BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039400
Article Type:	Protocol
Date Submitted by the Author:	15-Apr-2020
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Keywords:	DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Clinical trials < THERAPEUTICS

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Effects of Novel Flash Glucose Monitoring System on Glycemic Control in Adult Patients with Type 1 Diabetes Mellitus: Protocol of a Multicenter Randomized Controlled Trial

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Words: 3937

ABSTRACT

Introduction

Optimal glycemic control is beneficial to prevent and delay the microvascular complications in patients with type 1 diabetes mellitus (T1DM). However, poor glycemic control still exists in patients with T1DM. The benefits of factory-calibrated flash glucose monitoring (FGM) system have been proved among well-controlled adults with T1DM, but evidence for FGM in adults with T1DM who have sub-optimal glycemic control is limited. This study aims to evaluate the effect of FGM in adult patients with T1DM who have sub-optimal glycemic control.

Methods and analysis

This open-label, multi-centre, randomized, and parallel-group trial will be conducted at 8 tertiary hospitals and recruit 76 adult (≥18 years old) participants with T1DM diagnosed for at least one year and suboptimal glycemic control (glycated hemoglobin [HbA1c] ranged 7.0-10.0%). After a run-in period (baseline, 0-2 weeks), eligible

patients will be randomized 1:1 to either use of FGM or self-monitoring blood glucose (SMBG) alone consequently for 24 weeks. At baseline (0-2weeks), 12-14 weeks and 24-26 weeks, professional continuous glucose monitoring (professional CGM) systems were used in both groups for device-related data collection. Biological metrics, questionnaires, and advent events will be assessed at baseline, week 14 and week 26. All analyses will be conducted on the intent-to-treat population. Efficacy endpoints analyses will also be repeated on the per-protocol population. The primary outcome is the change of HbA1c from baseline to week 26. Secondary outcomes include the change of CGM metrics, including time spent in range (TIR), time spent in target (TIT), time below range (TBR), time above range (TAR), standard deviation, coefficient of variation, mean amplitude of glucose excursions and so on. Risks and advent events will be traced and assessed during the study period.

Ethics and dissemination

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University in January 2017. Ethical approval has been obtained at all centers. All the participants will be provided with oral and written information about the trial. The study will be disseminated by peer-review publications and conference presentations.

Trial register number: NCT03522870 (ClinicalTrials.gov);

Overall status: Recruiting

Study Start: May 1, 2018

Primary Completion: December 30, 2020

Strengths and limitations of this study

- This study is a multi-centre randomized controlled trial, comparing the flash glucose monitoring system with self-monitoring blood glucose among adult patients with T1DM who have sub-optimally glycemic control.
- The professional CGM system will provide detailed comparable data on efficacy and safety between the two study arms.
- There is a head-to-head comparison on the sensor-related metrics as patients randomized to use the flash glucose monitoring systems will wear the professional CGM systems additionally and simultaneously in the 14 days preceding the 3-month and 6-month visiting.
- The limitation of this study is that the questionnaires evaluating the satisfaction with the device are not used in this trial.

INTRODUCTION

The Diabetes Control and Complications Trial (DCCT) had clearly demonstrated that intensive glycemic control contributed to delay and prevent the development and

progression of microvascular complications (1). However, even with much advancement of diabetes management in these years such as the improvement of insulin analogs and insulin infusion pumps, it is still not easy for adult patients with type 1 diabetes mellitus (T1DM) to achieve the recommended goals of HbA1c level (<7%) and the target-achieving rate was only approximately 15-30% (2-6). As glucose monitoring is one of the key parts of diabetes management and previous studies had demonstrated a strong association between glucose monitoring and glycemic control in patients with T1DM (5, 7), the improvement or optimization of glucose monitoring is necessary.

The conventional glycemic monitoring methods are the daily self-monitoring blood glucose (SMBG) by fingerstick tests and the HbA1c tests. The SMBG is the most widely used glucose testing method and generally enjoys good accuracy whereas it only provides the single point-in-time glucose concentration instead of the overall daily profiles and the pain from fingerstick might lead to the decrease of the patients' adherences. And the HbA1c, the golden standard of glycemic monitoring methods, reflecting the average glucose concentration for approximately 3 months, is also not direct and convenient enough for not proving a measure of glycemic variability or alerting the hypoglycemia moments(6). Therefore, an alternative of the glucose monitoring method in recent years is the updated continuous glucose monitoring (CGM) technology, which provides near real-time glucose data continuously by tracking the glucose concentrations in the body's interstitial fluid and reflects the intra-/inter-day glycemic excursions. There are two basic types of CGM systems. One is the professional CGM systems with blinded data available to the users and clinicians, which is usually applied in the outpatient visits or clinical trials. The other one is the system that provides unblinded data to user such as the real-time CGM systems. It has been demonstrated that glycemic control and psychological status of the adult patient with T1DM can be improved after using the real-time CGM systems(8-10) and the benefits can be also sustained for 12 months when using properly(11).

For most CGM systems, confirmatory SMBG is still required for calibrations. While the new generation of CGMs approved by Food and Drug Association in 2017, the flash glucose monitoring system (FGM; FreeStyle Libre®; Abbott Diabetes Care, Witney, Oxon, UK) is factory-calibrated and provided a longer sensor lifetime of 14 days, which has further relieved the pain from frequent strip capillary glucose calibrations needed in other CGMs and thus is relatively more acceptable and easier for widespread use. To date, most relevant published articles were researches regarding its accuracy(12-14) and reviews discussing its clinical effectiveness, cost-effectiveness, and safety (15-17), while there were only a small number of randomized clinical trials (RCTs) available to prove its benefits in patients with T1DM(18-20). Although data from these trials are encouraging, it still remains unclear whether the FGM is effective in adult patients with T1DM who had suboptimal glycemic control. Therefore, we designed this 24-week comparative trial, aiming to evaluate the effect of FGM in adult patients with T1DM who have

sub-optimal glycemic control. The research protocol of the RCT study was presented below.

METHODS AND ANALYSIS

Study design

This trial is an open-label, multi-center, randomized, and parallel-group study conducted at 8 centers in 7 cities (Guangzhou, Hefei, Foshan, Zhongshan, Shanghai, Wuhan and Shenzhen) in China. Eligible participants will be recruited and the efficacy of FGM with SMBG in adult patients with T1DM who have sub-optimal glycemic control will be compared. Written informed consent will be obtained from all participants before study-related activities. This trial has been approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University and conformed to the Declaration of Helsinki. The register number was NCT03522870 (ClinicalTrials.gov).

Study procedure

The flowchart of this study is presented in Figure 1. After a run-in period of 2 weeks, eligible patients will be randomized 1:1 to either use of FGM or SMBG consequently for 24 weeks. At baseline (0-2 weeks), 12-14 weeks and 24-26 weeks, professional CGMs (Ipro2) will be additionally used in both groups. Demographic and biological data, questionnaires, and advent events will be also collected and assessed at baseline, week 14 and week 26.

Participant Recruitment (before 0 week)

The recruitment has begun in May 2018 and will end in December 2020. Major eligibility criteria includes age ≥ 18 years old, HbA1c between 7 and 10%, and duration of T1DM at least 1 year. The diagnostic criteria of T1DM is based on T1DM definition by American Diabetes Association and World Health Organization (WHO) (21, 22). Other inclusion criteria and exclusion criteria are shown in Table 1.

Run-in period (Baseline, week 0-2)

In this period, patients' information on the demographics, medical histories, smoking/drinking status, exercise and the results of physical examination (body mass index [BMI], waist-hip ratio [WHR], blood pressure and heart rate) will be collected by certified physicians and nurses in accordance with standardized protocols. Fasting blood samples are collected for biological measurements including liver enzymes, renal function, fasting plasma glucose (FPG), plasma lipids, HbA1c, blood routine, thyroid function and antibodies, C-peptide, diabetes antibodies, urine albumin-to-creatinine ratio (ACR) and urine pregnancy test. Biological metrics will be tested centrally in the laboratory of the Third Affiliated Hospital of Sun Yat-sen University. In addition, questionnaires including the Chinese version of Diabetes Distress Scale (DDS)(22), Hypoglycemia Fear Scale (HFS) (23)and European Quality of Life (EQ-5D) (24) are completed on the patients' own or by the assistance of research stuff without affecting the patients' responses.

Then, all participants will wear the professional CGM systems (Ipro2®, Medtronic, USA) on the back of the upper arms continuously for 2 weeks. Blood glucose meters and compatible test strips (Bayer®; Bayer Consumer Care AG) will be distributed to all for their capillary blood glucose tests during the whole study period and instructions about device use will be provided simultaneously. During this two weeks, capillary blood glucose tests (at least four times per day), diet diary, exercise will be required to record for calibration. Sensor glucose measurements will not be visible to the patients and the investigators until the data is downloaded via the Carelink Ipro Software® after 2 weeks and then calculated by the Glyculator 2.0 software which follows the guidelines on CGM reporting specified in the International Consensus on use of CGM(23). Participants in both groups will be instructed regarding the general diabetic education with standard algorithms such as therapy adjustment for hypoglycemia/hyperglycemia, types of foods elevating glucose levels, adjustment of physical activity and so on.

Randomization

After the 2-week run-in period, eligible patients will be randomized 1:1 to either daily SMBG alone or FGM. Sealed, opaque envelopes will be arranged in a computer-generated random order that is prepared by SPSS 20.0(Software, Inc, Chicago, IL) and distributed to each participating center, where envelopes will be opened sequentially to determine the participants' assignments.

Study intervention

After randomization, participants in the FGM group will be provided with FGM systems (FreeStyle Libre®; Abbott Diabetes Care, Witney, Oxon, UK) that measured glucose concentrations at home for the following 24 weeks. Instructions about device use will be provided according to the manufacture's user manual and access to the device software (FreeStyle Libre Software 1.0®; Abbott Diabetes Care, Witney, Oxon, UK) will be given. Participants will be required to report the advent events especially those relevant to the device such as the skin problems and the sensor early removement. An additional fingerstick test will be recommended for their decision making when sensor data is below 3.9mmol/l or over 13.9mmol/l but the times of the fingerstick tests are non-restricted. The first sensor will be applied by trained staffs and the rest will be applied without supervision every 2 weeks. And the participants assigned into the SMBG group will be required to perform capillary glucose tests for at least four times per day during the following 6 months and record their daily glucose data. The additional fingerstick tests will be recommended when hypoglycemia and hyperglycemia related symptoms occur in both groups.

Follow-up visits (week 12-14 and week 24-26)

Follow-up visits for both groups will be scheduled at week 12 to 14 and week 24 to 26, during which professional CGM systems will be additionally used in both groups to collect CGM data for 2 weeks. For both groups, data on fingerstick tests (at least 4 times per day), diet, exercises and insulin adjustment during this period will be required to record for calibration. And at week 14 and week 26, glucose data

collected from the Ipro2s during the respective two weeks will be downloaded via the Carelink iPro software (Medtronic, USA) and the sufficiency of sensor data during 2-weeks will also be assessed, ensuring at least 70% of data is available. In addition, for FGM group, glucose data stored in the FGM recorders from week 2 to week 14 and from week 14 to week 26 will be downloaded respectively by research stuffs via its corresponding software. And for SMBG group, fingerstick glucose data stored in the blood glucose meters from week 2 to week 14 and week 14 to week 26 will be also collected respectively. The demographic and physical information, questionnaires, the biomedical metrics and advent events will be collected. Then, the general diabetes education will be reinforced in both groups with standard algorithms. All biological metrics throughout the study were analyzed at a central laboratory in the Third Affiliated Hospital of Sun Yat-sen University.

Endpoints

The primary endpoint is the change in HbA1c levels from baseline to week 26. The major secondary endpoints include the change in time spent in range (TIR 3.9 to 7.8mmol/l), time spent in target (TIT, 3.9 to 10.0mmol/l), time below range (TBR[<3.9mmol/l]; TBR[<3.0mmol/l]) and time above range(TAR[>10.0mmol/l]; TAR[13.9mmol/l]) from baseline to week 26. All predefined endpoints and the timing of all assessment are shown in Table 2.

Risks and advent events (AEs)

Once included, responsible investigators will trace if any device or study-related risks and AEs have occurred. Disease related events that are chronic in nature and occur as part of the progression of the diabetes disease state (i.e. diagnosis of retinopathy, nephropathy, neuropathy) will not be captured as AEs in this study.

Insertion of the sensors may result in pain, erythema, bleeding, edema and abscess at the insertion site. However, the expected frequency of these events is low in the previous research (18) with 13 in 328 patients reported. Once it occurred, related factors including sensor and bandage will be recommended to be removed. After removal of the sensor, subjects may experience irritation due to the medical adhesive used to apply the sensor pod and any bandage that may be placed over the device. This reaction is self-limiting and should resolve within hours and not more than a week post-removal.

Confirmed diabetes ketoacidosis and severe hyperglycemic events will be captured as serious adverse events (SAEs). Hypoglycemic events are also considered reportable AEs if the criteria for severe hypoglycemia are not met but emergency evaluation or treatment is obtained from a health care provider. All study or device-related AEs will be monitored until adequately resolved or stable.

Laboratory Analyses and Data management

The HbA1c concentration is centrally measured by an automated analyzer (Bio-Rad D10; Bio-Rad Laboratories, Hercules, CA) using the high-performance liquid

chromatography (HPLC) technique, with a reference range 4.3–6.1% and intra-batch and inter-batch coefficients of variation 0.46% and 0.99%, respectively. Lipid profiles, are determined by enzymatic colorimetric test with Hitachi 7600 autoanalyzer. Fasting/postprandial C-peptide are measured by an iodine (^{125}I) human C-peptide radioimmunoassay kit (Beijing North Institute of Biological Technology, Beijing, China; Intra-batch and inter-batch coefficients of variation 0.46 and 0.99% respectively). The thyroid function and its antibodies are assessed by the chemilumniscence (CLIA) method using ADVIA Centaur system (Siemens, Massachusetts, USA).

Autoantibodies against the 65 kDa isoform of Glutamic acid-decarboxylase antibody (GADA), Insulinoma-associated protein-2 antibody (IA-2A) and Zinc transporter 8autoantibody (ZnT8A) were analyzed centrally using fasting serum with radio binding assay confirmed by the Islet Autoantibody Standardization Program (assay sensitivity and specificity for GADA were 64 and 98% respectively, 64 and 100% for IA-2A respectively, 36 and 98% for ZnT8A respectively) at the First Affiliated Hospital of Nanjing University. Patients with positive results for at least 1 antibody titer tested (GADA titer≧0.042 was seen as positive; ZnT8A titer≧0.054 was seen as positive; IA-2A titer ≧ 0.018 was seen as positive) were considered positive for diabetes autoantibodies.

The coordinator center is located in the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. Data in this trial will be collected from case report forms (CRFs) by responsible participated investigators and sent to the coordinator center periodically. To maintain the accessibility of the database, facilities will be conducted as follows: 1. All participated investigators will be trained before starts. Standardized procedures will be illustrated in detail; 2. The responsible associate investigators will monitor data collection process and evaluate the data integrity periodically during the course of the data collection phase;3. A secondary review of the accuracy of data recorded from all participated hospitals will be conducted by coauthors and the principle investigator will manage data flow and perform audits of the procedure of the study.

Sample size

Assuming a drop rate of 10%, a sample size of 76 participants would be required for providing 80% power to detect a group difference in mean changes of HbA1c of 0.4% (standard deviation of 0.8), using a two-sided test at the 0.05 level.

