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# Effects of novel flash glucose monitoring system on glycaemic control in adult patients with type 1 diabetes mellitus: protocol of a multicentre randomised controlled trial

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## ABSTRACT

**Introduction** Optimal glycaemic 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 glycaemic control is limited. This study aims to evaluate the effect of FGM in suboptimally controlled adult patients with T1DM .

**Methods and analysis** This open-label, multicentre, randomised trial will be conducted at eight tertiary hospitals and recruit 104 adult participants (≥18 years old) with T1DM diagnosed for at least 1 year and with suboptimal glycaemic control (glycated haemoglobin (HbA1c) ranging from 7.0% to 10.0%). After a run-in period (baseline, 0–2 weeks), eligible participants will be randomised 1:1 to either use FGM or self-monitoring of blood glucose alone consequently for the next 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 week 26. All analyses will be conducted on the intent-to-treat population. Efficacy endpoint 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 are the changes of CGM metrics, including time spent in range, time spent in target, time spent below range, time spent above range, SD, 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 of FGM use, total daily insulin dose and the 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 centres. 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 registration number** NCT03522870.

## Strengths and limitations of this study

- This study adopts a multicentre, open-label, randomised and parallel design.
- This study aims to evaluate the flash glucose monitoring system among adult patients with type 1 diabetes mellitus who have suboptimal glycaemic control with the comparison with self-monitoring of blood glucose.
- The retrospective continuous glucose monitoring (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 randomised to use the flash glucose monitoring systems will wear the retrospective CGM systems additionally and simultaneously in the 14 days preceding the 3 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 had demonstrated that intensive glycaemic control contributes to delay and prevents 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 analogues 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 glycaemic control in patients with T1DM,[5 7] the optimisation of glucose monitoring is necessary.

The conventional glycaemic monitoring methods include the daily self-monitoring of 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. The HbA1c, the golden standard of glycaemic monitoring method, reflecting the average glucose concentration for approximately 3 months, is also not direct and convenient enough for not proving a measure of glycaemic variability or an alert function of real-time hypoglycaemia 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 intraday/interday glycaemic 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 such as the real-time CGM systems. It has been demonstrated that glycaemic 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 also be sustained for 12 months when used properly.[11]

For most CGMs, SMBG is still required for calibrations. While the flash glucose monitoring (FGM) system (FreeStyle Libre; Abbott Diabetes Care, Witney, Oxon, UK), the new generation of CGMs, approved by Food and Drug Administration (FDA) in 2017, is factory calibrated and provides a longer sensor lifetime of 14 days, which has further relieved the pain from frequent strip capillary glucose calibrations and thus is relatively more acceptable and easier for widespread use. To date, most relevant published articles were research 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 randomised 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 glycaemic control. Therefore, we designed this 24-week comparative trial, aiming to evaluate the effect of FGM in adult patients with T1DM who have suboptimal glycaemic control. The research protocol of the RCT study is presented below.

## METHODS AND ANALYSIS

### Study design

This trial is an open-label, multicentre, randomised and parallel-group study conducted at eight centres in seven 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 glycaemic control will be compared. Written informed consent will be obtained from all participants before study-related activities (see online supplemental file 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.

### Study procedure

The flow chart of this study is presented in figure 1. After a run-in period of 2 weeks, eligible participants will be randomised 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 adverse events (AE) will also be 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

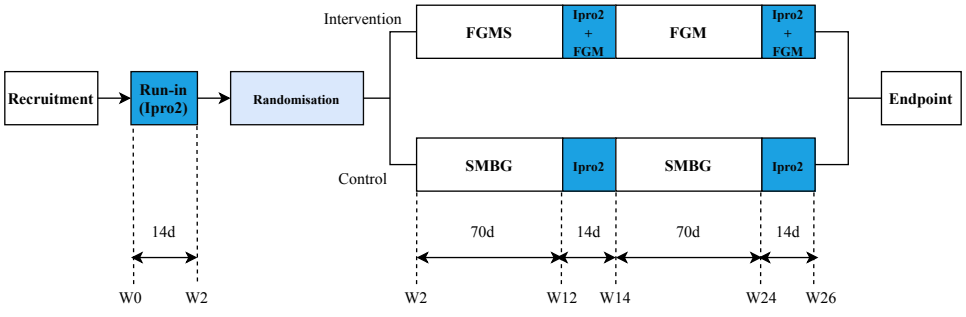


**Figure 1** Flow chart of the design. FGM, flash glucose monitoring; SMBG, self-monitoring of blood glucose.

**Box 1 Inclusive and exclusive criteria**

**Inclusive criteria**
- Aged ≥18 years .
- Diagnosed with T1DM with the criteria established by WHO in 1999, and with duration more than 1 year.
- Glycosylated haemoglobin A1c concentration between 7% and 10%.
- SMBG daily (≥3 times per day) for at least 2 months prior to study entry and willing to insist for at least 6 months.
- Stable insulin regimen medication including CSII and MDI for 3 months prior to study entry (change of insulin ≤20%), not including premixed insulin.
- Willing to wear CGM.
- Able to speak, read and write Chinese.

