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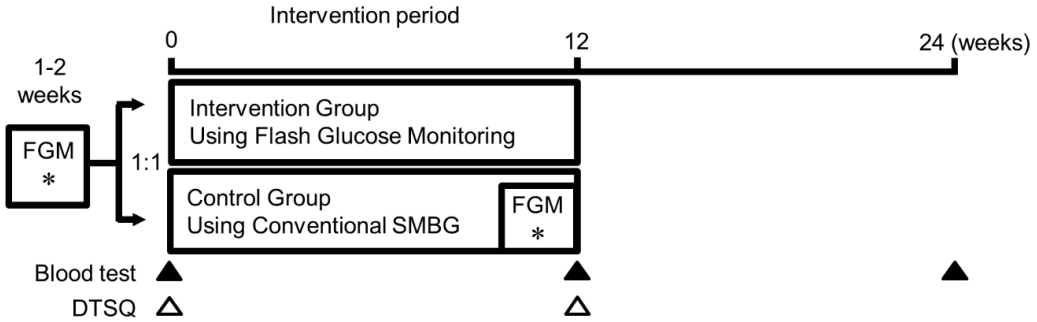
Wada E, *et al. BMJ Open Diab Res Care* 2020; 8:e001115. doi: 10.1136/bmjdrc-2019-001115

Online supplementary figure S1. Participant timeline of this trial. DTSQ, Diabetes Treatment Satisfaction Questionnaire. * Sensor glucose measurements were blinded (not visible).



Online supplementary table S1. Change in HbA1c using the linear mixed model.

HbA1c (%)	Difference in adjusted means (95%CI)	p-value
FGM group vs SMBG group at 12 weeks	−0.13 (−0.36 to 0.10)	0.282
FGM group vs SMBG group at 24 weeks	−0.29 (−0.53 to −0.06)	**0.014**
12 weeks vs 24 weeks in the FGM group	−0.03 (-0.16 to 0.10)	0.658
12 weeks vs 24 weeks in the SMBG group	0.14 (0.01 to 0.27)	**0.036**

A linear mixed model, which included baseline values, time, group, and interactions between time and group as fixed effects, was used to compare the change in HbA1c. CI, confidence interval. P-values < 0.05 are shown in bold.

Online supplementary table S2. Changes of antidiabetic drug.

	FGM group (n = 48)	SMBG group (n = 45)	p-value
12 weeks			
No change	43	43	
Increased medicine	1	0	0.557
Decreased medicine	4	2	
24 weeks			
No change	41	41	
Increased medicine	5	3	0.871
Decreased medicine	2	1	

Changes in antidiabetic drugs were analyzed using the Mantel-extension test stratified by sex, age (>60 or ≤60 years), BMI at entry (>25 or ≤25 kg/m^2), and the use or nonuse of oral hypoglycemic agents. Increasing the number or dosage of antidiabetic drugs was defined as “increased medicine” and decreasing the number or dosage of antidiabetic drugs was defined as “decreased medicine.”

Online supplementary table S3. Subgroup analysis in which antidiabetic drug were not changed.

HbA1c (%)	Baseline mean (SD)	Change at 24 weeks mean (95% CI)	Difference in adjusted means in FGM vs SMBG (95%CI)	p-value
FGM group (n = 41)	7.83 (0.25)	−0.46 (−0.60 to −0.31)	−0.14 (−0.27 to −0.00)	**0.044**
SMBG group (n = 41)	7.85 (0.26)	−0.18 (−0.41 to 0.05)		

HbA1c was compared using analysis of covariance (ANCOVA) model that included baseline values and group as covariates. SD, standard deviation; CI, confidence interval. P-values < 0.05 are shown in bold.

Online supplementary table S4. Adverse events.