Statistics analysis

All analyses will be conducted on the intent-to-treat (ITT) population. Data from all randomized patients with or without protocol violation including dropouts and withdrawals will be included in the analysis.

The calculation of the CGM metrics in the whole time, the night period (23:00-08:00) and the daytime period (08:00-23:00) is via the Glyculator 2.0 software. It is

anticipated that subjects with T1DM who are sub-optimally controlled will show an improvement in HbA1c level with the use of FGM in the intervention group after 26 weeks, over and above any improvement in subjects using SMBG in the control group. The magnitude of the change will be compared between two groups, using an analysis of covariance (ANCOVA) model adjusting for baseline HbA1c. The secondary efficacy analysis will also be compared between two groups, repeated the analysis of the ANCOVA model adjusted for the respective baseline value. A 95% confidence interval will also be given for the difference between the groups based on the ANCOVA model.

Information including demographics and physical measurements will be summarized. The calculation of the questionnaires will be presented in the below section. Continuous variables will be presented with the mean±standard deviation or median(25^{th} and 75^{th} quartile range). Categorical variables will be presented with the proportion of subjects in each category. If values are highly skewed, transformation or nonparametric analyses will be used. Chi-squared tests or Fisher's exact test will be used to analyzed the categorical data. The safety analysis will include all available data from all recruited patients. Any device-related AEs will be tabulated and reported. All null hypotheses will be tested against a two-sided alternative at the 5% significance level.

Tools used in this trial

Devices

In our study, two CGMs and a blood glucose meter will be applied: blood glucose meter for strip testing, professional CGM for assistance and FGM for interpretation. Both CGMs recorded glucose data collected in the interstitial fluid at different time intervals. Details would be described below.

Professional CGM system The professional CGM system (Ipro2®, Medtronic, USA) consists of an inserted sensor and a recorder connected. The sensor will be implanted on the back of the patients' upper arms and data is stored in the recorder every 5-minute, thus 288 glucose values will be collected per day in total. The lifetime of each sensor is usually from 3 to 7 days. The MARD of Ipro2 is 9.9% in adults and were lowest in the 240-400mg/dl range (6.8% in adults)(24). Thus, the professional CGMS was thought to be a perfect tool in the research with less interpretation.

FGM system The FGM system (FreeStyle Libre®; Abbott Diabetes Care, Witney, Oxon, UK) is a novel sensor-based intermittently scanned glucose monitoring system and is approved by the food and drug association (FDA) in September 2017. The sensor is around 1*1 cm and implanted by a single-use applicator, and automatically measures glucose every 15 minutes for up to 14 days without finger-stick calibration. The sensor will be implanted on the back of the upper arms which is thought to be the most accurate(25). A quick wireless scan of the sensor by the reader collects the glucose and collects the glucose and trend at that minute plus up to 8 hours of prior readings. The MARD tested in adult patients is 8.8% to 12.9% compared to BG reference and YSI pairs (13, 26). The most frequent safety problems of FGM is an

allergy, as shown in the study by Bolinder and colleague with 13 cutaneous adverse events reported(18).

Blood Glucose Meter (Bayer®) The blood Glucose Meter (Bayer®) is a reliable home-use device to perform finger-stick strip tests and meet the predetermined accuracy standard illustrated in a recent study(27). Therefore, it will be distributed into each patient as a tool to perform any finger-stick tests during the trial.

Questionnaires

In our study, the Chinese version of the DDS, HFS, EQ-5D-5L will be used to evaluate the change in distress from diabetes, the fear of hypoglycemia and the quality of life after the intervention. All scales had been tested reliability and validity in Chinese.

Diabetes Distress Scale (DDS) The Chinese version of the Diabetes Distress Scale is to evaluate diabetes-related emotional distress in patients with diabetes(28). The scale consists of 17 items, contains four domains including emotional burden sub-scale, physician-related distress subscale, regimen-related distress subscale, and diabetes-related interpersonal distress. Each item is rated on a 6-point Likert scale from 1(no problem) to 6(serious problem). An average score ≥3 is the cut-off point which is considered to more than moderate problem.

Hypoglycemia Fear Scale (HFS) The Chinses version of the Hypoglycemia Fear Survey II- Worry Scale is to evaluate psychological status for diabetic patients(29). These validated surveys consist of 18 questions that measure dimensions of anxiety and fear surrounding hypoglycemia. Each item is rated on a 5-point Likert scale from 0(never related) to 4(very related). Patients with higher scores are considered with more anxieties and fear of hypoglycemia.

European Quality of Life (EQ-5D-5L) Scale The Chinese version of the EQ-5D-5L is widely used to evaluate the quality of life in Chinese. The EQ-5D-5L is converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension(30). It contains the health description system and Visual Analogue Score (VAS). The health description system includes 5 dimensions including mobility, self-care, usual activities, pain or discomfort and anxiety/depression. Each item is rated on 5 levels from 1(no problem) to 5(extreme problem). And the VAS is to evaluate the health condition assessed by patients. The top score (100) means the best health conditions and the bottom one (0) means the worst.

PATIENT AND PUBLIC INVOLVEMENT

No patients were involved in the development of the research question or design of the study.

ETHICS AND DISSEMINATION

This trial will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the 1983 amendment per FDA's Guidance for Industry. It was also approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. Subjects will be provided the opportunity to review the informed consent prior to coming to the clinical site. The investigators or designees will explain the purpose and duration of the study, the procedure and requirements, the potential risks and benefits. Responsible research should answer all the questions the subjects asked. The consenting process will be documented in the subject's source document. A copy of the consent will be provided to the subject.

ACKNOWLEDGMENT

This study was supported by the National Key R&D Program of China (2017YFC1309600).

CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. JPW and JHY designed and organized the study. YWZ and HRD registered the trial and co-wrote the first draft of the manuscript. JPW, JHY and HXL undertook critical revision of the manuscript. YWZ, HRD and HXL are responsible for the recruitment and implementation of the protocol. DZY, WX and BY contributed to the data interpretation. JPW and JHY had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have read and approved the final manuscript.

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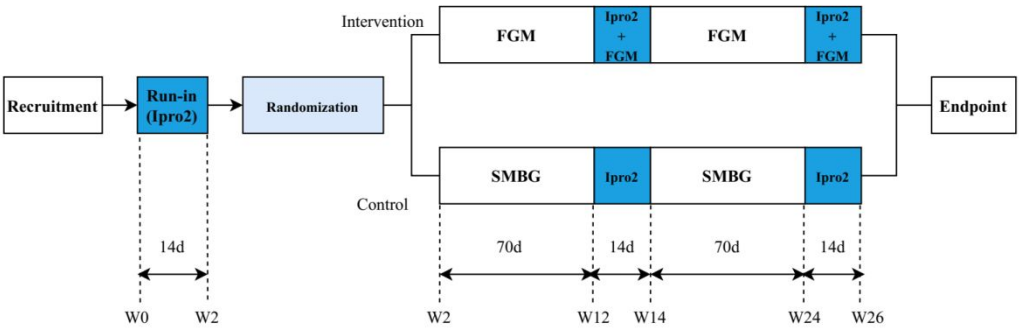


Figure 1. Flowchart of design

Table 1. Inclusive and exclusive criteria

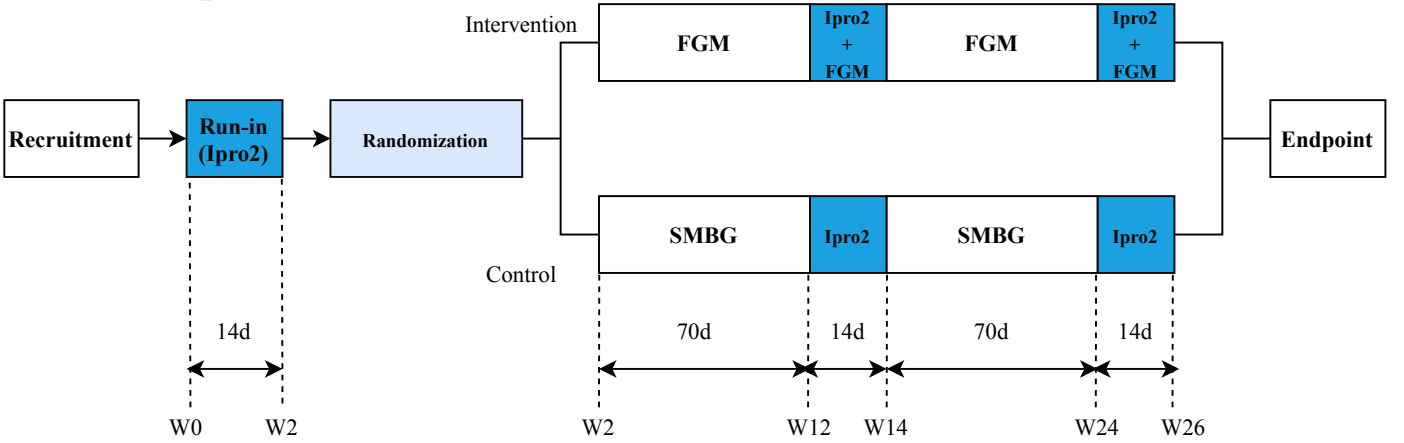
Inclusive criteria
1. Aged 18 years and older;
2. Diagnosed with T1DM with the criteria established by WHO in 1999, and with duration more than 1 year;
3. Glycosylated Hemoglobin A1c concentration between 7% and 10%;
4. SMBG daily (≥3 times per day) at least 2 months previous and have willing to insist for at least 6 months;
5. Stable insulin regimen medication including CSII and MDI for 3 months prior to study entry (change of insulin ≤20%), not including premix insulin;
6. Have the willing to wear CGM;
7. Able to speak, read and write Chinese.
Exclusive criteria
1. Having used any CGM 3 months prior to study entry;
2. Had severe diabetic complications such as proliferated diabetic retinopathy or end-stage renal disease of diabetic nephropathy, all assessed by investigators;
3. Receiving oral steroid therapy for any disorders and continuous use of paracetamol;
4. Had known allergy to medical-grade adhesives or CGM and its affiliated components;
5. Being pregnant or planning pregnancy (as demonstrated by a positive test at study entry);
6. Recent severe diseases like myocardial infarction, stroke, psychiatric diseases(historical/recent), malignant tumor, kidney disease (defined as estimated glomerular filtration rate<45 ml/min/1.73m), dermatosis, decided by investigator
7. Currently participating in another research (must have completed any study at least 30 days prior to being enrolled in this study);
8. Currently abusing illicit drugs, alcohol, or prescription drugs;
9. Any condition that could impact reliability of HbA1c measurement, such as hemoglobinopathy, hemolytic anemia, chronic liver disease, decided by investigator.

Abbreviations: T1DM: type 1 diabetes mellitus; WHO, world health organization; SMBG: self-monitoring for blood glucose CSII: continuous subcutaneous insulin infusion; MDI: multiple daily injections; CGM: continuous glucose monitoring.

Table 2. Endpoints

Primary endpoints	
HbA1c (%)	Difference in HbA1c at week 14 and week 26 adjusted for baseline
Secondary endpoints	
• **CGM metrics** (whole, night [23:00-08:00], daytime [08:00-23:00])	The difference in CGM profiles listed below collected via Ipro2 in week 12-14 and week 24-26 adjusted for baseline (week 0 to week 2)
TIR (%)	Range3.9-10.0mmol/l (70-180 mg/dl)
TIT (%)	Range 3.9-7.8mmol/l (70-140mg/dl)
TBR (%)	<3.9mmol/l (70 mg/dl); <3.0mmo/l (54 mg/dl)
TAR (%)	>10mmol/l (180mg/dl); >13.9mmol/l (250mg/dl)
Mean blood glucose(mmol/l)	
Estimated A1c (%)	
SD	
CV	
MAGE	
HBGI	
LBGI	
MODD	
$CONGA_{(n)}$	n=1h, 2h, 3h, 4h, 6h, respectively
AUC	>140mg/dl; >180mg/dl;>250mg/dl; <54mg/dl; <70mg/dl;
GRADE	Euglycemia; hypoglycemia; hyperglycemia
Number of hypoglycemia events	
• **Percentage of HbA1c value in Target (%)**	The difference in percentage of HbA1 in range (<7%) tested at week14 and week 26 adjusted for baseline.
• **Frequency in using FGM (times/d)**	Time frame: 24 weeks (from week 2 to week 26)
• **Frequency in using SMBG (times/d)**	Time frame: 24 weeks (from week 2 to week 26)
• **Total of daily insulin dose (IU/kg/d)**	The difference in insulin dose collected at week 14 and week 26 adjusted for baseline
• **Questionnaires**	The difference in scores of respective questionnaires collected at week 14 and week 26 adjusted for baseline
DDS	
HFS	
EQ-5D-5L	

Abbreviations: CGM: continuous glucose monitoring; TIR: Time spent in Range; TIT: Time spent in Target; TBR: Time below range; TAR: Time above range; SD: standard deviation; CV: coefficient of variation; MAGE: mean amplitude of glucose excursion; HBGI: high blood glucose index; LBGI: low blood glucose index; MODD: mean of daily differences; CONGA: continuous overlapping net glycemic action; AUC: area under the curve; GRADE: glycemic risk assessment in diabetes equation; FGM: flash glucose monitoring; SMBG: self-monitoring for blood glucose; DDS: Diabetes Distress Scale; HFS: Hypoglycemia Fear Scale; EQ-5D-5L: European Quality of Life Scale.



SPIRIT CHECKLISTS

This checklist is according to the recommendations presented in the https://www.spirit-statement.org/title/

SECTION/TOPIC	ADHERE TO RECOMMEDATIONS
ADMINISTRATIVE INFORMATION	
1: TITLE	√
2: TRIAL REGISTRATION	
2A: REGISTRY	√
2B: DATA SET	√
3: PROTOCOL VERSION	√
4: FUNDING	√
5: ROLES AND RESPONSIBILITIES	√
INTRODUCTION	
6: BACKGROUND AND RATIONALE	√
7: OBJECTIVES	√
8: TRIAL DESIGN	√
METHODS: PARTICIPANTS, INTERVENTIONS, OUTCOMES	
9: STUDY SETTING	√
10: ELIGIBILITY CRITERIA	√
11: INTERVENTIONS	√
12: OUTCOMES	√
13: PARTICIPANT TIMELINE	√
14: SAMPLE SIZE	√
15: RECRUITMENT	√
METHODS: ASSIGNMENT OF INTERVENTIONS (FOR	

CONTROLLED TRIALS)	
16: ALLOCATION	√
17: BLINDING (MASKING)	√
METHODS: DATA COLLECTION, MANAGEMENT, ANALYSIS	√
18:DATA COLLECTION METHODS	√
19:DATA MANAGEMENT	√
20:STATISTICAL METHODS	√
METHODS: MONITORING	
21: DATA MONITORING	√
22: HARMS	√
23: AUDITING	√
ETHICS AND DISSEMINATION	
24: RESEARCH ETHICS APPROVAL	√
25: PROTOCOL AMENDMENTS	√
26: CONSENT OR ASSENT	√
27: CONFIDENTIALITY	√
28: DECLARATION OF INTERESTS	√
29: ACCESS TO DATA	√
30: ANCILLARY AND POST-TRIAL CARE	√
31: DISSEMINATION POLICY	√
APPENDICES	
32: INFORMED CONSENT MATERIALS	√
33: BIOLOGICAL SPECIMENS	√

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	4
Participants	4a	Eligibility criteria for participants	4, 13
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	6
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	4

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5-7,13
	14b	Why the trial ended or was stopped	6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	15
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	15
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	7
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	6
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	2
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	2
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	/
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	/
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Effects of Novel Flash Glucose Monitoring System on Glycemic Control in Adult Patients with Type 1 Diabetes Mellitus: Protocol of a Multicenter Randomized Controlled Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039400.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Jul-2020
Complete List of Authors:	ZHOU, YONGWEN; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology; The First Affiliated Hospital of USTC, Department of Endocrinology and Metabolism Deng, Hongrong; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Liu, Hongxia; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Yang, Daizhi; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Xu, Wen; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Yao, Bin; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Yan, Jinhua; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Weng, Jianping; The First Affiliated Hospital of USTC, Department of Endocrinology and Metabolism
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Clinical trials < THERAPEUTICS

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Effects of Novel Flash Glucose Monitoring System on Glycemic Control in Adult Patients with Type 1 Diabetes Mellitus: Protocol of a Multicenter Randomized Controlled Trial

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Words: 3895

ABSTRACT

Introduction

Optimal glycemic control is beneficial to prevent and delay microvascular complications in patients with type 1 diabetes mellitus (T1DM). The benefits of flash glucose monitoring (FGM) have been proved among well-controlled adults with T1DM, but evidence for FGM in adults with T1DM who have suboptimal glycemic control is limited. This study aims to evaluate the effect of FGM in adult patients with T1DM who have suboptimal glycemic control.