**Exclusive criteria**
- Having used any CGM 3 months prior to study entry.
- Receiving oral steroid therapy for any disorders and continuous use of paracetamol.
- Had known allergy to medical grade adhesives or CGM and its affiliated components.
- Being pregnant or planning pregnancy (as demonstrated by a positive test at study entry).
- Recent severe diseases like myocardial infarction, stroke, psychiatric diseases (historical/recent), malignant tumour, kidney disease (defined as estimated glomerular filtration rate <45 mL/min/1.73 $m^2$) and dermatosis, decided by the investigator.
- Currently participating in another research (must have completed any study at least 30 days prior to being enrolled in this study).
- Currently abusing illicit drugs, alcohol or prescription drugs.
- Any condition that could impact reliability of HbA1c measurement, such as haemoglobinopathy, haemolytic anaemia and chronic liver disease, decided by the investigator.

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; SMBG, self-monitoring of blood glucose; T1DM, type 1 diabetes mellitus.

Diabetes Association and the WHO.[23 24] Other inclusive and exclusive criteria are shown in box 1.

### Run-in period (baseline, weeks 0–2)

In this period, demographics, medical histories, smoking or drinking status, exercise and the results of physical examination (body mass index, the waist to hip ratio, blood pressure and heart rate) will be collected by certified physicians and nurses in accordance with standardised protocols. Urine samples will be collected for the measurements of albumin to creatine ratio and female participants will have extra urine pregnancy tests in the participant centres. Fasting blood samples are collected for biological 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,[25] Hypoglycemia Fear Scale[26] and European Quality of Life Scale[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 metres and compatible test strips (Bayer; Bayer Consumer Care) 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 metres will be presented in the online supplemental file 2. During 2 weeks, capillary blood glucose tests, diet diary and exercise will be required to record for calibration. Sensor glucose measurements will not be visible to the patients and the investigators until the data are 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 hypoglycaemia/hyperglycaemia and suggestions for insulin titration (see online supplemental file 3).

### Randomisation

After the 2-week run-in period, eligible participants will be randomised 1:1 to either daily SMBG alone or FGM. The random sequence will be generated by SPSS 20.0 software 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 centre, where envelopes will be opened sequentially to determine the participants' assignments.

### Study intervention

After randomisation, participants in the FGM group will be provided with FGM (FreeStyle Libre; Abbott Diabetes Care) and measure glucose concentrations at home for the following 24 weeks. Detailed introduction of FGM system will be presented in the online supplemental file 2. Instructions about device use will be provided according to the manufacturer's user manual and access to the device software (FreeStyle Libre Software V.1.0; Abbott Diabetes Care) will be given. Participants will be required to report the AEs 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 are below 3.9 or over 13.9 mmol/L but the frequency of the fingerstick tests is non-restricted. The first sensor will be applied by the trained staff 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 hypoglycaemia and hyperglycaemia-related symptoms occur in both groups.

### Follow-up visits (weeks 12–14 and weeks 24–26)

Follow-up visits for both groups will be scheduled from week 12 to week 14 and from week 24 to week 26, during which professional CGM will be additionally used in both groups to collect CGM data for 2 weeks. During the 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 the 2-week data collection. At the end of weeks 14 and 26, glucose data collected from the Ipro2 during 2 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 are 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 CGM 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 staff via its corresponding software. For the SMBG group, fingerstick glucose data stored in the blood glucose metres from week 2 to week 14 and from week 14 to week 26 will also be 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 (3.9–10.0 mmol/L), time spent in target (3.9–7.8 mmol/L), time spent below range (TBR (<3.9 mmol/L); TBR (<3.0 mmol/L)) and time spent above range (TAR (>10.0 mmol/L); TAR (>13.9 mmol/L)) from baseline to week 26, SD, coefficient of variation, mean amplitude of glucose excursions, high or low blood glucose index, mean of daily differences, percentage of HbA1c in the target (<7%), frequency of FGM use, 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 1.