Variable	FGM group (n = 49)	SMBG group (n = 51)
Participants with AEs or SAEs, n (%)	10 (20)	3 (6)
Total number of AEs or SAEs	10	3
Participants with SAEs, n (%)	1 (2)	1 (2)
Total number of SAEs[a]	1	1
Participants with hypoglycaemic AEs, n (%)	2 (4)	1 (2)
Total number of hypoglycaemic AEs	2	1
Participants with device-related AEs, n (%)	7 (14)	1 (2)
Total number of device-related AEs[b]	7	1
Participants discontinuing owing to AEs, n (%)	0 (0)	0 (0)

AE, adverse event; SAE, serious adverse event. [a]One participant in the FGM group was hospitalized because of prostate cancer. One participant in the SMBG group was hospitalized because of ophthalmic surgery. [b]Device-related adverse events involved skin problems related to physical contact with the sensor.

Study protocol

Study of the impact of the Flash Glucose Monitoring System (FGM) on glycometabolism of type 2 diabetic patients

Study Protocol (Translation)

(**Interventional study**)

Principal Investigator: Hiroshi Arima, M.D., Ph.D.
Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine
Address: 65 Tsurumai-cho, Showa-ku, Nagoya City
Phone number: 052-744-2142
Fax number: 052-744-2206

Research Office: Motomitsu Goto, M.D., Ph.D.
Department of Endocrinology and Diabetes, Nagoya University Hospital
Address: 65 Tsurumai-cho, Showa-ku, Nagoya City
Phone number: 052-744-2142
Fax number: 052-744-2206

Approved Date (original ver.): June 20, 2017
Updated Date (ver. 8): July 5, 2019
Approved Date (ver. 8): August 5, 2019

I Study name

Study of the impact of the Flash Glucose Monitoring System（FGM） on glycometabolism of type 2 diabetic patients

II Research organization

1. Principal Investigator:

Nagoya University Graduate School of Medicine, Department of Diabetes and Endocrinology
Professor Hiroshi Arima

2. Sub-investigator:

Nagoya University Graduate School of Medicine, Department of Diabetes and Endocrinology
Motomitsu Goto
Takeshi Onoue
Tomoko Kobayashi
Norio Okada
Eri Wada
Mariko Furukawa
Center for Advanced Medicine and Clinical Research, Nagoya University Hospital
Masahiko Ando
Yachiyo Kuwatsuka

3. Co-researcher:

Department of Diabetes, Konan Kosei hospital
Yoh Ariyoshi
Department of Endocrinology and Diabetes, Japanese Red Cross Nagoya Daini Hospital
Akemi Inagaki
Department of Endocrinology and Diabetes, Saisyukan hospital
Koichi Mori
Department of Diabetes, Chunichi hospital

Kaori Hosokawa

4. Data and Safety Monitoring Board:
No board is established for this study.

III Background

Self-monitoring of blood glucose (SMBG) helps achieve better glycemic control in diabetes patients on insulin therapy by facilitating appropriate titration of insulin doses based on the blood glucose levels. SMBG has been shown to improve glycemic control both in patients with type 1 diabetes and type 2 diabetes treated with insulin. In addition to the adjustment of insulin dosage, the improved glycemic control achieved with SMBG may be attributable to lifestyle modification. Consistent with this hypothesis, the use of SMBG has been shown to improve glycemic control even in patients with type 2 diabetes who were not treated with insulin; in addition, the efficacy of SMBG as a tool for diabetes self-management is well documented.

The recently developed flash glucose monitoring (FGM)—also referred to as intermittently scanned continuous glucose monitoring—technology allows for continuous monitoring of interstitial glucose levels using a sensor worn on the back of the upper arm. Compared to SMBG with conventional finger-pricking method, FGM has been shown to reduce the time and frequency of hypoglycemia in a randomized controlled trial (RCT) and to reduce glycated hemoglobin (HbA1c) in observational studies in patients with type 1 diabetes. FGM has also been shown to be superior to SMBG in reducing hypoglycemia and HbA1c level in patients with type 2 diabetes treated with insulin.