Methods and analysis

This open-label, multicenter, randomized trial will be conducted at 8 tertiary hospitals and recruit 76 adult participants (≥18 years old) with T1DM diagnosed for at least one year and with suboptimal glycemic control (glycated hemoglobin [HbA1c] ranged from 7.0 to 10.0%). After a run-in period (baseline, 0-2 weeks), eligible participants will be randomized 1:1 to either use of FGM or self-monitoring blood glucose

(SMBG) alone consequently for 24 weeks. At baseline, 12-14 weeks, and 24-26 weeks, retrospective continuous glucose monitoring (CGM) systems will be used in both groups for device-related data collection. Biological metrics including HbA1c, blood routine, lipid profiles, and liver enzymes, questionnaires, and adverse events will be assessed at baseline, week 14, and week 26. All analyses will be conducted on the intent-to-treat population. Efficacy endpoints analyses will also be repeated on the per-protocol population. The primary outcome is the change of HbA1c from baseline to week 26. The secondary outcomes include the change of CGM metrics, including time spent in range, time spent in target, time below range, time above range, standard deviation, coefficient of variation, mean amplitude of glucose excursions, high or low blood glucose index, mean of daily differences, percentage of HbA1c in target(<7%), frequency in using FGM, total daily insulin dose and the differences in scores of questionnaires including diabetes distress scale, hypoglycemia fear scale and European quality of life scale.

Ethics and dissemination

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University in January 2017. Ethical approval has been obtained at all centers. All the participants will be provided with oral and written information about the trial. The study will be disseminated by peer-review publications and conference presentations.

Trial register number: NCT03522870 (ClinicalTrials.gov);

Overall status: Recruiting

Study Start: May 1, 2018

Primary Completion: December 30, 2020

Strengths and limitations of this study

- This study adopts a multicenter open-label, randomized, and parallel design.
- This study aims to evaluate the flash glucose monitoring system among adult patients with T1DM who have sub-optimally glycemic control with the comparison with self-monitoring blood glucose.
- The retrospective CGM system will provide detailed comparative data on efficacy and safety between the two study arms.
- There is a head-to-head comparison on the sensor-related metrics as patients randomized to use the flash glucose monitoring systems will wear the retrospective CGM systems additionally and simultaneously in the 14 days preceding the 3-month and 6-month visiting.
- The limitation of this study is that the questionnaires evaluating the satisfaction with the device are not used in this trial.

INTRODUCTION

The Diabetes Control and Complications Trial (DCCT) had demonstrated that intensive glycemic control contributed to delay and prevent the development and progression of microvascular complications (1). However, even with much advancement of diabetes management in these years such as the improvement of insulin analogs and insulin infusion pumps, it is still difficult for adult patients with type 1 diabetes mellitus (T1DM) to achieve the recommended goals of HbA1c level (<7%) and the target-achieving rate was only approximately 15-30% (2-6). As glucose monitoring is one of the key parts of diabetes management and previous studies had demonstrated a strong association between glucose monitoring and glycemic control in patients with T1DM (5, 7), the optimization of glucose monitoring is necessary.

The conventional glycemic monitoring methods include the daily self-monitoring blood glucose (SMBG) by fingerstick tests and HbA1c tests. The SMBG is the most widely used glucose testing method and generally enjoys good accuracy whereas it only provides the single point-in-time glucose concentrations instead of overall daily profiles and the pain from fingerstick might lead to decrease of the participants' adherence. And the HbA1c, the golden standard of glycemic monitoring method, reflecting the average glucose concentration for approximately 3 months, is also not direct and convenient enough for not proving a measure of glycemic variability or an alert function of real-time the hypoglycemia moments(6). Therefore, an alternative of the glucose monitoring method in recent years is the updated continuous glucose monitoring (CGM) technology, which provides near real-time glucose data continuously by tracking the glucose concentrations in the body's interstitial fluid and reflects the intra-/inter-day glycemic excursions. There are two basic types of CGMs. One is the retrospective CGM with blinded data available to users and clinicians, which is usually applied in the outpatient visits or clinical trials. The other one is the systems that provide unblinded data to use such as the real-time CGM systems. It has been demonstrated that glycemic control and psychological status of the adult patient with T1DM can be improved after using the real-time CGMs (8-10) and the benefits can be also sustained for 12 months when using properly(11).

For most CGMs, confirmatory SMBG is still required for calibrations. While the new generation of CGMs approved by Food and Drug Association in 2017, the flash glucose monitoring system (FGM; FreeStyle Libre®; Abbott Diabetes Care, Witney, Oxon, UK) is factory-calibrated and provided a longer sensor lifetime of 14 days, which has further relieved the pain from frequent strip capillary glucose calibrations in other CGMs and thus is relatively more acceptable and easier for widespread use. To date, most relevant published articles were researches regarding the accuracy of FGM(12-14) and reviews discussing its clinical effectiveness, cost-effectiveness, and safety (15-17), while there were only a small number of randomized clinical trials (RCTs) available to prove its benefits in patients with T1DM(18-20). Although data from these trials are encouraging, it remains unclear whether the FGM is effective in

adult patients with T1DM who had suboptimal glycemic control. Therefore, we designed this 24-week comparative trial, aiming to evaluate the effect of FGM in adult patients with T1DM who have sub-optimal glycemic control. The research protocol of the RCT study is presented below.

METHODS AND ANALYSIS

Study design

This trial is an open-label, multi-center, randomized, and parallel-group study conducted at 8 centers in 7 cities (Guangzhou, Hefei, Foshan, Zhongshan, Shanghai, Wuhan, and Shenzhen) in China. Eligible participants will be recruited and the efficacy of FGM and SMBG in adult patients with T1DM who have suboptimal glycemic control will be compared. Written informed consent will be obtained from all participants before study-related activities. This trial has been approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University and conformed to the Declaration of Helsinki. The register number is NCT03522870 (ClinicalTrials.gov).

Study procedure

The flowchart of this study is presented in Figure 1. After a run-in period of 2 weeks, eligible participants will be randomized 1:1 to either use of FGM or SMBG consequently for 24 weeks. At baseline (0-2 weeks), 12-14 weeks, and 24-26 weeks, retrospective CGMs (Ipro2®) will be additionally used in both groups. Demographic and biological data, questionnaires, and advent events will be also collected and assessed at baseline, week 14, and week 26.

Participant Recruitment (before 0 week)

The recruitment has begun in May 2018 and will end in December 2020. Major eligibility criteria include age ≥ 18 years old, HbA1c between 7 and 10%, and duration of T1DM at least 1 year. The diagnostic criteria of T1DM are based on the definition of T1DM by the American Diabetes Association and the World Health Organization (WHO) (21, 22). Other inclusion criteria and exclusion criteria are shown in Table 1.

Run-in period (Baseline, week 0-2)

In this period, demographics, medical histories, smoking or drinking status, exercise and the results of physical examination (Body mass index [BMI], the waist-hip ratio [WHR], blood pressure and heart rate) will be collected by certified physicians and nurses in accordance with standardized protocols. Urine samples will be collected for the measurements of albumin-to-creatine ratio (ACR) and female participants will have extra urine pregnancy tests in the participant centers. Fasting blood samples are collected for biological metrics measurements. Biological metrics including HbA1c, blood routine, lipid profiles, liver enzymes, thyroid function and antibodies, C-peptide, and diabetes antibodies will be tested centrally in the laboratory of the Third Affiliated Hospital of Sun Yat-sen University. In addition, questionnaires including the Chinese version of Diabetes Distress Scale (DDS) (23) , Hypoglycemia

Fear Scale (HFS)(24) and European Quality of Life (EQ-5D-5L) (25) will be completed by participants.

Then, all participants will wear the retrospective CGM (Ipro2®, Medtronic, USA) on the back of the upper arms continuously for 2 weeks. Blood glucose meters and compatible test strips (Bayer®; Bayer Consumer Care AG) will be distributed to all participants for capillary blood glucose tests during the whole study period and instructions about device use will be provided simultaneously. The detailed introduction of the questionnaires, the Ipro2® and the blood glucose meters will be presented in the **SUPPLEMENT.1**. During two weeks, capillary blood glucose tests (at least four times per day), diet diary, exercise will be required to record for calibration. Sensor glucose measurements will not be visible to the patients and the investigators until the data is downloaded via the Carelink Ipro Software® after 2 weeks and then calculated by the Glyculator 2.0 software which follows the guidelines on CGM reporting specified in the International Consensus on use of CGM(26). Participants in both groups will be instructed on the general diabetic education with standard algorithms including self-management suggestions for hypoglycemia/hyperglycemia and suggestions for insulin titration. (see **SUPPLEMENT.2**).

Randomization

After the 2-week run-in period, eligible participants will be randomized 1:1 to either daily SMBG alone or FGM. The random sequence will be generated by SPSS 20.0 (Software, Inc, Chicago, IL) and arranged into the sealed, opaque envelopes by investigators. To reduce the selection bias, there will be an independent researcher in charge of the envelope distribution only. When there is an eligible participant, the responsible investigator is required to inform the independent researcher. Then the sealed envelopes will be randomly distributed to the corresponding center, where envelopes will be opened sequentially to determine the participants' assignments.

Study intervention

After randomization, participants in the FGM group will be provided with FGM (FreeStyle Libre®; Abbott Diabetes Care, Witney, Oxon, UK) and measure glucose concentrations at home for the following 24 weeks. Detailed introduction of FGM system will be presented in the **SUPPLEMENT.1**. Instructions about device use will be provided according to the manufacture's user manual and access to the device software (FreeStyle Libre Software 1.0®; Abbott Diabetes Care, Witney, Oxon, UK) will be given. Participants will be required to report the adverse events especially those relevant to the device such as the skin problems and the sensor early removal. An additional fingerstick test will be recommended for their decision making when sensor data is below 3.9mmol/l or over 13.9mmol/l but the times of the fingerstick tests are non-restricted. The first sensor will be applied by trained staffs and the rest will be applied without supervision every 2 weeks. The participants assigned to the SMBG group will be required to perform capillary glucose tests for at least four times per day during the following 6 months and record their daily glucose data. The additional fingerstick tests will be recommended when hypoglycemia and

hyperglycemia related symptoms occur in both groups.

Follow-up visits (week 12-14 and week 24-26)

Follow-up visits for both groups will be scheduled from week 12 to 14 and from week 24 to 26, during which professional CGM will be additionally used in both groups to collect CGM data for 2 weeks. During 2-week follow-up, for both groups, data on fingerstick tests (at least 4 times per day), diet, exercises, and insulin adjustment during this period will be required to record for calibration but no extra education or suggestions on diabetic management will be provided by investigators until the end of 2-week data collection. At the end of the week 14 and week 26, glucose data collected from the Ipro2® during two weeks will be downloaded via the software and the sufficiency of sensor data during 2 weeks will also be assessed, ensuring at least 70% of data is available. Then, general diabetes education and insulin adjustment advice will be provided in both groups according to the standard algorithms and the ambulatory glucose profiles derived from the previous 2-week retrospective CGMs wearing. Demographics and physical information, questionnaires, and the biomedical samples will be collected at the same time.

For the FGM group, glucose data stored in the FGM recorders from week 2 to week 14 and from week 14 to week 26 will be downloaded respectively by research stuff via its corresponding software. And for the SMBG group, fingerstick glucose data stored in the blood glucose meters from week 2 to week 14 and week 14 to week 26 will be also collected respectively.

Endpoints

The primary endpoint is the change in HbA1c levels from baseline to week 26. The major secondary endpoints include the change in time spent in range (TIR 3.9 to 10.0mmol/l), time spent in the target (TIT, 3.9 to 7.8mmol/l), time below range (TBR[<3.9mmol/l]; TBR[<3.0mmol/l]) and time above range (TAR [>10.0mmol/l]; TAR[13.9mmol/l]) from baseline to week 26, standard deviation(SD), coefficient of variation(CV), mean amplitude of glucose excursions(MAGE), high or low blood glucose index (HBGI, LBGI), mean of daily differences(MODD), percentage of HbA1c in the target(<7%), frequency in using FGM, total daily insulin dose and the differences in scores of respective questionnaires. All predefined endpoints and the timing of all assessments are shown in **Table 2**.

Risks and adverse events (AEs)

Once included, responsible investigators will trace if any device or study-related risks and AEs have occurred. Disease-related events that are chronic in nature and occur as part of the progression of the diabetes disease state (i.e. diagnosis of retinopathy, nephropathy, neuropathy) will not be captured as AEs in this study.

As reported in the recent system reviews (27), the most common sensor wear-related cutaneous complication was erythema (55%), followed by itching/pruritus (11%), induration (9%), edema (6.9%), rash (6.4%), bruising (5.7%) and allergic reaction

(4.3%). The frequency of skin infection, dry skin, cellulitis, and the collection was seldom reported with a percentage only from 0.2 to 0.7%. The insertion of the sensor could also lead to cutaneous complications such as pain (61.7%), bleeding (37.6%), and hematoma (0.7%). However, the incidence rate of these events is low with one event reported per eight weeks of sensor wear-time and the reported complication severity is also low with 78.6% rated as mild and only 1.5% rated as severe. Once these events occur, participants will be encouraged to consult for the responsible investigator. If there are no symptoms of infection or inflammations such as redness, swelling and aggravated pain, removal of the sensor is not recommended. After removal of the sensor, irritation might occur due to the medical adhesive, the bandages that may be placed over the device and the healing process, which is normal. This reaction is self-limiting and should resolve within hours.

Confirmed diabetes ketoacidosis, hyperosmolar hyperglycemic state, and severe hypoglycemic events will be captured as serious adverse events (SAEs). According to the guidelines from the American Diabetes Association(6), the definition of severe hypoglycemia is the hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery. All study or device-related AEs will be monitored until adequately resolved or stable.

