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STUDY PROTOCOL

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Prevention of Worsening Diabetes through Behavioral Changes by an IoT-based Self-Monitoring System in Japan (PRISM-J): Study design and rationale for a multicenter, open-label, randomized parallel-group trial

Ryotaro Bouchi[1,2], Kazuo Izumi[3], Hiroshi Ohtsu[4], Kengo Miyo[5], Shigeho Tanaka[6,7], Noriko Satoh-Asahara[8], Kazuo Hara[9], Masato Odawara[10], Yoshiki Kusunoki[11], Hidenori Koyama[11], Takeshi Onoue[12], Hiroshi Arima[12], Kazuyo Tsushita[6,13], Hirotaka Watada[14], Takashi Kadowaki[15], Kohjiro Ueki[2,16,*]

[1] Diabetes and Metabolism Information Center, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Department of Diabetes and Endocrinology and Metabolism, Center Hospital, National Center for Global Health and Medicine, Tokyo, Japan;
[3] Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan;
[4] Department of Clinical Study and Informatics, Clinical Epidemiology Section/JCRAC Data Center, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan;
[5] Center for Medical Informatics Intelligence, National Center for Global Health and Medicine, Tokyo, Japan;
[6] Faculty of Nutrition, Kagawa Nutrition University, Saitama, Japan;
[7] Department of Nutrition and Metabolism, National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition, Tokyo, Japan;
[8] Department of Endocrinology, Metabolism, and Hypertension Research, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto, Japan;
[9] Department of Endocrinology and Metabolism, Saitama Medical Center, Jichi Medical University, Saitama, Japan;
[10] Department of Diabetology, Metabolism, and Endocrinology, Tokyo Medical University Hospital, Tokyo, Japan;
[11] Department of Diabetes, Endocrinology and Clinical Immunology, Hyogo College of Medicine, Hyogo, Japan;
[12] Departments of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya, Japan;
[13] Comprehensive Health Science Center, Aichi Health Promotion Foundation, Higashiura-cho, Aichi, Japan;
[14] Department of Metabolism and Endocrinology, Juntendo University Graduate School of Medicine, Tokyo, Japan;
[15] Toranomon Hospital, Tokyo, Japan;
[16] Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: The use of the Internet-of-Things has improved glycemic control in individuals with diabetes in several small-scale studies with a short follow-up period. This large-scale randomized controlled trial investigates whether a smartphone-based self-management support system prevents the worsening of glycemic control in individuals with type 2 diabetes. Individuals with type 2 diabetes (age range 20-74 years; n = 2,000) will be recruited, enrolled, and randomly assigned to two groups: the intensive therapy group and the conventional therapy group. Participants in the intensive therapy group will be supervised to use an automated Internet-of-Things system that demonstrates a summary of lifelogging data (*e.g.*, weight, blood pressure, and daily activities) obtained from each measurement device and will receive feedback messages *via* smartphone applications to encourage them to increase their physical activity and to monitor weight and blood pressure. Participants in the conventional therapy group are allowed to use the same measurement devices as part of the routine diabetes care but without the Internet-of-Things system. The primary endpoint is the between-group difference in HbA1c levels from baseline to 52 weeks. This randomized controlled study will test the hypothesis that an Internet-of-Things-based self-monitoring system could effectively prevent the worsening of diabetes in individuals with type 2 diabetes. The expected results of the study should facilitate the development of novel strategies for both diabetes treatment and social health.

***Keywords*:** behaviour modification, application, glycemic control, type 2 diabetes

Introduction

Individuals with diabetes who have inadequate glycemic control develop diabetes-related microvascular complications, including retinopathy and nephropathy, and have a 2- to 3-fold increased risk of incident cardiovascular disease (CVD) (*1,2*). Early detection of diabetes and its complications and ensuring adequate

glycemic, blood pressure, and lipid control by using pharmacotherapy is necessary to reduce the risk of both micro- and macrovascular diabetes-related complications (*3-6*). Moreover, regular medical check-ups are effective for diabetes prevention and to prevent or delay the worsening of diabetes-related complications. In Japan, healthcare activities for "specific medical check-up" and "specific health guidance" have been carried out since April 2008 (*7*). Specific health check-ups are available to people aged 40-74 years, and specific healthcare guidance is provided to those with increased abdominal circumference, blood glucose, blood pressure, and lipid levels. However, approximately 50% have never availed specific medical check-ups because individuals with early-stage non-communicable diseases, such as type 2 diabetes, are mostly asymptomatic. People who were newly diagnosed with diabetes during a medical check-up had a low persistence rate for regular visits for diabetes management (*8*). Accordingly, hurdles persist for the early detection of and initiation of interventions for diabetes; thus, novel strategies are necessary to overcome these challenges.