If the superiority of FGM over SMBG is due not only to adjustments in insulin dosage but also lifestyle modification, FGM may help achieve better glycemic control than that achieved with SMBG even in patients with type 2 diabetes who are not on insulin therapy. We conduct a RCT to compare the effects of glucose monitoring with FGM and SMBG on glycemic control of non-insulin-treated type 2 diabetic patients.

<Patients>

1. Inclusion criteria:

1) Patients with type 2 diabetes;
2) HbA1c level of ≥7.5% and <8.5%;
3) Age of ≥20 and <70 years;
4) Absence of any severe complications;
5) Provision of written informed consent for participation.

2. Exclusion criteria:

Patients are excluded if they

1) are on dialysis,
2) are treated with insulin,
3) have been using SMBG or FGM,
4) have severe renal failure (estimate glomerular filtration rate < 30 mL/min/1.73m^2),
5) have pre-proliferative diabetic retinopathy or proliferative diabetic retinopathy,
6) can not properly operate the devices,
7) are judged by their physicians to be unsuitable for participation in the study.

3. Number of patients:

50 patients in each group

Based on the results of previous clinical trials that evaluated the effects of educational intervention on type 2 diabetes patients (reference 1,2), the geometric SD of change in HbA1c at the last observation period is assumed to be 0.7%. We estimate that at least 48 participants are required in each treatment group to confer a statistical power of 80% to detect a significant difference of 0.4% (4.4 mmol/mol) change from baseline in the two groups at the end of the intervention. We thus plan to recruit 50 participants per group (100 in total) in consideration of potential discontinuation or dropout of enrolled participants during the study period.

4. Samples:

A. Samples obtained from the human body

■ Do not use samples obtained from the human body

B. Information

■ Items collected from medical records

Laboratory data (HbA1c, fasting plasma glucose, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid, urinary albumin), height, body weight, body mass index (BMI), blood pressure, medication, past history, adverse events, history of diet therapy, and family history.

■ Others

DTSQ score and FGM-sensor-derived glucose variability measures.

Period: From approval date to March 31, 2021

Storage place: Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine

New medical information or existing medical information: we collected new medical information and existing medical information (most recent laboratory data at the start of the study).

<Study period>

From approval date to March 31, 2022

<Method>

1. Study design:

   Randomized prospective clinical trial (multicenter collaborative study)

2. Role of Nagoya University:

   Researchers at Nagoya University will lead the research by collecting and analyzing patient information of each hospital.

3. Method:

Participants who qualify according to the above criteria and who visit one of the five participating hospitals are eligible for recruitment. After obtaining the consent of the participants, the researcher enters the information required for enrollment in a web-based registration system developed by the Department of Advanced Medicine at the Nagoya University Hospital. The system automatically determines the eligibility of each participant and randomly assign him/her in a 1:1 ratio to the FGM or SMBG group with a dynamic allocation strategy using a minimization method. Stratification criteria includes the hospital that the patient visited, sex, age (>60 or ≤60 years), body mass index (BMI; >25 kg/m^2 or ≤25 kg/m^2), and the use or nonuse of oral hypoglycemic agents. The participants, investigators, and study staff are not masked to group allocation.

All participants wear a sensor (Free Style Libre Pro®; Abbott Diabetes Care, Alameda, CA, USA) for a baseline period of >7 days; the sensor glucose measurements obtained during this period are blinded (not visible) to the participants and investigators.

Person in charge of registration assignment

Masahiko Ando

Center for Advanced Medicine and Clinical Research, Nagoya University Hospital

Telephone: 052-744-1957

FGM group

Participants in the FGM group will be provided an FGM device (Free Style Libre®; Abbott Diabetes Care, Alameda, CA, USA). FGM can continuously measure the glucose level in the interstitial fluid via a sensor worn on the back of the upper arm for two weeks. FGM does not require fingerstick for each measurement or calibration with fingerstick blood glucose measurements. The devices will be provided for 12 weeks.