Laboratory Analyses and Data management

The HbA1c concentration is centrally measured by an automated analyzer (Bio-Rad D10; Bio-Rad Laboratories, Hercules, CA) using the high-performance liquid chromatography (HPLC) technique, with a reference range 4.3–6.1% and intra-batch and inter-batch coefficients of variation 0.46% and 0.99%, respectively. Lipid profiles, liver enzymes, and renal function are determined by the enzymatic colorimetric test with Hitachi 7600 autoanalyzer. The thyroid function and its antibodies are assessed by the chemiluminescence (CLIA) method using the ADVIA Centaur system (Siemens, Massachusetts, USA).

Fasting C-peptide is measured by an iodine (^{125}I) human C-peptide radioimmunoassay kit (Beijing North Institute of Biological Technology, Beijing, China; Intra-batch and inter-batch coefficients of variation 0.46 and 0.99% respectively). Autoantibodies against the 65 kDa isoform of Glutamic acid-decarboxylase antibody (GADA), Insulinoma-associated protein-2 antibody (IA-2A) and Zinc transporter 8autoantibody (ZnT8A) were analyzed centrally using fasting serum with radio binding assay confirmed by the Islet Autoantibody Standardization Program (assay sensitivity and specificity for GADA were 64 and 98% respectively, 64 and 100% for IA-2A respectively, 36 and 98% for ZnT8A respectively) at the First Affiliated Hospital of Nanjing University. Patients with positive results for at least 1 antibody titer tested (GADA titer $\geqq$ 0.042 was seen as positive; ZnT8A titer $\geqq$ 0.054 was seen as positive; IA-2A titer $\geqq$ 0.018 was seen as positive) were considered positive for diabetes autoantibodies.

The coordinator center is located in the Third Affiliated Hospital of Sun Yat-sen

University, Guangzhou, China. Data in this trial including the demographics and non-centrally tested biological data will be collected by the case report forms (CRFs) by responsible participated investigators and sent to the coordinator center periodically. To maintain the accessibility of the database, facilities will be conducted as follows: 1. All participated investigators will be trained before study commencement. Standardized procedures will be illustrated in detail; 2. The responsible associate investigators will monitor the data collection process and evaluate the data integrity periodically during the course of the data collection phase; 3. A secondary review of the accuracy of data recorded from all participated hospitals will be conducted by coauthors and the principal investigator will manage data flow and perform audits of the procedure of the study.

Sample size

According to the results of the previous randomized clinical trials about CGM (8, 10, 28), assuming a drop rate of 10%, a sample size of 76 participants would be required for providing 80% power to detect a group difference in mean changes of HbA1c of 0.4% (standard deviation of 0.8), using a two-sided test at the 0.05 level.

Statistical analysis

All analyses will be conducted on the intent-to-treat (ITT) population. Data from all randomized patients with or without protocol violation including dropouts and withdrawals will be included in the analysis.

The calculation of the CGM metrics in the whole time, the night period (12:00A.M.-06:00A.M.) and the daytime period (06:00A.M.-12:00A.M.) is via the Glyculator 2.0 software. It is anticipated that subjects with T1DM who are sub-optimally controlled will show an improvement in HbA1c level with the use of FGM in the intervention group after 24 weeks, over and above any improvement in subjects using SMBG in the control group. The magnitude of the change will be compared between two groups, using an analysis of covariance (ANCOVA) model adjusting for baseline HbA1c. The secondary efficacy analysis will also be compared between two groups, repeated the analysis of the ANCOVA model adjusted for the respective baseline value. A 95% confidence interval will be given for the difference between the groups based on the ANCOVA model.

Information including demographics and physical measurements will be summarized. The calculation of the questionnaires will be presented in the below section. Continuous variables will be presented with mean ± SD or median(25^{th} and 75^{th} quartile range). Categorical variables will be presented with the proportion of subjects in each category. If values are highly skewed, transformation or nonparametric analyses will be used. Chi-squared tests or Fisher's exact test will be used to analyze the categorical data. The safety analysis will include all available data from all recruited patients. Any device-related AEs will be tabulated and reported. All null hypotheses will be tested against a two-sided alternative at the 5% significance level.

DISCUSSIONS

The utilization of CGM is increasing rapidly around the world. The benefits of the real-time CGM among adults, adolescents and elders with T1DM have been demonstrated previously(28-31). As a new category of CGM, the FGM remains interstitial data recorded every 15 minutes and functions specially with no needs of SMBG calibrations, extended sensor spans, and near real-time glucose value by scanning on demands. Several observational studies had demonstrated significant improvements in HbA1c with a change of -0.55% after 2-4 months use(32). In the multicenter randomized controlled study conducted on the well-controlled patients with T1DM, significant reductions in hypoglycemia after the use of FGM had been observed even though there was no improvement in HbA1c(18). However, to date, there is still no evidence from randomized clinical trials conducted in T1DM patients with suboptimal control. And different with the other CGM, there is no hypoglycemia alert function in FGM, which was thought to be less effective than real-time CGM system(19). Whether these patients who made up a large proportion of T1DM patients would derive similar benefits from FGM or have similar compliance on FGM use is required to be discussed.

This trial will be conducted at 8 centers that have abundant experience in the treatment and management of T1DM. The trial will provide a 24-week consistent use of FGM in the intervention group, and collect the HbA1c value and 2-weeks CGM-related glycemic metrics termly to compare their changes from baseline between FGM and SMBG. The result might provide a more comprehensive evaluation on clinical utility and reliability of the FGM in adults with T1DM under suboptimal glycemic control.

There are some limitations of this trial. Firstly, questionnaires evaluating the satisfaction with the devices are not used in this trial because there are no reliable Chinese versions of the scales until study commencement. Secondly, the period assessed in this trial is only for 6 months and the sustained effect of the FGM among patients with suboptimal glycemic control assessed in the RCTs is required in the future.

PATIENT AND PUBLIC INVOLVEMENT

No patients were involved in the development of the research question or design of the study.

ETHICS AND DISSEMINATION

This trial will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the 1983 amendment per FDA's Guidance for Industry. It was also approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. Subjects will be provided the opportunity to review the informed consent before coming to the clinical site. The

consenting process will be documented in the subject's source document.

FUNDING STATEMENT

This study was supported by the National Key Research and Development Program of China (2017YFC1309600, to JP Weng). All sensors will be purchased by this grant. The Bayer Company, Medtronic Company, and the Abbott Diabetes Care are not involved in carrying out the trial, data analysis, data management, and publication.

CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. JPW and JHY designed and organized the study. YWZ and HRD registered the trial and co-wrote the first draft of the manuscript. JPW, JHY, and HXL undertook a critical revision of the manuscript. YWZ, HRD, and HXL are responsible for the recruitment and implementation of the protocol. DZY, WX, and BY contributed to the data interpretation. JPW and JHY had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS

There are no competing interests for any author.

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Table 1. Inclusive and exclusive criteria

Inclusive criteria
1. Aged 18 years and older;
2. Diagnosed with T1DM with the criteria established by WHO in 1999, and with duration more than 1 year;
3. Glycosylated Hemoglobin A1c concentration between 7% and 10%;
4. SMBG daily (≥3 times per day) at least 2 months previous and have willing to insist for at least 6 months;
5. Stable insulin regimen medication including CSII and MDI for 3 months prior to study entry (change of insulin ≤20%), not including premix insulin;
6. Have the willing to wear CGM;
7. Able to speak, read and write Chinese.
Exclusive criteria
1. Having used any CGM 3 months prior to study entry;
2. Receiving oral steroid therapy for any disorders and continuous use of paracetamol;
3. Had known allergy to medical-grade adhesives or CGM and its affiliated components;
4. Being pregnant or planning pregnancy (as demonstrated by a positive test at study entry);
5. Recent severe diseases like myocardial infarction, stroke, psychiatric diseases(historical/recent), malignant tumor, kidney disease (defined as estimated glomerular filtration rate<45 ml/min/1.73m^2), dermatosis, decided by investigator
6. Currently participating in another research (must have completed any study at least 30 days prior to being enrolled in this study);
7. Currently abusing illicit drugs, alcohol, or prescription drugs;
8. Any condition that could impact reliability of HbA1c measurement, such as hemoglobinopathy, hemolytic anemia, chronic liver disease, decided by investigator.

Abbreviations: T1DM: type 1 diabetes mellitus; WHO, world health organization; SMBG: self-monitoring for blood glucose CSII: continuous subcutaneous insulin infusion; MDI: multiple daily injections; CGM: continuous glucose monitoring.

Table 2. Endpoints

Primary endpoints	
HbA1c (%)	Difference in HbA1c at week 26 adjusted for baseline
Secondary endpoints	
• **CGM metrics*** (whole, night [12:00A.M.-06:00A.M.], daytime [06:00A.M.-12:00A.M.])	The difference in CGM profiles listed below collected via Ipro2 in week 12-14 and week 24-26 adjusted for baseline (week 0 to week 2)
TIR (%)	Range3.9-10.0mmol/l (70-180 mg/dl)
TIT (%)	Range 3.9-7.8mmol/l (70-140mg/dl)
TBR (%)	<3.9mmol/l (70 mg/dl); <3.0mmo/l (54 mg/dl)
TAR (%)	>10mmol/l (180mg/dl); >13.9mmol/l (250mg/dl)
Mean blood glucose(mmol/l)	
Estimated A1c (%)	
SD	
CV	
MAGE	
HBGI	
LBGI	
MODD	
Number of hypoglycemia events	
• **Percentage of HbA1c value in Target (%)**	The difference in the percentage of HbA1 in range (<7%) tested at week14 and week 26 adjusted for baseline.
• **Frequency in using FGM (times/d) †**	Time frame: 24 weeks (from week 2 to week 26)
• **Frequency in using SMBG (times/d)**	Time frame: 24 weeks (from week 2 to week 26)
• **Total of daily insulin dose (IU/kg/d)**	The difference in insulin dose collected at week 14 and week 26 adjusted for baseline
• **Questionnaires**	The difference in scores of respective questionnaires collected at week 14 and week 26 adjusted for baseline
DDS	
HFS	

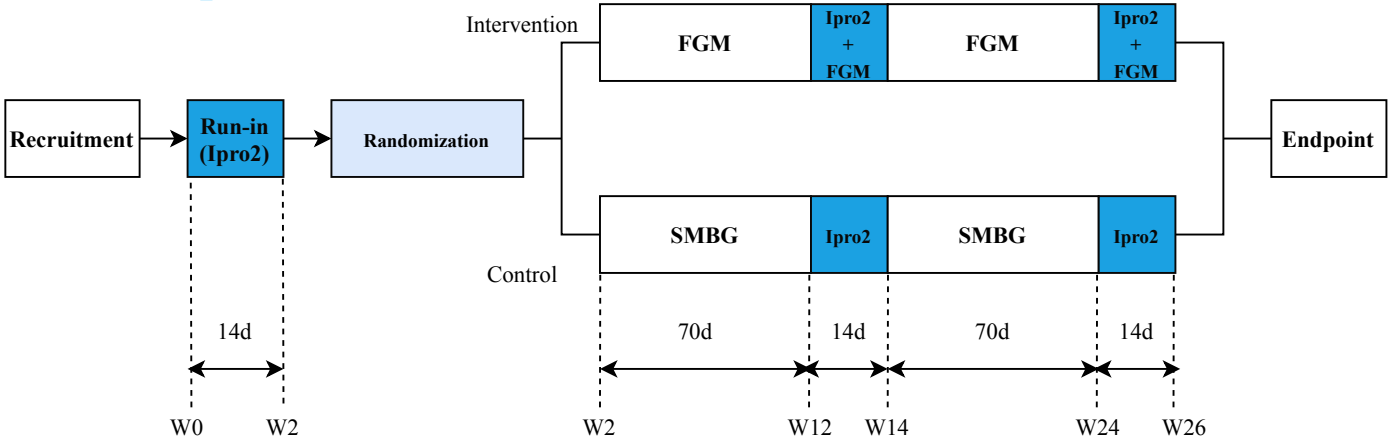
EQ-5D-5L

*CGM metrics analyzed here are calculated with the sensor data from Ipro2.

†The frequency in using FGM is calculated with the recordings derived from the FGM system.

Abbreviations: CGM: continuous glucose monitoring; TIR: Time spent in Range; TIT: Time spent in Target; TBR: Time below range; TAR: Time above range; SD: standard deviation; CV: coefficient of variation; MAGE: mean amplitude of glucose excursion; HBGI: high blood glucose index; LBGI: low blood glucose index; MODD: mean of daily differences; CONGA: continuous overlapping net glycemic action; AUC: area under the curve; GRADE: glycemic risk assessment in diabetes equation; FGM: flash glucose monitoring; SMBG: self-monitoring for blood glucose; DDS: Diabetes Distress Scale; HFS: Hypoglycemia Fear Scale; EQ-5D-5L: European Quality of Life Scale.

Figure 1. Flowchart of design



SUPPLEMENT 1

Introduction of the devices used in this trial

1. Devices

In our study, two CGMs and a blood glucose meter will be applied: blood glucose meter for strip test, retrospective CGM for assistance, and FGM for interpretation. Both CGMs recorded glucose data collected in the interstitial fluid at different time intervals. Details would be described below.

1.1 Retrospective CGM system

The retrospective CGM system (Ipro2®, Medtronic, USA) consists of an inserted sensor and a recorder connected. The sensor will be implanted on the back of the patients' upper arms and data is stored in the recorder every 5minute, thus 288 glucose values will be collected per day in total [1]. The lifetime of each sensor is usually from 3 to 7 days. The mean absolute relative difference (MARD) of Ipro2 is 9.9% in adults and was the lowest in the 240-400mg/dl range (6.8% in adults) [2]. During the wearing time, the sensor data derived are not visible and only after the removal of the sensor and data download with retrospective SMBG data calibrations, the glycemic metrics and ambulatory glucose profile will be accessible to the patients and investigators. Therefore, the retrospective CGM is thought to be a perfect tool in the research with less interpretation.

1.2 FGM system

The FGM system (FreeStyle Libre®; Abbott Diabetes Care, Witney, Oxon, UK) is a novel sensor-based intermittently scanned glucose monitoring system [3]. The sensor is around 1*1 cm and implanted by a single-use applicator, and automatically measures glucose every 15 minutes for up to 14 days without finger-stick calibrations. The sensor will be implanted on the back of the upper arms which is thought to be more accurate [4]. The MARD tested in adult patients is 8.8-12.9% compared with venous glucose reference and YSI pairs (Yellow Springs, OH) [5,6]. The most frequent safety problem of FGM is erythema, as shown in the system reviews about FGM [7,8].

1.3 Blood Glucose Meter (Bayer®)

The blood Glucose Meter (Bayer®; Bayer Consumer Care AG) is a reliable home-use device to perform finger-stick strip tests and meet the predetermined accuracy standard illustrated in a recent study [9,10]. Therefore, it will be distributed into each patient as a tool to perform any finger-stick tests during the trial.

2. Questionnaires

In our study, the Chinese version of the DDS, HFS, EQ-5D-5L will be used to evaluate the change in distress from diabetes, the fear of hypoglycemia, and the quality of life

after the intervention. The excellent reliability and validity of the scales in Chinese Version had been proved [11-13].

2.1 Diabetes Distress Scale (DDS)

The Chinese version of the DDS is to evaluate diabetes-related emotional distress in patients with diabetes [12]. The scale consists of 17 items, contains four domains including emotional burden sub-scale, physician-related distress subscale, regimen-related distress subscale, and diabetes-related interpersonal distress. Each item is rated on a 6-point Likert scale from 1(no problem) to 6(serious problem). An average score ≥3 is the cut-off point which is considered to more than the moderate problem.

