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Home telemonitoring study for Japanese patients with heart failure (HOMES-HF): protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction: Despite the encouraging results from several randomised controlled trials (RCTs) and meta-analyses, the ability of home telemonitoring for heart failure (HF) to improve patient outcomes remains controversial as a consequence of the two recent large-scale RCTs. However, it has been suggested that there is a subgroup of patients with HF who may benefit from telemonitoring. The aim of the present study was to investigate whether an HF management programme using telemonitoring could improve outcomes in patients with HF under the Japanese healthcare system.

Methods and analysis: The Home Telemonitoring Study for Japanese Patients with Heart Failure (HOMES-HF) study is a prospective, multicentre RCT to investigate the effectiveness of home telemonitoring on the primary composite endpoint of all-cause death and rehospitalisation due to worsening HF in recently admitted HF patients (aged 20 and older, New York Heart Association classes II–III). The telemonitoring system is an automated physiological monitoring system including body weight, blood pressure and pulse rate by full-time nurses 7 days a week. Additionally, the system was designed to make it a high priority to support patient's self-care instead of an early detection of HF decompensation. A total sample size of 420 patients is planned according to the Schoenfeld and Richter method. Eligible patients are randomly assigned via a website to either the telemonitoring group or the usual care group by using a minimisation method with biased-coin assignment balancing on age, left ventricular ejection fraction and a history of ischaemic heart disease. Participants will be enrolled until August 2013 and followed until August 2014. Time to events will be estimated using the Kaplan-Meier method, and HRs and 95% CIs will be calculated using the Cox proportional hazards models with stratification factors.

Trial Registration: The study is registered at UMIN Clinical Trials Registry (UMIN000006839).

ARTICLE SUMMARY

Article focus

- This study focuses on a role of the home telemonitoring system for patients with chronic heart failure (HF) to reduce hospital readmission under the Japanese healthcare system.

Key messages

- The ability of home telemonitoring for HF care to improve patient outcomes remains controversial. However, recent studies have suggested the existence of a subgroup of patients who might be able to benefit from the telemonitoring.
- The Home Telemonitoring Study for Japanese Patients with Heart Failure (HOMES-HF) study was specially designed for the participants and health-care professionals to maintain adherence to daily measurement of body weight and blood pressure, to enhance clinician–patient communication and to empower their self-management by introducing a concept based on the idea of patient-centered care into the telemonitoring system.

Strengths and limitations of this study

- The HOMES-HF study will be the first trial of home telemonitoring for Japanese patients with HF.
- Multidisciplinary HF management systems have been underdeveloped and there are still no practicable telemonitoring systems for HF management operated by either the public or private sector in Japan. Therefore, devices using the HOMES-HF study are not designed exclusively for HF management; rather, they are based on a commercial-based health-maintenance product and customised for the study.
- The responsibility for acting on the information from the telemonitoring centre rests with each patient's physician; therefore, treatment will vary with each physician and institute.

INTRODUCTION

Heart failure (HF) is one of the most common causes of hospital admission in developed countries. Hospital discharges of HF increased from 399 000 in 1979 to 1 099 000 in 2004 in the USA. Moreover, of the $33.2 billion in overall costs for HF care in 2007, $17.8 billion was spent on in-hospital care.[1] Available data for Japanese patients with HF indicate that approximately 70% of HF patients are older than 65 years of age and that about 35% of patients are readmitted for acute HF decompensation within 1 year of hospital discharge.[2–5] Owing to the rapid ageing of the population, there are growing concerns about the increased incidence and prevalence of HF, and the high readmission rates and medical costs of hospitalisation have become a growing burden on the healthcare system.

Multidisciplinary HF management programmes and home-based care might be able to reduce hospital readmissions due to worsening HF.[6–9] Telemonitoring has grown to have a place in the HF disease management programmes. Chaudhry *et al*[10] have expounded on the details of telemonitoring, categorising it into three groups with regard to the types of intervention, including telephone-based symptom monitoring, automated monitoring of signs and symptoms and automated physiological monitoring.