Behavioral change plays an important role in the efficacy of diabetes treatment and patient education. Meta-analyses of type 2 diabetes found that psychological interventions significantly improve glycemic control (*9*). Telephonic or web-based counselling and education by medical staff are effective for diabetes management (*10,11*). Multifaceted behavioral interventions, including lifestyle advice by telephone, can significantly reduce the dropout rate for regular visits and improve the quality of diabetes care in people with type 2 diabetes in primary-care settings (*12*). However, evidence-based lifestyle interventions are expensive and require extensive use of human resources (*13*). Therefore, an effective and low-cost self-management tool needs to be developed. With the technological advent of the Internet-of-Things (IoT), several studies have shown that IoT-based activation of self-monitoring can accelerate behavioral changes and improve glycemic control in people with diabetes (*14-19*). Given the limitations of small study samples or short follow-up period in these studies, their preliminary results need to be validated in larger randomized controlled trials (RCTs) with long follow-up durations. Therefore, this large-scale randomized controlled trial will investigate whether a smartphone-based self-management support system prevents the worsening of glycemic control in individuals with type 2 diabetes.

Methods

Study design

The Prevention of Worsening Diabetes through Behavioral Changes by an IoT-based Self-Monitoring System in Japan (PRISM-J) is a multicenter, open-label, parallel-group, RCT to investigate whether both behavioral changes and glycemic control could be improved by interventions *via* messages that are automatically generated from health-related information obtained from wearable devices in people with type 2 diabetes.

Organization and funding

This study is supported by the Japan Agency for Medical Research and Development (AMED), Research Program for Health Behavior Modification by using IoT during fiscal years 2017-2019.

Eligibility

The PRISM-J inclusion and exclusion criteria are presented in Table S1 (*https://www.ghmopen.com/site/supplementaldata.html?ID=22*). We initially planned to include patients who were receiving up to two oral antidiabetic agents; however, in April 2018, we modified the protocol to promote the recruitment of patients who were being treated with up to three oral antidiabetic agents. Patients who were treated with insulin or glucagon-like peptide-1 agonist were excluded in this study.

Screening and enrolment

Screening was performed through: *i*) regular medical check-ups provided by health insurance societies (Table S2, *https://www.ghmopen.com/site/supplementaldata.html?ID=22*) and *ii*) chart review of medical records of outpatients who regularly visited the participating hospitals/clinics of PRISM-J (Table S3, *https://www.ghmopen.com/site/supplementaldata.html?ID=22*). Eligible participants were recruited from January 1, 2018 to December 31, 2018.

Participation model for collaborators

This study comprises two participation models (Figure 1). One is a "Hospital registration group" wherein physicians in each hospital/clinic recruit candidates; obtain informed consent for study participation; register, allocate and educate the participants on diabetes management and IoT devices; and follow-up with them during the entire study period. The other model is an "On-site registration group" that research staff at National Center for Global Health and Medicine (NCGM) host for the orientation for participants who are introduced through collaborators, including health insurance societies (Table S2, *https://www.ghmopen.com/site/supplementaldata.html?ID=22*) and hospitals/clinics (Table S3, *https://www.ghmopen.com/site/supplementaldata.html?ID=22*); the staff also obtain informed consent and register, allocate, and