2.2 Hypoglycemia Fear Scale (HFS)

The Chinses version of the HFS is to evaluate psychological status for diabetic patients [13]. These validated surveys consist of 18 questions that measure dimensions of anxiety and fear surrounding hypoglycemia. Each item is rated on a 5-point Likert scale from 0(never related) to 4(very related). Patients with higher scores are considered with more anxieties and fear of hypoglycemia.

2.3 European Quality of Life (EQ-5D-5L) Scale

The Chinese version of the EQ-5D-5L is widely used to evaluate the quality of life in Chinese [11]. The EQ-5D-5L is converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. It contains the health description system and Visual Analogue Score (VAS). The health description system includes 5 dimensions including mobility, self-care, usual activities, pain or discomfort, and anxiety/depression. Each item is rated on 5 levels from 1(no problem) to 5(extreme problem). And the VAS is to evaluate the health condition assessed by patients. The top score (100) means the best health conditions and the bottom one (0) means the worst.

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Supplement-2

Effects of Novel Flash Glucose Monitoring System on Glycemic Control in Adult Patients with Type 1 Diabetes Mellitus: Protocol of a Multicenter Randomized Controlled Trial

General Diabetic Education

Version 1.0

Recommendations are based on the guideline by American Diabetes Association and the Chinese Diabetes Society.

1. **Goal of glycemic control**

For Adult patients:

- HbA1c<7%;
- Fasting/pre-prandial blood glucose: 4.4-7.2mmol/l;
- Postprandial blood glucose level: 5-10.0mmol/l;
- Blood glucose level during night/before sleep: 6.7-10.0mmol/L.

2. **General calculation of insulin sensitivity factor (ISF):** describes how much one unit of rapid or regular insulin will lower blood glucose. It is used to determine the amount of insulin to give to correct blood glucose readings that are above target

- **1800 Rule(Rapid-acting insulin analogs lispro):**

  ISF=1800/ (total daily use *18)

- **1500 Rule (Regular short-acting insulin):**

  ISF=1800/ (total daily use *18)

3. **General insulin: carbohydrate ratio:** estimation gram of carbohydrates per 1 U of insulin covering

- 500 Rule: Insulin: carbohydrate ratio=500/total daily dose

4. **Recommendations when facing hypoglycemia**

(1) **Definition**

Level	**Criteria**	**Description**
Hypoglycemia alert value (level 1)	≤3.9mmol/L	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level2)	<3.0mmol/L	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

(2) **Symptoms**: Shakiness, irritability, confusion, tachycardia, and hunger (not

limited).

(3) **Solutions:**

- Glucose (15–20 g) is the preferred treatment for the conscious individual with blood glucose <3.9mmol/L]) or any form of carbohydrate that contains glucose may be used.
- Fifteen minutes after treatment, if glucose trend shows continued hypoglycemia, the treatment should be repeated.
- Once glucose value returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia.
- Thinking back the possible factor contributing to hypoglycemia such as exercise, over-injection, diet and make adjustments before the similar situation next time.

Note: The glucose value mentioned here refers to the glucose derived from SMBG. For participants distributed to FGM group, we recommend you to have an additional finger-stick test for capillary glucose value if you are in hypoglycemia and make adjustment according to the capillary glucose value.

5. Recommendations when facing hyperglycemia

(1) **Definition:** Glucose value >10.0mmol/L(alert);

Glucose value>13.9mmol/L (immediate action required)

(2) **Solutions:**

- Take an extra dose of rapid acting insulin based on your personal ISF. And if glucose level is above 16.9mmol/L, ketone test is recommended.
- Be careful about “stacking” insulin. The rapid- acting insulin you take at meals may still be working 4 hours after your injection. Keep a careful watch on your glucose over the next hour or two.
- Thinking back the factor contributing to hyperglycemia. Consider what you would do differently the next time with your meal and/ or your mealtime insulin dose to avoid the high and rising glucose.
- If hyperglycemia is sustained the whole day, think about if you miss the

injection of insulin previously or if your additional bolus is not enough and make some additional adjustments. . If you use insulin pump, think about if there is any blockage of tube or noneffective insulin in your pump. And if hyperglycemia is sustained for more than 1 day and you cannot find the reason, we recommend you to consult your investigator.

Note: The glucose value mentioned here refers to the glucose derived from SMBG. For participants distributed to FGM group, we recommend you to have an additional finger-stick test for capillary glucose value if your glucose is higher than 13.9mmol/L and make adjustment according to the capillary glucose value.

APPENDIX.1--The Chinese version of the general diabetes education

自我血糖监测及管理手册

一．血糖控制目标：

	HbA1c（%）	空腹/餐前血糖（mmo/l）	睡前/夜间血糖（mmo/l）	餐后血糖
成人	<7.0	4.4-7.2	6.7-10	5-10.0
儿童和青少年	<7.5	5.0-7.2	5.0-8.3	5-10.0

在不增加低血糖发生的前提下，尽可能做到血糖达标。

参考文献：中国 1 型糖尿病诊治指南（2015 年版），2017 年美国 ADA 指南。

二．指尖血糖监测

☺每天至少4 次或以上指尖血糖监测（三餐前，睡前，餐后，必要时凌晨夜间加测一次）；

☺生病、剧烈运动前或有急性感染等情况时加测；

☺没有症状≠控制良好≠不用监测。

三．动态血糖监测

☺至少每 8 小时扫描获取数据（≧3 次/天），扫描次数无限制，可以随时扫描；

☺当你发现扫描的血糖值＜3.9mmol/l或＞13.9mmol/l时，加测 1 次指尖血糖，以指尖血糖值为准，进行低血糖或高血糖的处理；

☺探头仅能用 14 天，14 天后需更换；

☺做 X 光检查、CT（计算机断层成像）、MRI 核磁共振检查时需移除；

☺动态血糖监测期间请详细记录饮食、运动、治疗等生活事件。

自我血糖监测及管理手册

四．低血糖处理

★怎么知道自己低血糖？

1. 看血糖值*：

㊣轻-中度低血糖 ＜3.9mmol/l；

㊣㊣严重低血糖 ＜3.0mmol/l；

瞬感使用者提示“低葡萄糖”或“↘”（葡萄糖正在下降）、“🡻”（葡萄糖正在迅速下降）时应及时预防低血糖。

*瞬感使用者若监测到血糖值低，建议测量指尖血糖，并以指尖血糖值为准。

2. 低血糖症状：心跳加快、饥饿、发抖、出虚汗、头晕犯困、焦虑不安、四肢无力、抽搐、视觉模糊、头疼。

★发生低血糖时你该怎么办？

❶吃 15-20g 碳水化合物类食物（如葡萄糖 4 片、半杯果汁、一汤勺蜂蜜等吸收快作用快的食物），血糖值＜2.8mmol/l 时适量再增加 15-20g 食物；

❷15 分钟后测量指尖血糖，若症状未改善重复上述步骤，若仍未改善或出现神志不清、突发昏迷者送院就诊；

❸血糖恢复后，瞬感使用者若提示“↘”（葡萄糖正在下降）、“🡻”（葡萄糖正在迅速下降）时，可适当增加进食以预防下一次低血糖发生，在接下来的 30-60 分钟内密切关注血糖的变化，适当增加扫描次数（15 分钟/间隔），必要时予指尖血糖测准。指尖血糖组则适当加测血糖值以进一步了解血糖是否稳定。

❹血糖恢复后，回顾发生低血糖原因，若是在饮食、运动情况不变的情况下发生血糖偏低，考虑胰岛素注射过多所致。结合患者达标目标，及时调整胰岛素用量。（具体方案见 5-6 页）

五．血糖偏高时怎么办？

㊣血糖值＞13.9mmol/l；

瞬感使用者若发现血糖值高，测指尖血糖，并以指尖血糖值为准。

处理方法：

❶**目标血糖<血糖<13.9mmol/l**：根据胰岛素敏感系数（见后），计算需要追加多少单位胰岛素，结合自己的经验、目前情况（餐后、睡前、运动等）等，追加合适的补充大剂量，1 小时后再次复测血糖。

❷**血糖>13.9mmol/l**：检测血酮，若是阴性：同以上处理。酮体阳性：多饮水，补充大剂量纠正高血糖，每 1 小时检测血糖，严重时医院就诊处理。

❸当血糖恢复稳定 30-60 分钟内，密切留意血糖变化瞬感使用者若提示“🡹”葡萄糖正在迅速升高）、“↗”（葡萄糖正在缓慢升高），结合你的胰岛素敏感系数追加剂量。（详细计算方法见 4-6 页）。

六．追加大剂量怎么算？

掌握两个定义！

★胰岛素敏感系数：1 单位胰岛素能降低的血糖值

公式（或参考表格）：

速效：敏感系数(X)=1800/（每日总量×18)=100/每日胰岛素总量

短效：敏感系数(X)=1500/（每日总量×18)

每日胰岛素用量	1800 法则 速效	1500 法则 短效
20	5	4.2
25	4	3.3
30	3.3	2.8
35	2.9	2.4
40	2.5	2.1
50	2.0	1.7
60	1.7	1.4
75	1.3	1.1
100	1.0	0.8

★碳水化合物系数：1 单位胰岛素能平衡的食物中碳水化合物克数。公式（或参考表格）：

速效：500÷每日胰岛素总量=___g/u

短效：450÷每日胰岛素总量=___g/u

每日胰岛素用量	500 法则 速效	450 法则 短效
20	25	23
25	20	18
30	17	15
35	14	13
40	13	11
50	10	9
60	8	8

SPIRIT CHECKLISTS

This checklist is according to the recommendations presented in the https://www.spirit-statement.org/title/

SECTION/TOPIC	ADHERE TO RECOMMEDATIONS
ADMINISTRATIVE INFORMATION	
1: TITLE	**√ P1**
2: TRIAL REGISTRATION	
2A: REGISTRY	**√ P4**
2B: DATA SET	**√P7**
3: PROTOCOL VERSION	**√P1**
4: FUNDING	**√P9**
5: ROLES AND RESPONSIBILITIES	**√P10**
INTRODUCTION	
6: BACKGROUND AND RATIONALE	**√P3**
7: OBJECTIVES	**√P3**
8: TRIAL DESIGN	**√P4**
METHODS: PARTICIPANTS, INTERVENTIONS, OUTCOMES	
9: STUDY SETTING	**√P4**
10: ELIGIBILITY CRITERIA	**√P4;P13**
11: INTERVENTIONS	**√P4-6**
12: OUTCOMES	**√P4-6**
13: PARTICIPANT TIMELINE	**√P4-P6**
14: SAMPLE SIZE	**√P8**
15: RECRUITMENT	**√P4**
METHODS: ASSIGNMENT OF INTERVENTIONS (FOR	

CONTROLLED TRIALS)	
16: ALLOCATION	**√P4**
17: BLINDING (MASKING)	Na
METHODS: DATA COLLECTION, MANAGEMENT, ANALYSIS	**√P7-8**
18:DATA COLLECTION METHODS	**√P4-6**
19:DATA MANAGEMENT	**√P7**
20:STATISTICAL METHODS	**√P8**
METHODS: MONITORING	
21: DATA MONITORING	**√P7**
22: HARMS	**√P6-7**
23: AUDITING	**√P7**
ETHICS AND DISSEMINATION	
24: RESEARCH ETHICS APPROVAL	**√P4**
25: PROTOCOL AMENDMENTS	NA
26: CONSENT OR ASSENT	**√P4;P9**
27: CONFIDENTIALITY	**√P9**
28: DECLARATION OF INTERESTS	**√P9**
29: ACCESS TO DATA	**√P9**
30: ANCILLARY AND POST-TRIAL CARE	NA
31: DISSEMINATION POLICY	**√P9**
APPENDICES	
32: INFORMED CONSENT MATERIALS	**√P8**
33: BIOLOGICAL SPECIMENS	**√P7**

BMJ Open

Effects of Novel Flash Glucose Monitoring System on Glycemic Control in Adult Patients with Type 1 Diabetes Mellitus: Protocol of a Multicenter Randomized Controlled Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039400.R2
Article Type:	Protocol
Date Submitted by the Author:	16-Oct-2020
Complete List of Authors:	ZHOU, YONGWEN; The First Affiliated Hospital of USTC, Department of Endocrinology and Metabolism; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Deng, Hongrong; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Liu, Hongxia; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Yang, Daizhi; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Xu, Wen; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Yao, Bin; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Yan, Jinhua; Third Affiliated Hospital of Sun Yat-Sen University, Department of Endocrinology and Metabolism;Guangdong Provincial Key Laboratory of Diabetology Weng, Jianping; The First Affiliated Hospital of USTC, Department of Endocrinology and Metabolism
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Clinical trials < THERAPEUTICS

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Effects of Novel Flash Glucose Monitoring System on Glycemic Control in Adult Patients with Type 1 Diabetes Mellitus: Protocol of a Multicenter Randomized Controlled Trial

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Words: 3946

ABSTRACT

Introduction

Optimal glycemic control is beneficial to prevent and delay microvascular complications in patients with type 1 diabetes mellitus (T1DM). The benefits of flash glucose monitoring (FGM) have been proved among well-controlled adults with T1DM, but evidence for FGM in adults with T1DM who have suboptimal glycemic control is limited. This study aims to evaluate the effect of FGM in adult patients with T1DM who have suboptimal glycemic control.

Methods and analysis

This open-label, multicenter, randomized trial will be conducted at eight tertiary hospitals and recruit 104 adult participants (≥18 years old) with T1DM diagnosed for at least one year and with suboptimal glycemic control (glycated hemoglobin [HbA1c] ranged from 7.0 to 10.0%). After a run-in period (baseline, 0-2 weeks), eligible participants will be randomized 1:1 to either use of FGM or self-monitoring

blood glucose (SMBG) alone consequently for 24 weeks. At baseline, 12-14 weeks, and 24-26 weeks, retrospective continuous glucose monitoring (CGM) systems will be used in both groups for device-related data collection. Biological metrics, including HbA1c, blood routine, lipid profiles, liver enzymes, questionnaires, and adverse events, will be assessed at baseline, week 14, and 26. All analyses will be conducted on the intent-to-treat population. Efficacy endpoints analyses will also be repeated on the per-protocol population. The primary outcome is the change of HbA1c from baseline to week 26. The secondary outcomes include the change of CGM metrics, including time spent in range, time spent in target, time below range, time spent above range, standard deviation, coefficient of variation, mean amplitude of glucose excursions, high or low blood glucose index, mean of daily differences, percentage of HbA1c in target(<7%), frequency in using FGM, total daily insulin dose and the differences in scores of questionnaires including diabetes distress scale, hypoglycemia fear scale and European quality of life scale.

Ethics and dissemination

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University in January 2017. Ethical approval has been obtained at all centers. All participants will be provided with oral and written information about the trial. The study will be disseminated by peer-review publications and conference presentations.

Trial register number: NCT03522870 (ClinicalTrials.gov);

Overall status: Recruiting

Study Start: May 1, 2018

Primary Completion: December 30, 2021

Strengths and limitations of this study

- This study adopts a multicenter open-label, randomized, and parallel design.
- This study aims to evaluate the flash glucose monitoring system among adult patients with T1DM who have sub-optimally glycemic control with the comparison with self-monitoring blood glucose.
- The retrospective CGM system will provide detailed comparative data on efficacy and safety between the two study arms.
- There is a head-to-head comparison on the sensor-related metrics as patients randomized to use the flash glucose monitoring systems will wear the retrospective CGM systems additionally and simultaneously in the 14 days preceding the 3-month and 6-month visiting.
- The limitation of this study is that the questionnaires evaluating the satisfaction with the device are not used in this trial.