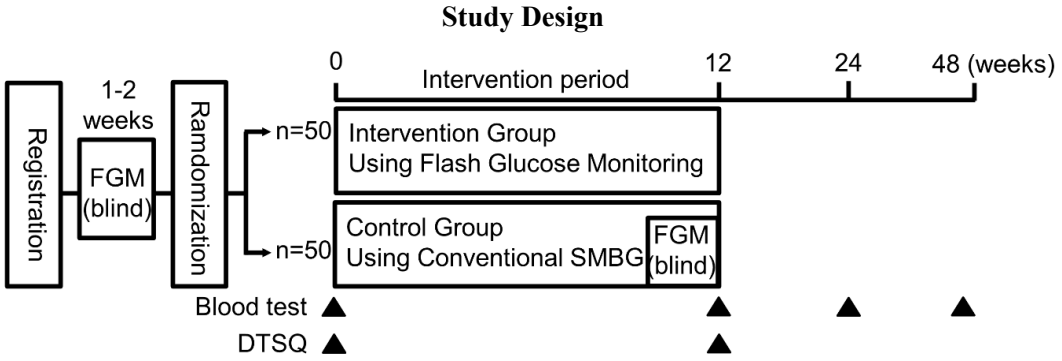
SMBG group

Participants in the SMBG group will be provided an SMBG device (Free Style Precision Neo®; Abbott Diabetes Care, Alameda, CA, USA). Patients will be provided sensors and puncture

needles to enable measurement of blood glucose three times a day. The devices will be provided for 12 weeks. Participants in the SMBG group will wear a blinded sensor (Free Style Libre Pro®) again for the last 2 weeks of the devices provision period.

Participants in each group will be instructed on how to use each device and how to adjust their diet and lifestyle based on the blood glucose levels. The target value of fasting and postprandial blood glucose level is set at <130 and <180 mg/dL.

In both groups, laboratory data in fasting condition, weight, blood pressure, and antidiabetic drug changes will be collected at enrollment and at 12, 24, and 48 weeks. The Diabetes Treatment Satisfaction Questionnaire (DTSQ) is a questionnaire used to assess patient satisfaction with diabetes treatment, and the Japanese version of DTSQ will be answered anonymously at enrollment and 12 weeks.
Researchers at the Nagoya University will collect and analyze patient data from each hospital.



4. Outcomes

A Primary outcome:

Changes in HbA1c levels (12, 24 weeks)

B Secondary outcomes:

Changes in HbA1c levels (48 weeks)

BMI, blood pressure (BP), fasting plasma glucose (FPG), triglyceride (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, uric acid (UA),

urinary albumin,

DTSQ score,

Change in antidiabetic drug

Sensor-derived glucose variability measures.

FGM and SMBG measurement frequency and measurement time

Adverse events

Relationship between glucose data obtained by FGM before intervention and patient background

5. Statistical analysis

Primary outcome:

The primary outcome, change in HbA1c, is compared using analysis of covariance (ANCOVA) model that includes baseline values and group as covariates. In case of significant between-group difference at 24 weeks, the changes in HbA1c at 12 weeks are compared in the same way. In addition, a linear mixed model, which includes baseline values, time, group, and interactions between time and group as fixed effects, is used to compare the change in HbA1c from baseline at 12 and 24 weeks between groups. Student's paired t test is used to compare changes in HbA1c between baseline and 12 or 24 weeks in each group.