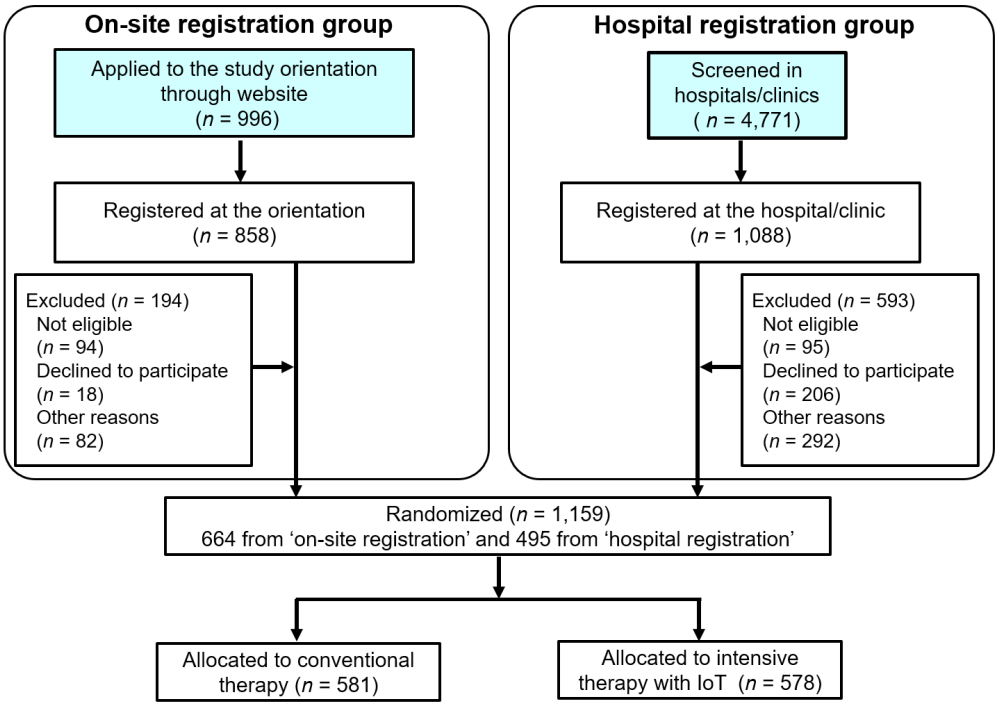

Figure 1. Flowchart of study processes and participant disposition.

educate participants on diabetes management and IoT devices. Thereafter, the participating medical institutions will follow up on the participants. For participants who were newly diagnosed with type 2 diabetes and did not have a primary care physician, PRISM-J indicated medical institutions where they could be introduced (Table S3, *https://www.ghmopen.com/site/supplementaldata.html?ID=22*).

Informed consent, registration, and random allocation

All participants provided written informed consent before participation. Participants were randomized to either the conventional therapy group (CTG) or the IoT group (ITG) with an allocation ratio of 1:1 using a stratified blocked randomization (block size set to 10) based on age (≥ 50 or < 50 years), sex (male/female), body mass index (BMI; ≥ 25 or < 25 kg/m^2) and glycated hemoglobin (HbA1c; ≥ 8.0 [64 mmol/mol], < 8.0%). Based on the eligibility information, registration forms were sent on website or faxed to the Data Center (JCRAC Data Center of NCGM, Tokyo, Japan) for registration and randomization. The registration codes and the assigned treatment groups were emailed or faxed to the attending medical staff on the same day.

Interventions

All participants were lent free IoT devices, including a weight and body composition monitor (HBF-255T, Omron Healthcare, Kyoto, Japan), blood pressure monitor (HEM-7271T, Omron Healthcare, Kyoto, Japan) and activity monitor (HJA-405T, Omron Healthcare, Kyoto, Japan). This activity monitor has been proven to provide valid estimation of total and physical activity-related energy expenditure (*20*). All devices could transmit measurement data over a wireless network to a cloud server *via* a Bluetooth connection (Figure S1, *https://www.ghmopen.com/site/supplementaldata.html?ID=22*). Participants were instructed to measure weight once a day at approximately the same time. Home blood pressure was measured according to the Japanese Society of Hypertension guidelines for the management of hypertension 2014 (*21*). Participants were instructed to wear the activity monitor from the time they woke up until they went to bed every day for the assessment of daily physical activity. In both groups, participants are treated in accordance with the "Treatment Guide for Diabetes 2016-2017" edited by the Japan Diabetes Society (JDS) (*22*), and physicians were, at their discretion, allowed to select and adjust the medications for diabetes, hypertension, and dyslipidemia for the optimal control of these diseases. Investigators recommended practical ways to reduce or maintain weight with careful consideration of the participants' lifestyles and physical activity.

