21. Ish-Shalom M, Wainstein J, Raz I, Mosenzon O: Improvement in Glucose Control in Difficult-to-Control Patients With Diabetes Using a Novel Flash Glucose Monitoring Device. J Diabetes Sci Technol 2016;10:1412-1413

22. Holcombe A, Karunakaran V, Streeting J, Addington H, Smyth S: Trial of FreeStyle Libre in a local service: impact on diabetes outcomes. Diabetic Med 2017;34:160-160

23. Campbell F, Kordonouri O, Murphy N, Stewart C: FreeStyle Libre Use for Self-Management of Diabetes in Children and Adolescents. Diabetes 2017;66 Suppl. 1A:LB28-LB28

24. Olafsdottir AF, Attvall S, Sandgren U, Dahlqvist S, Pivodic A, Skrtic S, Theodorsson E, Lind M: A Clinical Trial of the Accuracy and Treatment Experience of the Flash Glucose Monitor FreeStyle Libre in Adults with Type 1 Diabetes. Diabetes Technol Ther 2017;19:164-172

25. McPhater A, Gardiner M, Modgil G: The impact of the Libre device for families and children with Type 1 diabetes. Diabetic Med 2017;34:104-104

26. Edge J, Acerini C, Campbell F, Hamilton-Shield J, Moudiotis C, Rahman S, Randell T, Smith A, Trevelyan N: An alternative sensor-based method for glucose monitoring in children and young people with diabetes. Archives of disease in childhood 2017;102:543-549

27. Dunn T, Xu Y, Hayter G: Evidence of a strong association between frequency of flash glucose monitoring and glucose control measures during real-world usage. Diabetes technology & therapeutics 2017;19, Suppl. 1:A12-A12

28. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R: Cutaneous adverse events related to FreeStyle Libre device - Authors' reply. Lancet 2017;389:1396-1397

29. Herman A, Aerts O, Baeck M, Bruze M, De Block C, Goossens A, Hamnerius N, Huygens S, Maiter D, Tennstedt D, Vandeleene B, Mowitz M: Allergic contact dermatitis caused by isobornyl acrylate in Freestyle(R) Libre, a newly introduced glucose sensor. Contact dermatitis 2017;

30. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R: Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36:1384-1395

31 REPOSE Study Group: Relative effectiveness of insulin pump treatment over multiple daily injections and structured education during flexible intensive insulin treatment for type 1 diabetes: cluster randomised trial (REPOSE). BMJ. 2017 Mar 30;356:j1285. doi: 10.1136/bmj.j1285.

32 Seibold A, Welsh Z. K, Ells S, Schlaeger C: A Meta-analysis of Real-World Observational Studies on the Impact of Flash Glucose Monitoring on Glycemic Control as Measured by HbA1c. Diabetes 2018 Jul; 67 (Supplement 1): 72-LB. Available at: https://doi.org/10.2337/db18-72-LB

33. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH,Mauskopf J, Loder E: Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting. Practices Task Force. Value in Health 2013;16:231-250

34. Personal Social Services Research Unit: PSSRU Unit Costs of Health and Social Care 2016. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2016/2016. Last accessed 29/12/2017

35. Department of Health: NHS Reference Costs 2015 to 2016. London, Department of Health, 2016 Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016. Last accessed 29/12/2017

36. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, Lammert M, Spinas GA: Validation of theCORE Diabetes Model against epidemiological and clinical studies. Curr Med Res Opin 2004;20 Suppl 1:S27-40

37. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D: Validation of the IMS CORE Diabetes Model.Value in Health 17:714-724

38. Riemsma R, Corro Ramos I, Birnie R, Büyükkaramikli N, Armstrong N, Ryder S, Duffy S, Worthy G, Al M, Severens J, Kleijnen J: Integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm™ Veo system and the Vibe™ and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes: a systematic review and economic evaluation. Health Technology Assessment (Winchester, England) 2016;20:1-252

39. Bellg AJ, Borrelli B, Resnick B, Hecht J, Minicucci DS, Ory M, et al. Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH Behavior Change Consortium. Health Psychol [Internet]. 2004 [cited 2012 Mar 19];23(5):443–51

40. Linnan L, Steckler A. Process evaluation for public health interventions and research: an overview. In: Linnan L, Steckler A, editors. Process evaluation for public health interventions and research. 1st ed. San Francisco: Jossey-Bass; 2002. p. 1–23.

41. Farmer T, Robinson K, Elliott SJ, Eyles J. Developing and implementing a triangulation protocol for qualitative health research. Qual Health Res. 2006;16(3):377–94.