**Table 1** Endpoints

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

*CGM metrics analysed here are calculated with the sensor data from Ipro2.
†The frequency of using FGM is calculated with the recordings derived from the FGM system.
CGM, continuous glucose monitoring; CV, coefficient of variation; DDS, Diabetes Distress Scale; EQ-5D-5L, European Quality of Life Scale; FGM, flash glucose monitoring; HBGI, high blood glucose index; HFS, Hypoglycemia Fear Scale; LBGI, low blood glucose index; MAGE, mean amplitude of glucose excursion; MODD, mean of daily differences; SMBG, self-monitoring of blood glucose; TAR, time above range; TBR, time below range; TIR, time spent in range; TIT, time spent in target.

## Risks and 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 (ie, 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%), oedema (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 haematoma (0.7%). However, the incidence rate of these events is low with one event reported per 8 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 hyperglycaemic state and severe hypoglycaemic events will be captured as serious AEs. According to the guidelines from the American Diabetes Association,[6] the definition of severe hypoglycaemia is hypoglycaemia 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 analyser (Bio-Rad D10; Bio-Rad Laboratories, Hercules, California) using the high-performance liquid chromatography technique, with a reference range of 4.3%–6.1% and intrabatch and interbatch coefficients of variation of 0.46% and 0.99%, respectively. Lipid profiles, liver enzymes and renal function are determined by the enzymatic colorimetric test with Hitachi 7600 autoanalyser. The thyroid function and its antibodies are assessed by the chemiluminescence immunoassay 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; intrabatch and interbatch coefficients of variation of 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 8 autoantibody (ZnT8A) were analysed centrally using fasting serum with radiobinding 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 one antibody titre tested (GADA titre ≥0.042 was seen as positive; ZnT8A titre ≥0.054 was seen as positive; IA-2A titre ≥0.018 was seen as positive) were considered positive for diabetes autoantibodies.

The coordinator centre 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 using the case report forms by responsible participating investigators and sent to the coordinator centre periodically. To maintain the accessibility of the database, facilities will be conducted as follows: (1) All participating investigators will be trained before study commencement. Standardised 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 participating hospitals will be conducted by coauthors and the principal investigator will manage the data flow and perform audits of the procedure of the study.

### Sample size

According to the RCTs 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% (SD 0.8, correlation 0.6) using a two-sided test at the 0.05 level.

### Statistical analysis

All analyses will be conducted on the intent-to-treat population. Data from all randomised 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 suboptimally 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 analysed using a linear mixed model with management, time 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 them based on whether we regard the imbalance as clinically significant. A 95% CI will be given for the difference between the groups.

The calculation of the CGM metrics during the whole time, the night period (00:00–06:00) and the daytime period (06:00–00:00) is via the Glyculator 2.0 software. Information including demographics and physical measurements will be summarised. The calculation of the questionnaires is presented in the online supplemental file 2. Continuous variables will be presented with mean±SD or median (25th and 75th quartile ranges). Categorical variables will be presented with the proportion of subjects in each category. If values are highly skewed, transformation or non-parametric analyses will be used. $X^2$ tests or Fisher's exact test will be used to analyse 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 utilisation 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 min and special functions 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 of use.[34] In the multicentre randomised controlled studies which was conducted either on well-controlled adult patients with T1DM or high-risk young adults (13–20 years), the group using FGM showed insignificant improvements in HbA1c change while only those adults with well-controlled had reduced time spent in hypoglycaemia.[18 21] However, to date, there is still no evidence from RCTs conducted in adult patients with T1DM and suboptimal control. Different from the other CGMs, there is no hypoglycaemia 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 patients with T1DM would derive similar benefits from FGM or have similar compliance on FGM use is required to be discussed.

This trial will be conducted at eight centres that have an 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-week CGM-related glycaemic 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 glycaemic control.

There are some limitations to this trial. First, 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. Second, the period assessed in this trial is only for 6 months and the sustained effect of the FGM among patients with suboptimal glycaemic 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 wis conducted in accordance with the Declaration of Helsinki (1964) including all amendments and 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.

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**Contributors** JW and JY designed and organised the study. YZ and HD registered the trial and cowrote the first draft of the manuscript. JW, JY and HL undertook a critical revision of the manuscript. YZ, HD and HL were responsible for the recruitment and implementation of the protocol. DY, WX and BY contributed to the data interpretation. JW and JY had full access to all the data in the study and had the final responsibility on the decision to submit for publication. All authors have read and approved the final manuscript.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

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# 知情同意书

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**【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 0-2、

12-14、24-26 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，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3个月内已经使用 CGM 监测；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12-14周、24-26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。

**【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 |