After randomization, participants in the ITG download the "Omron connect App", which allows them to transfer measurements to their smartphone. Data are displayed in clear and insightful graphs that can help participants see their health trends. In addition to the "Omron connect App", participants in the ITG download the "*Shichifukujin*" application (SFJA),

which has been described elsewhere (*23*). *Shichifukujin* means "The Seven Deities of Good Luck" (Figure S1, *https://www.ghmopen.com/site/supplementaldata.html?ID=22*); each god has a specific role for the patient's self-monitoring and gives feedback messages for lifestyle modification to the patient twice a week based on data obtained from the "Omron connect App". All the ITG participants are provided printed support materials that describe the use of both applications. Every four weeks, participants in the ITG received summary messages, including the number of days that the participants used the devices and the changes and means of weight, blood pressure, and physical activity. The SFJA automatically sends reminder messages when the participants do not access the SFJA or they do not use the devices for 3 and 7 consecutive days (Table S4, *https://www.ghmopen.com/site/supplementaldata.html?ID=22*). These messages are generated automatically, according to the 'Treatment Guide for Diabetes 2016-2017' edited by the JDS (*22*), "JSH Guideline for the Management of Hypertension 2014" (*21*), 'Treatment Guideline for Obesity Disease 2016' edited by the Japan Society for the Study of Obesity (*24*), the Exercise and Physical Activity Reference for Health Promotion 2013 (*25*), and the Japanese official physical activity guidelines for health promotion (*26*). Primary care physicians can access patient data *via* the *Shichifukujin* cloud that regularly connects to the device database (Omron Cloud); check/confirm the summary of the measurement data, graphs and lifestyle habits; and use them appropriately as supportive data/documents for medical treatment and guidance based on the participant's lifelogging records (Figure S1, *https://www.ghmopen.com/site/supplementaldata.html?ID=22*).

Observation and evaluation schedule

The data collection schedule is summarized in Table 1 and Figure S2 (*https://www.ghmopen.com/site/supplementaldata.html?ID=22*). Participants regularly visited their outpatient clinic at least once every 12 weeks. At 52 weeks or later, participants in the ITG continue to use the IoT system until the end of the study whereas participants in the CTG receive education and instructions related to IoT, similar to that in the ITG, and the period during which IoT can be used will be specified as a maximum of 52 weeks before study termination (until December 31, 2019). Therefore, the maximum study participation period of the study participants is presumed to be 104 weeks (~2 years).

The lifestyle questionnaire included medical history, family history, and behavioral modification stages related to diet and exercise (Table S5, *https://www.ghmopen.com/site/supplementaldata.html?ID=22*). Treatment satisfaction and quality of life (QOL) were assessed using the Diabetes Therapy-Related QOL (DTR-QOL) (*27*). Food intake was estimated using a Brief-type Self-administered Diet History Questionnaire (BDHQ) that was developed for the assessment of Japanese diets (*28*). Information obtained *via* connected devices are listed in Table 2.

The method used for providing data in this study is unique in that participants take pictures of laboratory data and of the forms of their weight and blood pressure measurements, which are measured at clinics/hospitals and of prescription information, and upload them to a portal site. After anonymization, data are sent to the Data Center. To promote participant retention and complete follow-up, the Research Support Center will contact

Table 1. Schedule of data collection

	Baseline	12 weeks	24 weeks	36 weeks	52 weeks	Study end
Physical examination						
Height	○					
Weight	○	○	○	○	○	○
Blood pressure	○	○	○	○	○	○
Laboratory examination						
HbA1c	○	○	○	○	○	○
Glucose	○	○	○	○	○	○
Total cholesterol	○	○	○	○	○	○
HDLC	○	○	○	○	○	○
ALT	○	○	○	○	○	○
Creatinine	○	○	○	○	○	○
Urinary protein	○	○	○	○	○	○
Health assessment questionnaire						
Lifestyle questionnaire	○	○	○	○	○	○
DTR-QOL	○		○		○	○
BDHQ	○				○	
Information on medication	○	○	○	○	○	○

ALT, alanine transaminase; BDHQ, Brief-type Self-administered Diet History Questionnaire; DTR-QOL, diabetes therapy-related quality of life; HDLC, high-density lipoprotein cholesterol.