INTRODUCTION

The Diabetes Control and Complications Trial (DCCT) had demonstrated that intensive glycemic control contributed to delay and prevent the development and progression of microvascular complications (1). However, even with much advancement of diabetes management in these years such as the improvement of insulin analogs and insulin infusion pumps, it is still difficult for adult patients with type 1 diabetes mellitus (T1DM) to achieve the recommended goals of HbA1c level (<7%) and the target-achieving rate was only approximately 15-30% (2-6). As glucose monitoring is one of the key parts of diabetes management and previous studies had demonstrated a strong association between glucose monitoring and glycemic control in patients with T1DM (5, 7), the optimization of glucose monitoring is necessary.

The conventional glycemic monitoring methods include the daily self-monitoring blood glucose (SMBG) by fingerstick tests and HbA1c tests. The SMBG is the most widely used glucose testing method and generally enjoys good accuracy whereas it only provides the single point-in-time glucose concentrations instead of overall daily profiles and the pain from fingerstick might lead to decrease of the participants' adherence. And the HbA1c, the golden standard of glycemic monitoring method, reflecting the average glucose concentration for approximately 3 months, is also not direct and convenient enough for not proving a measure of glycemic variability or an alert function of real-time the hypoglycemia moments(6). Therefore, an alternative of the glucose monitoring method in recent years is the updated continuous glucose monitoring (CGM) technology, which provides near real-time glucose data continuously by tracking the glucose concentrations in the body's interstitial fluid and reflects the intra-/inter-day glycemic excursions. There are two basic types of CGMs. One is the retrospective CGM with blinded data available to users and clinicians, which is usually applied in the outpatient visits or clinical trials. The other one is the systems that provide unblinded data to use such as the real-time CGM systems. It has been demonstrated that glycemic control and psychological status of the adult patient with T1DM can be improved after using the real-time CGMs (8-10) and the benefits can be also sustained for 12 months when using properly(11).

For most CGMs, confirmatory SMBG is still required for calibrations. While the new generation of CGMs approved by Food and Drug Association in 2017, the flash glucose monitoring system (FGM; FreeStyle Libre®; Abbott Diabetes Care, Witney, Oxon, UK) is factory-calibrated and provided a longer sensor lifetime of 14 days, which has further relieved the pain from frequent strip capillary glucose calibrations in other CGMs and thus is relatively more acceptable and easier for widespread use. To date, most relevant published articles were researches regarding the accuracy of FGM(12-14) and reviews discussing its clinical effectiveness, cost-effectiveness, and safety (15-17), while there were only a small number of randomized clinical trials (RCTs) and protocols available to prove its benefits in patients with T1DM(18-22). Although data from these trials are encouraging, it remains unclear whether the FGM

is effective in adult patients with T1DM who had suboptimal glycemic control. Therefore, we designed this 24-week comparative trial, aiming to evaluate the effect of FGM in adult patients with T1DM who have sub-optimal glycemic control. The research protocol of the RCT study is presented below.

METHODS AND ANALYSIS

Study design

This trial is an open-label, multicenter, randomized, and parallel-group study conducted at 8 centers in 7 cities (Guangzhou, Hefei, Foshan, Zhongshan, Shanghai, Wuhan, and Shenzhen) in China. Eligible participants will be recruited and the efficacy of FGM and SMBG in adult patients with T1DM who have suboptimal glycemic control will be compared. Written informed consent will be obtained from all participants before study-related activities (see **SUPPLEMENT 1**). This trial has been approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University and conformed to the Declaration of Helsinki. The register number is NCT03522870 (ClinicalTrials.gov).

Study procedure

The flowchart of this study is presented in Figure 1. After a run-in period of 2 weeks, eligible participants will be randomized 1:1 to either use of FGM or SMBG consequently for 24 weeks. At baseline (0-2 weeks), 12-14 weeks, and 24-26 weeks, retrospective CGMs (Ipro2®) will be additionally used in both groups. Demographic and biological data, questionnaires, and advent events will be also collected and assessed at baseline, week 14, and week 26.

Participant Recruitment (before 0 week)

The recruitment has begun in May 2018 and will extend to December 2021. Major eligibility criteria include age ≥ 18 years old, HbA1c between 7 and 10%, and duration of T1DM at least 1 year. The diagnostic criteria of T1DM are based on the definition of T1DM by the American Diabetes Association and the World Health Organization (WHO) (23, 24). Other inclusion criteria and exclusion criteria are shown in Table 1.

Run-in period (Baseline, week 0-2)

In this period, demographics, medical histories, smoking or drinking status, exercise and the results of physical examination (Body mass index [BMI], the waist-hip ratio [WHR], blood pressure and heart rate) will be collected by certified physicians and nurses in accordance with standardized protocols. Urine samples will be collected for the measurements of albumin-to-creatine ratio (ACR) and female participants will have extra urine pregnancy tests in the participant centers. Fasting blood samples are collected for biological metrics measurements. Biological metrics including HbA1c, blood routine, lipid profiles, liver enzymes, thyroid function and antibodies, C-peptide, and diabetes antibodies will be tested centrally in the laboratory of the Third Affiliated Hospital of Sun Yat-sen University. In addition, questionnaires including the Chinese version of Diabetes Distress Scale (DDS) (25) , Hypoglycemia

Fear Scale (HFS)(26) and European Quality of Life (EQ-5D-5L) (27) will be completed by participants.

Then, all participants will wear the retrospective CGM (Ipro2®, Medtronic, USA) on the back of the upper arms continuously for 2 weeks. Blood glucose meters and compatible test strips (Bayer®; Bayer Consumer Care AG) will be distributed to all participants for capillary blood glucose tests during the whole study period and instructions about device use will be provided simultaneously. The detailed introduction of the questionnaires, the Ipro2® and the blood glucose meters will be presented in the **SUPPLEMENT.2**. During two weeks, capillary blood glucose tests, diet diary, exercise will be required to record for calibration. Sensor glucose measurements will not be visible to the patients and the investigators until the data is downloaded via the Carelink Ipro Software® after 2 weeks and then calculated by the Glyculator 2.0 software which follows the guidelines on CGM reporting specified in the International Consensus on use of CGM(28). Participants in both groups will be instructed on the general diabetic education with standard algorithms including self-management suggestions for hypo-/hyperglycemia and suggestions for insulin titration (see **SUPPLEMENT.3**).

Randomization

After the 2-week run-in period, eligible participants will be randomized 1:1 to either daily SMBG alone or FGM. The random sequence will be generated by SPSS 20.0 (Software, Inc, Chicago, IL) and arranged into the sealed, opaque envelopes by investigators. To reduce the selection bias, there will be an independent researcher in charge of the envelope distribution only. When there is an eligible participant, the responsible investigator is required to inform the independent researcher. Then the sealed envelopes will be randomly distributed to the corresponding center, where envelopes will be opened sequentially to determine the participants' assignments.

Study intervention

After randomization, participants in the FGM group will be provided with FGM (FreeStyle Libre®; Abbott Diabetes Care, Witney, Oxon, UK) and measure glucose concentrations at home for the following 24 weeks. Detailed introduction of FGM system will be presented in the **SUPPLEMENT.2**. Instructions about device use will be provided according to the manufacture's user manual and access to the device software (FreeStyle Libre Software 1.0®; Abbott Diabetes Care, Witney, Oxon, UK) will be given. Participants will be required to report the adverse events especially those relevant to the device such as the skin problems and the sensor early removal. An additional fingerstick test will be recommended for their decision making when sensor data is below 3.9mmol/l or over 13.9mmol/l but the times of the fingerstick tests are non-restricted. The first sensor will be applied by trained staffs and the rest will be applied by patients themselves every 2 weeks. The participants assigned to the SMBG group will be required to perform capillary glucose tests for at least three times per day during the following 6 months and record their daily glucose data. The additional fingerstick tests will be recommended when hypoglycemia and hyperglycemia related symptoms occur in both groups.

Follow-up visits (week 12-14 and week 24-26)

Follow-up visits for both groups will be scheduled from week 12 to 14 and from week 24 to 26, during which professional CGM will be additionally used in both groups to collect CGM data for 2 weeks. During 2-week follow-up, for both groups, data on fingerstick tests, diet, exercises, and insulin adjustment during this period will be required to record for calibration but no extra education or suggestions on diabetic management will be provided by investigators until the end of 2-week data collection. At the end of the week 14 and week 26, glucose data collected from the Ipro2® during two weeks will be downloaded via the software and the sufficiency of sensor data during 2 weeks will also be assessed, ensuring at least 70% of data is available. Then, general diabetes education and insulin adjustment advice will be provided in both groups according to the standard algorithms and the ambulatory glucose profiles derived from the previous 2-week retrospective CGMs wearing. Demographics and physical information, questionnaires, and the biomedical samples will be collected at the same time.

For the FGM group, glucose data stored in the FGM recorders from week 2 to week 14 and from week 14 to week 26 will be downloaded respectively by research stuff via its corresponding software. And for the SMBG group, fingerstick glucose data stored in the blood glucose meters from week 2 to week 14 and week 14 to week 26 will be also collected respectively.

Endpoints

The primary endpoint is the change in HbA1c levels from baseline to week 26. The major secondary endpoints include the change in time spent in range (TIR 3.9 to 10.0mmol/l), time spent in the target (TIT, 3.9 to 7.8mmol/l), time below range (TBR[<3.9mmol/l]; TBR[<3.0mmol/l]) and time above range (TAR [>10.0mmol/l]; TAR[>13.9mmol/l]) from baseline to week 26, standard deviation(SD), coefficient of variation(CV), mean amplitude of glucose excursions(MAGE), high or low blood glucose index (HBGI, LBGI), mean of daily differences(MODD), percentage of HbA1c in the target(<7%), frequency in using FGM, total daily insulin dose and the differences in scores of respective questionnaires. All predefined endpoints and the timing of all assessments are shown in **Table 2**.

Risks and adverse events (AEs)

Once included, responsible investigators will trace if any device or study-related risks and AEs have occurred. Disease-related events that are chronic in nature and occur as part of the progression of the diabetes disease state (i.e. diagnosis of retinopathy, nephropathy, neuropathy) will not be captured as AEs in this study.

As reported in the recent system reviews (29), the most common sensor wear-related cutaneous complication was erythema (55%), followed by itching/pruritus (11%), induration (9%), edema (6.9%), rash (6.4%), bruising (5.7%) and allergic reaction (4.3%). The frequency of skin infection, dry skin, cellulitis, and the collection was seldom reported with a percentage only from 0.2 to 0.7%. The insertion of the sensor

could also lead to cutaneous complications such as pain (61.7%), bleeding (37.6%), and hematoma (0.7%). However, the incidence rate of these events is low with one event reported per eight weeks of sensor wear-time and the reported complication severity is also low with 78.6% rated as mild and only 1.5% rated as severe. Once these events occur, participants will be encouraged to consult for the responsible investigator. If there are no symptoms of infection or inflammations such as redness, swelling and aggravated pain, removal of the sensor is not recommended. After removal of the sensor, irritation might occur due to the medical adhesive, the bandages that may be placed over the device and the healing process, which is normal. This reaction is self-limiting and should resolve within hours.

Confirmed diabetes ketoacidosis, hyperosmolar hyperglycemic state, and severe hypoglycemic events will be captured as serious adverse events (SAEs). According to the guidelines from the American Diabetes Association(6), the definition of severe hypoglycemia is the hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery. All study or device-related AEs will be monitored until adequately resolved or stable.

Laboratory Analyses and Data management

The HbA1c concentration is centrally measured by an automated analyzer (Bio-Rad D10; Bio-Rad Laboratories, Hercules, CA) using the high-performance liquid chromatography (HPLC) technique, with a reference range 4.3–6.1% and intra-batch and inter-batch coefficients of variation 0.46% and 0.99%, respectively. Lipid profiles, liver enzymes, and renal function are determined by the enzymatic colorimetric test with Hitachi 7600 autoanalyzer. The thyroid function and its antibodies are assessed by the chemiluminescence (CLIA) method using the ADVIA Centaur system (Siemens, Massachusetts, USA).

Fasting C-peptide is measured by an iodine (^{125}I) human C-peptide radioimmunoassay kit (Beijing North Institute of Biological Technology, Beijing, China; Intra-batch and inter-batch coefficients of variation 0.46 and 0.99% respectively). Autoantibodies against the 65 kDa isoform of Glutamic acid-decarboxylase antibody (GADA), Insulinoma-associated protein-2 antibody (IA-2A) and Zinc transporter 8autoantibody (ZnT8A) were analyzed centrally using fasting serum with radio binding assay confirmed by the Islet Autoantibody Standardization Program (assay sensitivity and specificity for GADA were 64 and 98% respectively, 64 and 100% for IA-2A respectively, 36 and 98% for ZnT8A respectively) at the First Affiliated Hospital of Nanjing University. Patients with positive results for at least 1 antibody titer tested (GADA titer $\geqq$ 0.042 was seen as positive; ZnT8A titer $\geqq$ 0.054 was seen as positive; IA-2A titer $\geqq$ 0.018 was seen as positive) were considered positive for diabetes autoantibodies.

The coordinator center is located in the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. Data in this trial including the demographics and non-centrally tested biological data will be collected by the case report forms (CRFs)

by responsible participated investigators and sent to the coordinator center periodically. To maintain the accessibility of the database, facilities will be conducted as follows: 1. All participated investigators will be trained before study commencement. Standardized procedures will be illustrated in detail; 2. The responsible associate investigators will monitor the data collection process and evaluate the data integrity periodically during the course of the data collection phase; 3. A secondary review of the accuracy of data recorded from all participated hospitals will be conducted by coauthors and the principal investigator will manage data flow and perform audits of the procedure of the study.

Sample size

According to the randomized clinical trials about CGM (8, 10, 30), assuming a drop rate of 10%, a sample size of 104 participants would be required for providing 80% power to detect a group difference in mean changes of HbA1c of 0.4% (standard deviation of 0.8,correlation of 0.6), using a two-sided test at the 0.05 level.

Statistical analysis

All analyses will be conducted on the intent-to-treat (ITT) population. Data from all randomized patients with or without protocol violation including dropouts and withdrawals will be included in the analysis.

It is anticipated that subjects with T1DM who are sub-optimally controlled will show an improvement in HbA1c level with the use of FGM in the intervention group after 24 weeks, over and above any improvement in subjects using SMBG in the control group. Changes in the primary and secondary outcomes will be analyzed using a linear mixed model with management, week and their interaction as covariates. Change in outcome measures within each group and difference of the changes between groups from baseline to follow-up will be calculated using linear combinations of the estimated coefficients. If there are baseline imbalances between treatment groups, we will consider adjusting for them based on whether we regard the imbalance as clinically significant. A 95% confidence interval will be given for the difference between the groups.