Recent meta-analyses and comprehensive reviews of several randomised controlled trials (RCTs) and cohort studies have shown that home telemonitoring as an adjunct to usual care reduces HF-related hospitalisations. In some trials, home telemonitoring has been found to reduce all-cause mortality and improve health-related quality of life.[10–14] In contrast, recently published, well-designed, large, prospective, multicentre RCTs have ended with disappointing results. In the Telemonitoring to Improve Heart Failure Outcomes (Tele-HF) trial, there were no significant differences between the automated monitoring of the signs and symptoms group and the usual care group with regard to the primary composite endpoint of all-cause readmission and death or the secondary endpoints including HF readmission.[15] Although there has been criticism concerning patient adherence in the Tele-HF study, the incidences of the primary endpoint of all-cause mortality and the secondary endpoints of the composite of cardiovascular death and HF hospitalisation did not differ between the automated physiological monitoring group and the usual care group in the Telemedical Interventional Monitoring in Heart Failure (TIM-HF) study; nevertheless, the patient adherence to the telemonitoring intervention was acceptable.[16] Therefore, the ability of home telemonitoring for HF care to improve patient outcomes remains controversial.[17 18] The prospectively defined subgroup analysis of the TIM-HF study, which attempted to identify patients who may potentially benefit from telemonitoring, showed that treatment was significantly effective in the subgroup of patients with a prior history of HF decompensation, implantable cardiac defibrillator/cardioverter (ICD) implants or Patient Health Questionnaire (PHQ-9) scores of <10 for outcome days lost due to HF hospitalisation or death.[19]

AIMS AND OBJECTIVES

In Japan, multidisciplinary HF management remains underdeveloped and there are few data regarding telemonitoring for HF management. Although Japan has a unique universal health insurance system, home telemonitoring for HF management has not been covered by the system except telemonitoring using implantable devices. Therefore, we aimed to investigate whether an HF management programme using a telemonitoring system consisting of automated physiological monitoring devices could reduce mortality and hospital readmission for acute decompensated HF among patients recently hospitalised for HF under the Japanese healthcare system.

Swedberg *et al*, in their correspondence to the authors of the Tele-HF study, suggested that patient-centred care (PCC) would increase the effectiveness of telemonitoring. They emphasised that telemonitoring needs to focus on patients' self-care instead of reporting data.[20 21] Therefore, we introduced the concept of PCC into the telemonitoring system used in the present study in order to motivate the patients assigned to the telemonitoring group to maintain adherence to daily measurement of body weight and blood pressure, to enhance clinician–patient communication and to empower patients in their self-management.

METHODS AND ANALYSIS

Study patients

Patients aged 20 or older with New York Heart Association functional classes II–III who are discharged or scheduled to be discharged following admission for acute HF or acute decompensated chronic HF within 30 days of enrolment into the study are eligible for this study (box 1). The exclusion criteria are as follows: patients with an implantable device (ie, pacemaker, ICD), because an alternating-current signal travels through the body when the patients measure their body weight and body fat using an electronic scale; patients undergoing dialysis or those with a serum creatine level ≥3.0 mg/dl; patients with severe liver dysfunction; patients with planned percutaneous coronary intervention or coronary artery bypass grafting; patients unable to stand on a scale safely; patients with a limited life

Box 1 Inclusion criteria

- Scheduled to discharge or discharged from an admission for acute heart failure (HF) or acute decompensated chronic HF within 30 days.
- Age ≥20 years.
- New York Heart Association functional classes II–III.