Table 2. Information obtained *via* connected devices

Weight and body composition monitor (HBF-255T)
Weight
Body fat percent level
Percent body fat
Basal metabolic rate
Body mass index
Physical age
Visceral fat level
Impedance
Fat-free mass
Blood pressure monitor (HEM-7271T)
Systolic blood pressure
Diastolic blood pressure
Pulse
Posture
Room temperature
Flag related to irregular pulse wave
Flag related to the detection of body motion
Frequency of artefact detection
Frequency of irregular pulse wave detection
Activity monitor (HJA-405T)
Steps
Exercise steps
Brisk steps
Stair steps
Calories related to activity
Calories related to moderate- to high-strength activity
Total calorie consumption
Calories related to walking
Distance
Fitting flag
Unrecorded flag
Fat combustion amount
Exercise amount
Exercise (walking) amount
Basal metabolic rate
Sedentary time
Activity time related to low-intensity exercise
Activity time related to moderate-intensity exercise
Activity time related to high-intensity exercise

participants by email or phone if they do not send the data.

Outcomes

The study endpoints are shown in Table 3.

Sample size

In this study, the difference between the effects of HbA1c was set at 0.2, assuming a 1-year intervention throughout Japan. Furthermore, it is assumed that the variations of other data would be widened. Due to the study design, participants are expected to be recruited from both primary-care settings and clinics/hospitals specializing in diabetes care. To estimate the SD of HbA1c in patients with type 2 diabetes in clinics/hospitals specializing in diabetes care in Japan, we calculated the SD of people with type 2 diabetes who were enrolled in the Japan Diabetes CompREhensive database project based on an Advanced Electronic Medical record System (J-DREAMS) (*29*), met the inclusion criteria of this study and whose HbA1c values were available in 2017. The HbA1c was 7.05 ± 0.67% in 8,416 people with type 2 diabetes (unpublished data). Most patients in the registry are enrolled from facilities designated by the JDS as educational facilities; thus, the data are considered representative of patients in clinics/hospitals specializing in diabetes care in Japan. Therefore, we initially estimated SD of HbA1c as 0.6, but it was finally confirmed as 1.2 because of the multicenter study design and evidence that HbA1c levels were 7.4 ± 1.2% in 2,199 Japanese patients with type 2 diabetes in primary care (*30*). Based on these facts, when the power was set to 0.8 or 0.9, the required number of cases was calculated to be 567 or 758, respectively (SAS Ver 9.4 [SAS Institute Inc., Cary, NC, USA]) in this study to prevent loss. As the dropout rate is assumed to be 20%, 680 to 910 people are required in each group. Therefore, the total number of patients in each group was 1,000. To recruit a sufficient number of participants, we extended the registration period from 6 to 9 months in February 2018 and, subsequently, to 12 months in September 2018.

Safety

Serious adverse events (SAEs) include those that: *i*) result in death, *ii*) are life-threatening, *iii*) require inpatient hospitalization or prolongation of existing hospitalization, *iv*) result in persistent or significant disability or incapacity, or *v*) cause a congenital anomaly or birth defect in the offspring. Serious hypoglycemia, defined as hypoglycemia necessitating someone else's assistance and/or hospitalization, was included as an SAE in this study. The safety assessment committee oversees the evolving safety profile by reviewing cumulative SAEs.

Discontinuance and dropout

The criteria for discontinuance in this study were: *i*) refusal to participate in the study, *ii*) participants were judged as unsuitable for the study participation by physicians, *iii*) treatment continuation would be difficult due to the worsening of diabetes and its complications or other adverse events, *iv*) pregnancy confirmation, *v*) aborting of the study, and *vi*) investigators determine that the discontinuance of the study is appropriate for reasons other than those mentioned above. Even in the case of discontinuance, a patient who consented to participate can be followed up until the end of the study. Dropout in this study was defined as participants with whom the study team had lost contact or those who had revoked consent during the follow-up after discontinuing the study.