The calculation of the CGM metrics in the whole time, the night period (12:00A.M.-06:00A.M.) and the daytime period (06:00A.M.-12:00A.M.) is via the Glyculator2.0 software. Information including demographics and physical measurements will be summarized. The calculation of the questionnaires will be presented in the below section. Continuous variables will be presented with mean ± SD or median(25^{th} and 75^{th} quartile range). Categorical variables will be presented with the proportion of subjects in each category. If values are highly skewed, transformation or nonparametric analyses will be used. Chi-squared tests or Fisher's exact test will be used to analyze the categorical data. The safety analysis will include all available data from all recruited patients. Any device-related AEs will be tabulated and reported. All null hypotheses will be tested against a two-sided alternative at the 5% significance level.

DISCUSSIONS

The utilization of CGM is increasing rapidly around the world. The benefits of the real-time CGM among adults, adolescents and elders with T1DM have been demonstrated previously(30-33). As a new category of CGM, the FGM remains interstitial data recorded every 15 minutes and functions specially with no needs of SMBG calibrations, extended sensor spans, and near real-time glucose value by scanning on demands. Several observational studies had demonstrated significant improvements in HbA1c with a change of -0.55% after 2-4 months use(34). In the multicenter randomized controlled studies conducted either on well-controlled adult patients with T1DM or high-risk young adults (13-20 yrs), comparing with the control group, the group using FGM showed insignificant improvements in HbA1c change while only those with well-controlled had reduced time spent in hypoglycemia(18, 21). However, to date, there is still no evidence from randomized clinical trials conducted in adult patients with T1DM and suboptimal control. And different with the other CGMs, there is no hypoglycemia alert function in FGM, which was thought to be less effective than real-time CGM system(19). Whether these patients who made up a large proportion of T1DM patients would derive similar benefits from FGM or have similar compliance on FGM use is required to be discussed.

This trial will be conducted at 8 centers that have abundant experience in the treatment and management of T1DM. The trial will provide a 24-week consistent use of FGM in the intervention group, and collect the HbA1c value and 2-weeks CGM-related glycemic metrics termly to compare their changes from baseline between FGM and SMBG. The result might provide a more comprehensive evaluation on clinical utility and reliability of the FGM in adults with T1DM under suboptimal glycemic control.

There are some limitations of this trial. Firstly, questionnaires evaluating the satisfaction with the devices are not used in this trial because there are no reliable Chinese versions of the scales until study commencement. Secondly, the period assessed in this trial is only for 6 months and the sustained effect of the FGM among patients with suboptimal glycemic control assessed in the RCTs is required in the future.

PATIENT AND PUBLIC INVOLVEMENT

No patients were involved in the development of the research question or design of the study.

ETHICS AND DISSEMINATION

This trial will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the 1983 amendment per FDA's Guidance for Industry. It was also approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. Subjects will be provided the

opportunity to review the informed consent before coming to the clinical site. The consenting process will be documented in the subject's source document.

FUNDING STATEMENT

This study was supported by the National Key Research and Development Program of China (2017YFC1309600, to JP Weng). All sensors will be purchased by this grant. The Bayer Company, Medtronic Company, and the Abbott Diabetes Care are not involved in carrying out the trial, data analysis, data management, and publication.

CONTRIBUTIONS STATEMENT

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. JPW and JHY designed and organized the study. YWZ and HRD registered the trial and co-wrote the first draft of the manuscript. JPW, JHY, and HXL undertook a critical revision of the manuscript. YWZ, HRD, and HXL are responsible for the recruitment and implementation of the protocol. DZY, WX, and BY contributed to the data interpretation. JPW and JHY had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have read and approved the final manuscript.

COMPETING INTERESTS

There are no competing interests for any author.

DATA SHARING STATEMENT

The data used to support the findings of this trial are available from the corresponding author upon request.

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Table 1. Inclusive and exclusive criteria

Inclusive criteria
1. Aged 18 years and older;
2. Diagnosed with T1DM with the criteria established by WHO in 1999, and with duration more than 1 year;
3. Glycosylated Hemoglobin A1c concentration between 7% and 10%;
4. SMBG daily (≥3 times per day) at least 2 months previous and have willing to insist for at least 6 months;
5. Stable insulin regimen medication including CSII and MDI for 3 months prior to study entry (change of insulin ≤20%), not including premix insulin;
6. Have the willing to wear CGM;
7. Able to speak, read and write Chinese.
Exclusive criteria
1. Having used any CGM 3 months prior to study entry;
2. Receiving oral steroid therapy for any disorders and continuous use of paracetamol;
3. Had known allergy to medical-grade adhesives or CGM and its affiliated components;
4. Being pregnant or planning pregnancy (as demonstrated by a positive test at study entry);
5. Recent severe diseases like myocardial infarction, stroke, psychiatric diseases(historical/recent), malignant tumor, kidney disease (defined as estimated glomerular filtration rate<45 ml/min/1.73m^2), dermatosis, decided by investigator
6. Currently participating in another research (must have completed any study at least 30 days prior to being enrolled in this study);
7. Currently abusing illicit drugs, alcohol, or prescription drugs;
8. Any condition that could impact reliability of HbA1c measurement, such as hemoglobinopathy, hemolytic anemia, chronic liver disease, decided by investigator.

Abbreviations: T1DM: type 1 diabetes mellitus; WHO, world health organization; SMBG: self-monitoring for blood glucose CSII: continuous subcutaneous insulin infusion; MDI: multiple daily injections; CGM: continuous glucose monitoring.

Table 2. Endpoints

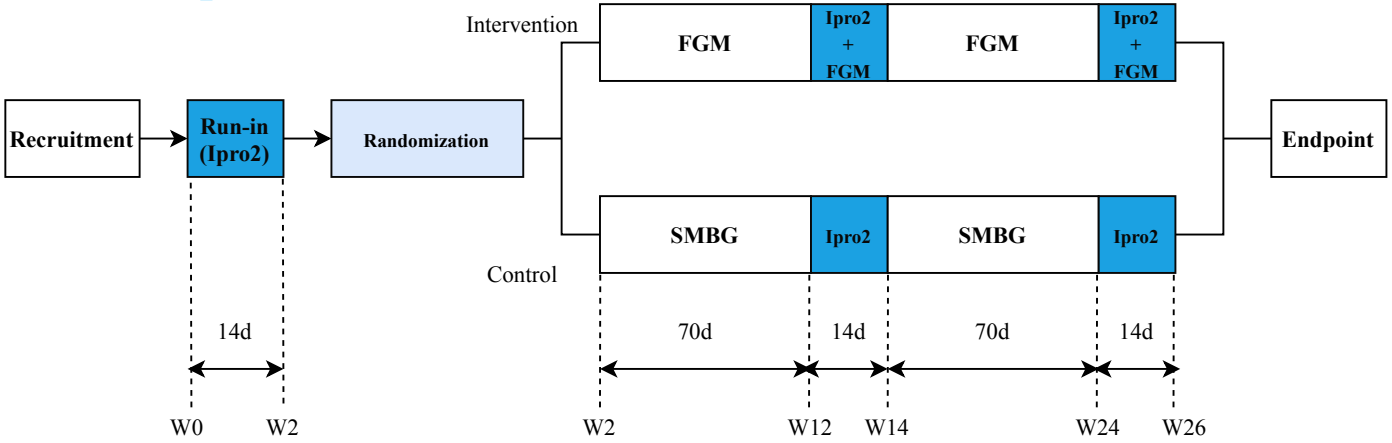
Primary endpoints	
HbA1c (%)	Difference in HbA1c at week 26 adjusted for baseline
Secondary endpoints	
• **CGM metrics*** (whole, night [12:00A.M.-06:00A.M.], daytime [06:00A.M.-12:00A.M.])	The difference in CGM profiles listed below collected via Ipro2 in week 12-14 and week 24-26 adjusted for baseline (week 0 to week 2)
TIR (%)	Range3.9-10.0mmol/l (70-180 mg/dl)
TIT (%)	Range 3.9-7.8mmol/l (70-140mg/dl)
TBR (%)	<3.9mmol/l (70 mg/dl); <3.0mmo/l (54 mg/dl)
TAR (%)	>10mmol/l (180mg/dl); >13.9mmol/l (250mg/dl)
Mean blood glucose(mmol/l)	
Estimated A1c (%)	
SD	
CV	
MAGE	
HBGI	
LBGI	
MODD	
Number of hypoglycemia events	
• **Percentage of HbA1c value in Target (%)**	The difference in the percentage of HbA1 in range (<7%) tested at week14 and week 26 adjusted for baseline.
• **Frequency in using FGM (times/d) †**	Time frame: 24 weeks (from week 2 to week 26)
• **Frequency in using SMBG (times/d)**	Time frame: 24 weeks (from week 2 to week 26)
• **Total of daily insulin dose (IU/kg/d)**	The difference in insulin dose collected at week 14 and week 26 adjusted for baseline
• **Questionnaires**	The difference in scores of respective questionnaires collected at week 14 and week 26 adjusted for baseline
DDS	
HFS	
EQ-5D-5L	

*CGM metrics analyzed here are calculated with the sensor data from Ipro2.

†The frequency in using FGM is calculated with the recordings derived from the FGM system.

Abbreviations: CGM: continuous glucose monitoring; TIR: Time spent in Range; TIT: Time spent in Target; TBR: Time below range; TAR: Time above range; SD: standard deviation; CV: coefficient of variation; MAGE: mean amplitude of glucose excursion; HBGI: high blood glucose index; LBGI: low blood glucose index; MODD: mean of daily differences; CONGA: continuous overlapping net glycemic action; AUC: area under the curve; GRADE: glycemic risk assessment in diabetes equation; FGM: flash glucose monitoring; SMBG: self-monitoring for blood glucose; DDS: Diabetes Distress Scale; HFS: Hypoglycemia Fear Scale; EQ-5D-5L: European Quality of Life Scale.

Figure 1. Flowchart of design



知情同意书

版本日期：2017 年 10 月 30 日版本号：1.0

【课题名称】T1D 各阶段的优化监测和急性并发症预警模型

【所属项目名称】1 型糖尿病优化监测与治疗方案的研究及关键新技术推广

【项目牵头单位】中山大学附属第三医院

【课题牵头单位】上海市第六人民医院

【主要研究者】

您或您的子女将被邀请参加一项临床研究。本知情同意书提供给您一些信息以帮助您决定是否参加此项临床研究。请您仔细阅读，如有任何疑问请向负责该项研究的研究者提出。

本次研究已通过本研究机构医学伦理审查委员会审查。您或您的子女参加本项研究是自愿的，如果您同意参加该研究，您需要签署知情同意书，以表示您已经同意参加。

【项目目的和背景】

项目目标：通过比较新型“无创”瞬感血糖仪®和传统血糖监测方法对血糖控制不佳的 1 型糖尿病患者血糖控制的影响，建立 1 型糖尿病优化的血糖监测方案及急性并发症预警模型。

研究背景：1 型糖尿病患者由于其自身免疫的严重破坏所导致胰岛素的绝对缺乏以及强化胰岛素治疗方案在治疗期间需根据个体化逐步调整，在治疗期间，临床上容易出现高血糖及低血糖事件，并且造成血糖波动幅度大。因此，严格的自我血糖监测对于 1 型糖尿病患者控制血糖、发现风险和及时治疗尤为重要。目前常用的血糖监测方法虽能改善糖化血红蛋白水平，但存在本身探头寿命短、数据保留时间短、需要每日数次指末血糖输入校正以及价格昂贵等缺点。而新研发的“无创”瞬感血糖仪则有其探头寿命长达 14 天、无需指尖血糖校正等优点。并有最新研究表明，在控制良好的成人糖尿病患者中，瞬感血糖仪监测能有效降低糖化血红蛋白水平，降低低血糖事件的发生时长以及减少发作次数，且患者自觉生活质量得到明显提高。但是，儿童青少年患者在此方面的数据并不完善，对于血糖控制不佳的 1 型糖尿病患者而言此类研究更是缺乏。由此，我们想通过比较在血糖控制不佳的各年龄阶段的 T1DM 患者中，传统血糖监测方法和新型“无创”瞬感血糖仪对于血糖控制的影响，制定最优化的 T1DM 患者血糖监测方案和建立糖尿病急性并发症预警模型，从而及时有效地临床干预 T1DM 患者的治疗情况，提高血糖控制水平及生活质量，减少对该人群生命的威胁。

如果您想知道更具体的细节，您的研究医生将会向您更详尽地解释。

【项目设计】

通过进行一项随机对照、多中心、前瞻性研究，观察在血糖控制不佳的 1 型糖尿病患者使用“无创”瞬感血糖仪®（Freestyle Libre；Abbott Diabetes Care，Witney，Oxon，UK）或传统血糖监测方法后血糖控制情况的变化，并在基线、研究中期及研究结束时（第 0、4、

12-14、26-28 周）完成随访，测量糖化血红蛋白水平及记录低血糖发生的频率等，在第 3、8、20 周时完成电话访视，以了解患者血糖控制情况及生活质量的变化。

【入选标准】

1. 根据 1999 年 WHO 的标准临床诊断为 1 型糖尿病，病程≥1 年；2. 年龄≧6 岁；3. 糖化血红蛋白 7.0%-10%；4. 胰岛素泵或每日多次胰岛素皮下注射治疗≧3 个月，胰岛素量改变≦20%；5. 入组前每天自我规律测血糖（≧3 次/天），至少维持 2 个月；6. 有戴动态血糖监测仪的意愿；7、入组前 3 个月糖尿病口服药方案及体重稳定，且整个干预试验期无计划进行任何结构化的药物及减轻体重的干预措施，如增减口服降糖药、处方减肥药，减肥手术等；8、有组织语言的能力及可读、讲中文或英文。

【排除标准】

1. 入组前已经使用 CGM 监测≧3 个月；2. 入组前 3 个月内严重糖尿病慢性并发症；3. 目前或即将使用固醇类或扑热息痛类药物；4. 已经怀孕或者有怀孕打算；5. 对 CGM 设备及其附件过敏（包括医用黏胶等）；6. 由研究者评估决定目前存在影响研究结果的严重疾病如严重心脏疾病、脑血管梗塞、恶性肿瘤、肾脏疾病（eGFR＜45 ml/min）、严重皮肤疾病、精神心理疾病及认知功能障碍等；7. 入组前 1 月及未来 6 月同时参与其他研究；8. 目前滥用非法药物、酒精或其他处方药；9. 任何可能影响糖化血红蛋白测量的因素。

【项目内容】

本项目的主要内容为通过糖化血红蛋白水平、低血糖事件发生频率的变化等比较新型“无创”瞬感血糖仪和传统血糖监测方法对血糖控制不佳的1型糖尿病患者血糖控制的影响。本研究将会在中山大学附属第三医院进行。如果您同意，并签署了这份知情同意书。您将会通过随机数字表的形式，确定在您目前强化胰岛素治疗方案的基础上，您是用“无创”瞬感血糖仪®或快速血糖仪针刺取血的指末血糖测定(拜耳拜安捷)。观察指标：基线、第4、12-14、26-28周随访，检测糖化血红蛋白水平，记录低血糖发生的频率及血糖漂移情况等；在第3、8、20周时完成电话访视，以了解患者血糖控制情况及生活质量的变化。

【参加项目的义务】

作为研究受试者，您有以下职责：提供有关自身疾病史和当前身体状况的真实情况；做好饮食和血糖日志，定时完成随访。您将需要仔细遵守医生的针对研究的指示【备注：CGM 组：至少 85%的时间的佩戴瞬感，至少每 8 小时扫描 1 次；SMBG 组：监测频率≥3 次/天】。如果您从研究中退出，我们将会在您结束研究时进行最后体检和问卷。