Secondary outcomes:

Changes in HbA1c between baseline and 48 weeks are compared in the same way. A linear mixed model, which includes baseline values, time, group, and interactions between time and group as fixed effects, is used to compare the change in BMI, BP FPG, TG, HDL cholesterol, LDL cholesterol, UA, and urinary albumin from baseline at 12 and 24 weeks between groups. The amount of changes in both groups at each evaluation time-point is compared after correcting multiplicity using the Tukey–Kramer method. Changes in antidiabetic drugs are classified as increased dose, no change, or decreased dose, and analyzed using the Mantel-extension test stratified by sex, age (>60 or ≤60 years), BMI at entry (>25 or ≤25 kg/m^2), and the use or nonuse of oral hypoglycemic agents.

Relationship between the adverse events and their frequency and the frequency of treatment.
Changes in questionnaire responses are compared using ANCOVA model including baseline values and group as covariates. For the sensor data-derived secondary outcomes, the 120 hours after excluding the first 24 hours of the available recorded results are used. Sensor results of the FGM group are available from the final sensor wear. Sensor-derived glucose variability measures are compared between groups using ANCOVA model including baseline values and group as covariates. Glucose variability measures include SD of glucose, glucose coefficient of variation (CV), mean amplitude of glycemic excursions (MAGE), blood glucose risk index (BGRI), continuous overlapping net glycemic action (CONGA) 2h, and mean of daily difference (MODD).

The main analysis and the secondary analysis up to 24 weeks will be performed and reported when the data of the last registered case at 24 weeks are available. Sub-analysis after 48 weeks will be performed when all data are available.

Analyses will be conducted using two-sided tests at a significance level of 0.05.

<Research expenses>
Trust Accounts of Nagoya University
The funder of the study had no role in the study design, and will have no role in data collection, data analysis, data interpretation, or writing of the report.

<Joint research institute>
Department of Endocrinology, Department of Diabetes, Konan Kosei hospital
Department of Endocrinology and Diabetes, Japanese Red Cross Nagoya Daini Hospital
Department of Endocrinology and Diabetes, Saisyukan hospital
Department of Diabetes, Chunichi hospital

<Outsourcing>
No outsourcing.

IV Study site

Department of Diabetes and Endocrinology, Nagoya University Graduate School of Medicine

Department of Diabetes, Konan Kosei hospital

Department of Endocrinology and Diabetes, Japanese Red Cross Nagoya Daini Hospital

Department of Endocrinology and Diabetes, Saisyukan hospital

Department of Diabetes, Chunichi hospital

V Ethical considerations

V-1 <Informed Consent> Name of the presenter

Nagoya University Graduate School of Medicine, Department of Diabetes and Endocrinology

Hiroshi Arima

Ryoichi Banno

Hidetaka Suga

Motomitsu Goto

Shintaro Iwama

Yoshihiro Ito

Hiroshi Takagi

Taku Tsunekawa

Takeshi Onoue

Mariko Sugiyama

Yoshinori Yasuda

Kazuki Mitsumoto

Kaori Tsuru

Ayaka Hayase

Masaaki Ito

Tomoko Handa

Takashi Miyata

Akira Mizoguchi

Mayuko Kano

Tomoko Kobayashi

Norio Okada
Eri Wada
Mariko Furukawa

Department of Diabetes, Konan Kosei hospital
Yoh Ariyoshi
Department of Endocrinology and Diabetes, Japanese Red Cross Nagoya Daini Hospital
Akemi Inagaki
Department of Endocrinology and Diabetes, Saisyukan hospital
Koichi Mori
Department of Diabetes, Chunichi hospital
Kaori Hosokawa

Method of explanation
■ Use documents (Informed Consent Form [ICF]).
□ Make records of the consent.
□ Do not get consent.
The reason:

Storage place and storage method of ICF:
The collected ICFs will be stored under lock at a study office in Nagoya University.

Existence of information disclosure about research:
Do not disclose information.

Research that cannot be specified when consent is obtained
Although the information obtained for this study is not planned to be used for other studies at this time, it will be used after being approved by the Ethics Review Board.