Ethical principles

This study is to be conducted in accordance with the

Table 3. Study endpoints

Primary endpoint
- Intergroup differences in HbA1c levels from baseline to 52 weeks

Secondary endpoints
- Intergroup differences in HbA1c levels from baseline to 12, 24, and 36 weeks and the end of the study
- Intergroup differences in plasma glucose, total cholesterol, HDLC, ALT, creatinine, weight, systolic and diastolic blood pressures, and total number of antidiabetic agents for the following 12, 24, 36, and 52 weeks from the baseline.
- Intragroup changes in scores obtained from the BDHQ from baseline to 52 weeks and the DTR-QOL from baseline to 24 and 52 weeks and the end of the study

Explanatory endpoints
- Self-measurement (sphygmomanometer, scale and activity monitor)
  The transition from the start date is illustrated for each group.
  Information from the day closest to 12, 24, 36, and 52 weeks from the start of the study is extracted, and repeated-measures analysis of variance is performed.
- Stages in dietary and exercise-related behavioral change
  Create a contingency table for each time point and repeat the entire test for intergroup comparison. Comparison between time points is performed for reference.
- Prescription information
  Total number of prescriptions at each time (except for oral antidiabetic agents)

ALT, alanine transaminase; BDHQ, Brief-type Self-administered Diet History Questionnaire; DTR-QOL, diabetes therapy-related quality of life; HDLC, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin.

principles of Declaration of Helsinki, as well as the "Ethical Guidelines for the Conduct of Clinical Studies" and the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" both of which are established by the Ministry of Health, Labour and Welfare in Japan. This study was approved by the Ethical Committee of NCGM (NCGM-G-002373) and by the Institutional Review Board/Ethics Committee at each study site in a hospital registration group and in the facilities of the executive committee members (Table S6, *https://www.ghmopen.com/site/supplementaldata.html?ID=22*). Primary care physicians who intend to access the administrator section in the SFJA would need to be ethically reviewed. Following approval by the ethical committee, the protocol of this study and its revisions are to be reviewed and approved by the ethics committee of each institution for their feasibility as well as their ethical and scientific validity. For collaborators who do not have a local Institutional Review Board/Ethics Committee, the ethical committee of the NCGM assumes ethical review. This study was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) before the first participant was enrolled (UMIN 000030823).

Data management

Data obtained from the weight and body composition, blood pressure, and activity monitors were captured electronically and stored on a server. Laboratory and QOL data were reported through the patient portal or through the healthcare institutions. The JCRAC Data Center oversees data management.

Statistical analyses

All analyses will be based on an intention-to-treat principal and will be performed with two-sided *P*-values which are considered significant when they are below 0.05. For the missing values, there are no plans at this time to supplement them with the last observation carried forward method or with other methods. Furthermore, given the difficulty in defining non-compliance with this study's protocol, a per-protocol analysis will be performed to check the agreement of the analysis. For a detailed analysis, the statistician will make a statistical analysis plan before the data lock, as indicated below:

i) Primary endpoint:

• Difference in HbA1c levels from baseline to 52 weeks

Calculate the difference 1 year after the baseline and compare the two groups.

ii) Secondary endpoint:

• HbA1c, plasma casual glucose, total cholesterol, high-density lipoprotein cholesterol, alanine transaminase, and creatinine levels; weight; systolic and diastolic blood pressures; and total number of antidiabetic agents

Repeated data for the 12, 24, 36, and 52 weeks from the baseline for between-group comparisons (except for HbA1c levels at 52 weeks).

• BDHQ

Analyse the change for each subgroup based on the values surveyed at baseline and at 52 weeks.

• DTR-QOL

We analysed the change for each subgroup based on the values surveyed at baseline, at 24 and 52 weeks and at the end of the study.

iii) Planned other analyses

• Self-measurement (sphygmomanometer, scale, activity monitor)

The transition from the start date is illustrated for each group.

• Blood pressure and weight

Information from the day closest to 12, 24, 36, and 52 weeks from the study initiation was extracted, and a repeated-measures analysis of variance was performed.

• The dietary and exercise-related behavioral change stages

Create a contingency table for each time point and repeat the entire test to ascertain the between-group differences. Moreover, a comparison between time points is performed for reference.

• Prescription information

The total number of prescriptions at each time (except for antidiabetic agents).

iv) Safety

Based on the adverse event surveys conducted individually, the reported cases are added using the reported cases as the denominator. The chi-squared test is performed because it depends on the report, but it is used as a reference value.