【项目的风险和个人信息保护】

如果您决定参加本项研究，您参加试验及在试验中的个人资料均属保密。您的血/尿标本将以研究编号数字而非您的姓名加以标识。可以识别您身份的信息将不会透露给研究小组以外的成员，除非获得您的许可。您的档案仅供研究人员查阅。为确保研究按照规定进行，必要时，政府管理部门或伦理审查委员会的成员按规定可以在研究单位查阅您的个人资料。

这项研究结果发表时，将不会披露您个人的任何资料。

【参加项目的受益】

糖尿病教育；整个观察期内分泌科指导下的胰岛素强化治疗；免费糖尿病相关检查和定期免费使用动态血糖监测。

【参加和退出项目】

您可以选择不参加本项研究，或者在任何时候通知研究者要求退出研究，您的数据将不纳入研究结果，您的任何医疗待遇与权益不会因此而受到影响。您的医生、申办者或者管理机构也可能任何时候终止您的参与。在任何情况下，您都不会受到处罚。

【受试者补偿和保险】

如发生与本试验相关的损害，由本课题组依照法律规定承担合理、通常和必要的治疗费用。根据法律法规的有关规定，对于下列情形所导致的对您的伤害，研究者将不承担任何责任：与本研究无关的医疗事故；您在参加本研究前自身原有的疾病造成的损害；您采取自杀、自残的行为；您不遵循本知情同意书、临床研究方案或在您参加本研究期间研究人员给您的治疗造成的损害；与本研究无关的其他事件和/或不可抗力。

您不会因为签署本知情同意书而丧失任何法律权益。

【研究联系人】

如果您在研究过程中，需要进一步了解有关研究资料信息，或因参加研究受到损伤，请联系本研究的医生_____，电话_____。

【同意声明】

我已阅读了本知情同意书。

我有机会提问而且所有问题均已得到解答。

我理解参加本项研究是自愿的。

我可以选择不参加本项研究，或者在任何时候通知研究者后退出而不会遭到歧视或报复，我的任何医疗待遇与权益不会因此而受到影响。

如果我需要其它治疗，或者我没有遵守研究计划，或者发生了与研究相关的损伤或者有任何其它原因，研究医师可以终止我继续参与本项研究。

我将收到一份签过字的“知情同意书”副本。

受试者姓名（正楷）：　　联系电话：

受试者签名：　　日期：　　年　　月　　日

受试者法定代理人姓名（正楷）：

受试者法定代理人签名：　　日期：　　年　　月　　日

与受试者的关系：

受试者法定代理人联系电话：

研究者姓名（正楷）：

研究者签名：日期：　　日期：　　年　　月　　日

（注：如果受试者不识字时需见证人签名，如果受试者无行为能力时则需代理人签名）

SUPPLEMENT 2

Introduction of the devices used in this trial

1. Devices

In our study, two CGMs and a blood glucose meter will be applied: blood glucose meter for strip test, retrospective CGM for assistance, and FGM for interpretation. Both CGMs recorded glucose data collected in the interstitial fluid at different time intervals. Details would be described below.

1.1 Retrospective CGM system

The retrospective CGM system (Ipro2®, Medtronic, USA) consists of an inserted sensor and a recorder connected. The sensor will be implanted on the back of the patients' upper arms and data is stored in the recorder every 5minute, thus 288 glucose values will be collected per day in total [1]. The lifetime of each sensor is usually from 3 to 7 days. The mean absolute relative difference (MARD) of Ipro2 is 9.9% in adults and was the lowest in the 240-400mg/dl range (6.8% in adults) [2]. During the wearing time, the sensor data derived are not visible and only after the removal of the sensor and data download with retrospective SMBG data calibrations, the glycemic metrics and ambulatory glucose profile will be accessible to the patients and investigators. Therefore, the retrospective CGM is thought to be a perfect tool in the research with less interpretation.

1.2 FGM system

The FGM system (FreeStyle Libre®; Abbott Diabetes Care, Witney, Oxon, UK) is a novel sensor-based intermittently scanned glucose monitoring system [3]. The sensor is around 1*1 cm and implanted by a single-use applicator, and automatically measures glucose every 15 minutes for up to 14 days without finger-stick calibrations. The sensor will be implanted on the back of the upper arms which is thought to be more accurate [4]. The MARD tested in adult patients is 8.8-12.9% compared with venous glucose reference and YSI pairs (Yellow Springs, OH) [5,6]. The most frequent safety problem of FGM is erythema, as shown in the system reviews about FGM [7,8].

1.3 Blood Glucose Meter (Bayer®)

The blood Glucose Meter (Bayer®; Bayer Consumer Care AG) is a reliable home-use device to perform finger-stick strip tests and meet the predetermined accuracy standard illustrated in a recent study [9,10]. Therefore, it will be distributed into each patient as a tool to perform any finger-stick tests during the trial.

2. Questionnaires

In our study, the Chinese version of the DDS, HFS, EQ-5D-5L will be used to evaluate the change in distress from diabetes, the fear of hypoglycemia, and the quality of life

after the intervention. The excellent reliability and validity of the scales in Chinese Version had been proved [11-13].

2.1 Diabetes Distress Scale (DDS)

The Chinese version of the DDS is to evaluate diabetes-related emotional distress in patients with diabetes [12]. The scale consists of 17 items, contains four domains including emotional burden sub-scale, physician-related distress subscale, regimen-related distress subscale, and diabetes-related interpersonal distress. Each item is rated on a 6-point Likert scale from 1(no problem) to 6(serious problem). An average score ≥3 is the cut-off point which is considered to more than the moderate problem.

2.2 Hypoglycemia Fear Scale (HFS)

The Chinses version of the HFS is to evaluate psychological status for diabetic patients [13]. These validated surveys consist of 18 questions that measure dimensions of anxiety and fear surrounding hypoglycemia. Each item is rated on a 5-point Likert scale from 0(never related) to 4(very related). Patients with higher scores are considered with more anxieties and fear of hypoglycemia.

2.3 European Quality of Life (EQ-5D-5L) Scale

The Chinese version of the EQ-5D-5L is widely used to evaluate the quality of life in Chinese [11]. The EQ-5D-5L is converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. It contains the health description system and Visual Analogue Score (VAS). The health description system includes 5 dimensions including mobility, self-care, usual activities, pain or discomfort, and anxiety/depression. Each item is rated on 5 levels from 1(no problem) to 5(extreme problem). And the VAS is to evaluate the health condition assessed by patients. The top score (100) means the best health conditions and the bottom one (0) means the worst.

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Supplement

Effects of Novel Flash Glucose Monitoring System on Glycemic Control in Adult Patients with Type 1 Diabetes Mellitus: Protocol of a Multicenter Randomized Controlled Trial

General Diabetic Education

Version 1.0

Recommendations are based on the guideline by American Diabetes Association and the Chinese Diabetes Society.

1. **Goal of glycemic control**

For Adult patients:

- HbA1c<7%;
- Fasting/pre-prandial blood glucose: 4.4-7.2mmol/l;
- Postprandial blood glucose level: 5-10.0mmol/l;
- Blood glucose level during night/before sleep: 6.7-10.0mmol/L.

2. **General calculation of insulin sensitivity factor (ISF):** describes how much one unit of rapid or regular insulin will lower blood glucose. It is used to determine the amount of insulin to give to correct blood glucose readings that are above target

- **1800 Rule(Rapid-acting insulin analogs lispro):**

  ISF=1800/ (total daily use *18)

- **1500 Rule (Regular short-acting insulin):**

  ISF=1800/ (total daily use *18)

3. **General insulin: carbohydrate ratio:** estimation gram of carbohydrates per 1 U of insulin covering

- 500 Rule: Insulin: carbohydrate ratio=500/total daily dose

4. **Recommendations when facing hypoglycemia**

(1) **Definition**

Level	**Criteria**	**Description**
Hypoglycemia alert value (level 1)	≤3.9mmol/L	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level2)	<3.0mmol/L	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

(2) **Symptoms**: Shakiness, irritability, confusion, tachycardia, and hunger (not

limited).

(3) **Solutions:**

- Glucose (15–20 g) is the preferred treatment for the conscious individual with blood glucose <3.9mmol/L]) or any form of carbohydrate that contains glucose may be used.
- Fifteen minutes after treatment, if glucose trend shows continued hypoglycemia, the treatment should be repeated.
- Once glucose value returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia.
- Thinking back the possible factor contributing to hypoglycemia such as exercise, over-injection, diet and make adjustments before the similar situation next time.

Note: The glucose value mentioned here refers to the glucose derived from SMBG. For participants distributed to FGM group, we recommend you to have an additional finger-stick test for capillary glucose value if you are in hypoglycemia and make adjustment according to the capillary glucose value.

5. Recommendations when facing hyperglycemia

(1) **Definition:** Glucose value >10.0mmol/L(alert);

Glucose value>13.9mmol/L (immediate action required)

(2) **Solutions:**

- Take an extra dose of rapid acting insulin based on your personal ISF. And if glucose level is above 16.9mmol/L, ketone test is recommended.
- Be careful about “stacking” insulin. The rapid- acting insulin you take at meals may still be working 4 hours after your injection. Keep a careful watch on your glucose over the next hour or two.
- Thinking back the factor contributing to hyperglycemia. Consider what you would do differently the next time with your meal and/ or your mealtime insulin dose to avoid the high and rising glucose.
- If hyperglycemia is sustained the whole day, think about if you miss the

injection of insulin previously or if your additional bolus is not enough and make some additional adjustments. . If you use insulin pump, think about if there is any blockage of tube or noneffective insulin in your pump. And if hyperglycemia is sustained for more than 1 day and you cannot find the reason, we recommend you to consult your investigator.

Note: The glucose value mentioned here refers to the glucose derived from SMBG. For participants distributed to FGM group, we recommend you to have an additional finger-stick test for capillary glucose value if your glucose is higher than 13.9mmol/L and make adjustment according to the capillary glucose value.

APPENDIX.1--The Chinese version of the general diabetes education

自我血糖监测及管理手册

一．血糖控制目标：

	HbA1c（%）	空腹/餐前血糖（mmo/l）	睡前/夜间血糖（mmo/l）	餐后血糖
成人	<7.0	4.4-7.2	6.7-10	5-10.0
儿童和青少年	<7.5	5.0-7.2	5.0-8.3	5-10.0

在不增加低血糖发生的前提下，尽可能做到血糖达标。

参考文献：中国 1 型糖尿病诊治指南（2015 年版），2017 年美国 ADA 指南。

二．指尖血糖监测

☺每天至少4 次或以上指尖血糖监测（三餐前，睡前，餐后，必要时凌晨夜间加测一次）；

☺生病、剧烈运动前或有急性感染等情况时加测；

☺没有症状≠控制良好≠不用监测。

三．动态血糖监测

☺至少每 8 小时扫描获取数据（≧3 次/天），扫描次数无限制，可以随时扫描；

☺当你发现扫描的血糖值＜3.9mmol/l或＞13.9mmol/l时，加测 1 次指尖血糖，以指尖血糖值为准，进行低血糖或高血糖的处理；

☺探头仅能用 14 天，14 天后需更换；

☺做 X 光检查、CT（计算机断层成像）、MRI 核磁共振检查时需移除；

☺动态血糖监测期间请详细记录饮食、运动、治疗等生活事件。

自我血糖监测及管理手册

四．低血糖处理

★怎么知道自己低血糖？

1. 看血糖值*：

㊣轻-中度低血糖 ＜3.9mmol/l；

㊣㊣严重低血糖 ＜3.0mmol/l；

瞬感使用者提示“低葡萄糖”或“↘”（葡萄糖正在下降）、“↓”（葡萄糖正在迅速下降）时应及时预防低血糖。

*瞬感使用者若监测到血糖值低，建议测量指尖血糖，并以指尖血糖值为准。

2. 低血糖症状：心跳加快、饥饿、发抖、出虚汗、头晕犯困、焦虑不安、四肢无力、抽搐、视觉模糊、头疼。

★发生低血糖时你该怎么办？

❶吃 15-20g 碳水化合物类食物（如葡萄糖 4 片、半杯果汁、一汤勺蜂蜜等吸收快作用快的食物），血糖值＜2.8mmol/l 时适量再增加 15-20g 食物；

❷15 分钟后测量指尖血糖，若症状未改善重复上述步骤，若仍未改善或出现神志不清、突发昏迷者送院就诊；

❸血糖恢复后，瞬感使用者若提示“↘”（葡萄糖正在下降）、“↓”（葡萄糖正在迅速下降）时，可适当增加进食以预防下一次低血糖发生，在接下来的 30-60 分钟内密切关注血糖的变化，适当增加扫描次数（15 分钟/间隔），必要时予指尖血糖测准。指尖血糖组则适当加测血糖值以进一步了解血糖是否稳定。

❹血糖恢复后，回顾发生低血糖原因，若是在饮食、运动情况不变的情况下发生血糖偏低，考虑胰岛素注射过多所致。结合患者达标目标，及时调整胰岛素用量。（具体方案见 5-6 页）

五．血糖偏高时怎么办？

㊣血糖值＞13.9mmol/l；

瞬感使用者若发现血糖值高，测指尖血糖，并以指尖血糖值为准。

处理方法：

❶**目标血糖<血糖<13.9mmol/l**：根据胰岛素敏感系数（见后），计算需要追加多少单位胰岛素，结合自己的经验、目前情况（餐后、睡前、运动等）等，追加合适的补充大剂量，1 小时后再次复测血糖。

❷**血糖>13.9mmol/l**：检测血酮，若是阴性：同以上处理。酮体阳性：多饮水，补充大剂量纠正高血糖，每 1 小时检测血糖，严重时医院就诊处理。

❸当血糖恢复稳定 30-60 分钟内，密切留意血糖变化瞬感使用者若提示“↑”葡萄糖正在迅速升高）、“↗”（葡萄糖正在缓慢升高），结合你的胰岛素敏感系数追加剂量。（详细计算方法见 4-6 页）。

六．追加大剂量怎么算？

掌握两个定义！

★胰岛素敏感系数：1 单位胰岛素能降低的血糖值

公式（或参考表格）：

速效：敏感系数(X)=1800/（每日总量×18)=100/每日胰岛素总量

短效：敏感系数(X)=1500/（每日总量×18)

每日胰岛素用量	1800 法则 速效	1500 法则 短效
20	5	4.2
25	4	3.3
30	3.3	2.8
35	2.9	2.4
40	2.5	2.1
50	2.0	1.7
60	1.7	1.4
75	1.3	1.1
100	1.0	0.8

★碳水化合物系数：1 单位胰岛素能平衡的食物中碳水化合物克数。公式（或参考表格）：

速效：500÷每日胰岛素总量=___g/u

短效：450÷每日胰岛素总量=___g/u

每日胰岛素用量	500 法则 速效	450 法则 短效
20	25	23
25	20	18
30	17	15
35	14	13
40	13	11
50	10	9
60	8	8

SPIRIT CHECKLISTS

This checklist is according to the recommendations presented in the https://www.spirit-statement.org/title/

SECTION/TOPIC	ADHERE TO RECOMMEDATIONS
ADMINISTRATIVE INFORMATION	
1: TITLE	**√ P1**
2: TRIAL REGISTRATION	
2A: REGISTRY	**√ P4**
2B: DATA SET	**√P7**
3: PROTOCOL VERSION	NA
4: FUNDING	**√P9**
5: ROLES AND RESPONSIBILITIES	**√P10**
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