V-2 <Handling of Personal Information>

1. Method of personal information protection:

We will assign a subject identification code to each patient, create a consolidated table, and make it connectable but anonymized. A personal information manager will keep this consolidated table under lock. The personal computer and HDD that will store the anonymized data will be secured with a password and kept locked separately from the consolidated table.

The information collected at the joint research institution is not taken out. Nagoya University receives only the data after anonymization, and the consolidated tables are stored at each medical institution.

2. Personal information of manager:

Name: Motomitsu Goto

Qualification: Doctor

Personal information of management assistant:

Name: Takeshi Onoue

Qualification: Doctor

V-3 <Withdrawal of Consent>

The ICF clearly states that withdrawal is always possible, and no disadvantages will be associated with it. If consent of the patient is withdrawn, the information will be discarded.

V-4 <Participants Who Are Juveniles or Adults without Sufficient Judgment>

■ The following persons are not eligible:

□ A Juveniles

□ B Adults without sufficient judgment

□ C Unconscious adult

□ D Adults who are not informed of the name of his/her disease

□ E other

V-5 <Disclosure of Analysis Results>

Individual results will be disclosed to the individual. The results obtained from the analysis will be

published as a paper in an academic journal or presented at an academic conference.

V-6 <In case of an urgent and obvious life crisis in the research subject>
Not applicable.

V-7 <Genetic information >
Genetic information is not included in the collected information.

V-8 <Reward and Allowance>
Not paid.

V-9 <Cost>
There is no self-payment for participating in the study.

VI Use of existing samples

VI-1 Use of existing samples ■Yes □ No
■ Items collected from medical records
Sex, age, height, body weight, blood pressure, medication, past history, adverse events, history of diet therapy, family history, and laboratory data (HbA1c, fasting plasma glucose, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, AST, ALT, uric acid, urinary albumin).

VI-2 Samples obtained from the human body
■ Do not use samples obtained from the human body

VI-3 Information
1 Consent for use
□ Acquired.
■ I have not obtained in the past, but get new consent.

□ I have not acquired it in the past, and I do not get new consent.

2 Anonymization
□ Non-linkable anonymization ■ Linkable anonymization □ No anonymization.

3 If you do not obtain consent and do not anonymize connection
□ Make research information public.
□ Ensures the opportunity for the sample provider to refuse.

IV-4 Provision of samples from outside the organization
Yes

IV-5 Provision of samples outside the organization
No

VII Expected research results or expected benefits

Expected research results:
In the intervention group, participants can easily measure continuous blood glucose changes at any time, and know the effects of diet and exercise on their blood glucose levels. As a result, FGM is expected to induce behavioral changes that lead to continued diet and exercise therapy.

Expected benefits for patients:
Participants are provided with FGM or conventional SMBG device. Participants in both groups will be able to measure their blood glucose levels, and know the effects of diet and exercise on their blood glucose levels.

VIII Predicted risks and disadvantages

VIII-1 <Considerations for Potential Risks and Disadvantages in Patients>
In the intervention group, in which “Freestyle libre” FGM device is provided, participants need to keep wearing the glucose sensor on the upper arm for 2 weeks, which may be accompanied by

physical pain and/or pruritus. In addition, the effect of X-rays, computed tomography scans, and magnetic resonance imaging on the performance of the System has not been evaluated. For this reason, the participant is informed in advance that it is necessary to remove the attached sensor before any such examination inspections and to apply a new sensor after completion of the examination.

In the control group, in which the SMBG device is provided, participants may experience physical pain due to finger-prick. SMBG is practiced as a standard approach for management of patients with type 1 and type 2 diabetes using insulin and is not a risk factor.

If treatment is necessary due to the above events, the patient is treated with health insurance.
Participants in both groups will be fully informed of how to use the device and how to deal with troubles at the beginning.

VIII-2 <Compensation and Response when Adverse Events Occur in Patients>

1. Type of study

■ Interventional studies using drugs or medical devices

2. Types of compensation

□ Insurance for compensation.
□ Insurance for compensation (planned).
□ Take measures other than insurance.
■ Explain that there is no compensation.