For SAEs (*e.g.*, death, hospitalization), events reported individually to the secretariat are to be tabulated.

The PRISM-J clinical investigators are not allowed to access data on outcome measurements until the end of this study, when the primary endpoint data analysis is completed.

History of modifications of the protocol

Modifications in the protocol, including those on the inclusion criteria and registration period, have been approved by the Ethical Committee of NCGM as stated earlier.

Discussion

We have presented the study design of and rationale for the PRISM-J study. This is the first large-scale RCT to investigate the efficacy of an IoT-based self-monitoring system on behavioral changes and glycemic control in individuals with type 2 diabetes. This study aimed to obtain daily physical activity and behavioral changes, both in exercise and diet, over 1 year in more than 1,000 people with type 2 diabetes. We recognize that this study may face challenge in terms of participant adaption to the IoT system and retention for long term follow up, however, due to strengths in the large sample size, we will be able to descriptively determine the types of food and exercise behaviors that could be associated with the improvement of glycemic control, which could presumably lead to the development of customized exercise and diet therapies. We believe that the expected results of the PRISM-J trial will provide novel strategies for both diabetes treatment and social health.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

Additional Statement

Authors' contributions

RB designed the protocol, guided the study, enrolled participants, managed onsite registration, researched the data, and wrote the manuscript. KI designed the protocol, guided the study, and researched the data. HO designed the protocol, generated the allocation sequence, assigned participants to interventions, and guided the study as a biostatistician. KM guided the study as an expert of medical information. ST designed the protocol and guided the study as an expert in exercise physiology. NSA, KH, MO, YK, HK, TO, and HA guided the study, enrolled participants, and researched the data. KT designed the protocol, guided the study, and researched the data. HW and TK supervised the study. UK designed the protocol, guided the study, researched the data, and reviewed and edited the manuscript and, as the guarantor of this work, takes responsibility for the integrity of the data and the accuracy of the data analysis.

Steering Committee

Ryotaro Bouchi (National Center for Global Health and Medicine, Tokyo), Kazuo Izumi (National Center for Global Health and Medicine, Tokyo), Hiroshi Ohtsu

(National Center for Global Health and Medicine, Tokyo), Kengo Miyo (National Center for Global Health and Medicine, Tokyo) and Kohjiro Ueki* (National Center for Global Health and Medicine, Tokyo). *Principal investigator

Safety Assessment Committee
Hiroshi Sakura* (Tokyo Women's Medical University Medical Center East, Tokyo) *Chief

Data Center
Hiroshi Ohtsu* (JCRAC Data Center, Tokyo) *Chief
Koji Kitajima (JCRAC Data Center, Tokyo)

Statistical Team and Allocation
Hiroshi Ohtsu* (National Center for Global Health and Medicine, Tokyo) *Chief

Data Monitoring
Shinji Inagaki* (ACCERISE, Inc., Tokyo, Japan) *Chief

Audit
Natsue Matsumoto (ACCERISE, Inc., Tokyo, Japan), and Otoji Mori* (ACCERISE, Inc., Tokyo, Japan) *Chief
Auditing will be conducted at four sites, including Nagoya University, Hyogo Medical University, ACCERISE, and IBERICA, which are independent of the investigators and the sponsor.

Collaborators
The PRISM-J Study Group.

Ethics and Dissemination

Patient consent: Obtained prior to study participation.

Ethics approval: NCGM-G-002373-13.

Dissemination policy: The researchers plan to present their findings to the participants, healthcare professionals, the public, and other relevant groups *via* publications and conference presentations.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

Compliance with Ethical Standards: This study is to be conducted in accordance with the ethical standards of the responsible committee on human experimentation (Ethical Committee of NCGM/September 29, 2017/ NCGM-G-002373-13) and with the Helsinki Declaration of 1964 and later versions. No potential conflicts of interest relevant to this article were reported. Informed consent is to be obtained from all patients for being included in the study.

Trial registration number: University Hospital Medical Information Network Clinical Trials Registry (ref: UMIN000030823).

Protocol Version: Ver 13.0 (Approval date: July 10, 2020).

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**Address correspondence to*:
Kohjiro Ueki, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: uekik@ri.ncgm.go.jp