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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

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.

trial. The study will be disseminated by peer-review publications and conference presentations.

Trial registration number NCT03522870.

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
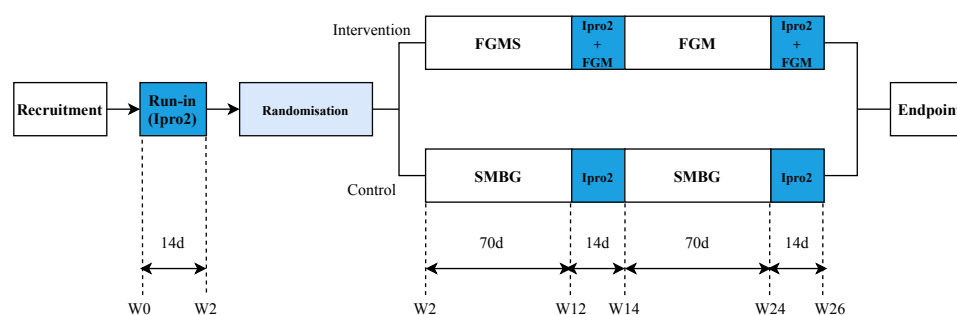

Figure 1.Flowchart of design

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.

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%),

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.

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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