3. Measures

If treatment is necessary due to the above events, the patient is treated with health insurance.
We describe compensation in the ICF.

4. Response to adverse events

In case of any adverse events, the patients will be properly treated. If consent of the patient is

withdrawn, their information is discarded.

5. In the case of research involving medical practices beyond standard medical care, measures for medical care to participants

The use of FGM and SMBG is beyond the scope of health insurance, although it is within the intended use of the products. For this reason, if treatment is necessary due to adverse events, the patient is treated with health insurance.

IX Handling of samples after research

■ Save

A) Name of sample: Glucose level data from FGM and SMBG.
B) Sample storage location: Department of Endocrinology and Diabetes, Nagoya University, Graduate School of Medicine.
C) Sample management personnel: Nagoya University Hospital, Department of Endocrinology and Diabetes/Hospital Lecturer/Motomitsu Goto.
D) Content of consent obtained from subjects: There is a possibility of using data for research other than this research.
E) Storage period: 5 years.
   Disposal method after the storage period ends: Electromagnetic data should be deleted appropriately, and paper materials will be destroyed after shredding.
F) Usage: Data analysis.

Anonymization method (If "Discard" is selected, delete it.)

■ Connectable anonymization (Reason: It is assumed that the research participant information can be traced back in the case of retrospective data analysis.)

□ Anonymization that cannot be consolidated

Presence or absence of donation to the bank

None

X Monitoring and audit

1 Monitoring

■ Do □ Do not

Monitoring person:

Shintaro Iwama, M.D., Ph.D.

Nagoya University Hospital, Department of Diabetes and Endocrinology

Frequency and implementation method of monitoring:

Monitoring will be conducted to confirm that the study is being conducted safely and in accordance with the study protocol. The person in charge will directly examine the consent form and case reports sent to the research office and will investigate the following monitoring items.

<Monitoring items>

1) Number of registered cases

2) Eligibility of registered cases

3) Reporting of serious adverse events

4) Significant deviation from the study protocol

5) Other problems related to study progress, safety, and reliability

6) Compliance with ethical guidelines

Monitoring will be conducted at the start of the study, twice a year during the study period, and at the end of the study.

2. audit

□ Yes ■ No

XI Conflict of interest

None

There is no funding source for this study.

XII Responding to consultations from research participants

The following is the contact address.

Motomitsu Goto (phone 052-744-2187, fax 052-744-2212)

If you have any questions about the research or any related questions or concerns, please consult the above doctor.

In addition, the following will be accepted for complaints.

Nagoya University School of Medicine Management Planning Section: (052-744-2479)

XIII Remarks

History of important protocol changes:

- Adverse events were added as secondary outcomes. (ver. 2: August 10, 2017)
- This study was aimed to evaluate the effect of glucose measurement devices on lifestyle modification, and it is important to assess glycemic control after cessation of glucose monitoring. Therefore, the primary outcome was changed from HbA1c at 12 weeks to HbA1c at 12 and 24 weeks. (ver. 7: November 9, 2018)

All changes were made before the dataset was finalized or analyzed.

XIV References

1) Arambepola C1, Ricci-Cabello I, Manikavasagam P, Roberts N, French DP, Farmer A. The Impact of Automated Brief Messages Promoting Lifestyle Changes Delivered Via Mobile Devices to People with Type 2 Diabetes: A Systematic Literature Review and Meta-Analysis of Controlled Trials. J Med Internet Res. 2016 Apr 19;18(4):e86
2) Orsama AL, Lähteenmäki J, Harno K, Kulju M, Wintergerst E, Schachner H, et al. Active assistance technology reduces glycosylated hemoglobin and weight in individuals with type 2 diabetes: results of a theory-based randomized trial. Diabetes Technol Ther 2013 Aug;15(8):662-669.