Box 2 Exclusion criteria

- Patients with an implantable device (ie, pacemaker, implantable cardioverter defibrillator), because an alternating-current signal travels through the body when the patients measure their body weight and body fat using an electronic scale.
- Undergoing dialysis or serum creatine level ≥3.0 mg/dl.
- Severe liver dysfunction.
- Planned percutaneous coronary intervention or coronary artery bypass grafting.
- Unable to stand on a scale safely.
- Limited life expectancy (malignancy or other cause).
- Severe depression (eg, Patient Health Questionnaire score ≥20).
- Severe dementia.
- Pregnancy.
- Without access to a telephone line.

expectancy due to malignancy or other cause; patients in whom severe depression is highly suspected (eg, PHQ-9≥20); patients with severe dementia; in pregnancy; and patients without access to a telephone line (box 2). Patients suspected of having mild-to-moderate depression (eg, PHQ score: 5–19) are recommended to receive adequate intervention from a psychiatrist or clinical psychologist.

Study design

The Home Telemonitoring Study for Japanese Patients with Heart Failure (HOMES-HF) is a multicentre, prospective RCT, funded by the Japanese Ministry of Health, Labor and Welfare (Clinical Trials registration number UMIN000006839; http://www.umin.ac.jp/ctr/index.htm) and conducted to compare automated physiological data monitoring with usual care. Written informed consent will be obtained by the patient's physician prior to discharge or within 30 days of hospital discharge after admission for acute HF or acute exacerbation of HF. Eligible patients are randomly assigned via a website to either the telemonitoring group or the usual care group by using a minimisation method with biased-coin assignment balancing on age (≥65 vs <65 years), left-ventricular ejection fraction (LVEF) (≥30% vs <30%), and having a history of ischaemic heart disease (IHD; IHD vs non-IHD). The patients and treating physicians are not masked to the treatments, while assessment of the outcome is masked. According to the study protocol, participants will be enrolled until August 2013 and followed until August 2014.

Endpoints

The primary endpoint is a composite of all-cause death and rehospitalisation due to worsening HF. The secondary endpoints are: all-cause death; cardiac death; all-cause rehospitalisation; rehospitalisation due to a cardiovascular cause; rehospitalisation due to worsening HF; worsening of symptoms; cost of medical care; worsening of LVEF or the levels of N-terminal pro B-type natriuretic peptide, high-sensitivity C reactive protein, pentraxin-3 (PTX3), high-sensitivity cardiac troponin T or high-molecular weight adiponectin; changes in the Mini Mental State Examination (MMSE) score, the General Self Efficacy Scale (GSES), the Minnesota Living With Heart Failure (MLWHF) score or the PHQ-9 score and adherence to medication.

Telemonitoring system

The telemonitoring system of the HOMES-HF study consists of an electronic scale, a sphygmomanometer and a device that receives acquired physiological data (blood pressure, pulse rate and body weight) wirelessly and transmits the data to the central web server via the internet. It is commercially available as a health-maintenance product (Karada Karte Tanita health-link Co. Ltd, Tokyo, Japan). These devices are distributed to the participants assigned to the telemonitoring group when they are discharged from the hospital. Patients' physicians encourage the participants assigned to the telemonitoring group, when they demonstrate how to use the monitoring devices after obtaining the informed consent, to measure their body weight and blood pressure by themselves at least once a day at approximately the same time in order to minimise daily variance caused by meals, micturition and bowel movement. The acquired physiological data are automatically transmitted to a central web server immediately after measurement. The telemonitoring centre was newly established at Saga University for the present study, and full-time nurses monitor the acquired data on the secure website 7 days a week (see online supplementary appendix 1). At first contact with the participant by telephone, the monitoring nurses establish communication connection between the monitoring devices and the central web server and arrange a time zone convenient to the participant for regular measuring. Before telemonitoring is started, the patient's physician determines an acceptable range of body weight, blood pressure and pulse rate for each patient and makes a declaration of these ranges to the telemonitoring centre. If the body weight, blood pressure or heart rate would exceed the acceptable range, the monitoring nurses serve a notice to the patient's physician. There are no restrictions on the ability of the patient's physician to perform any interventions in response to the notice, such as providing telephone guidance, changing or adding medications and ordering hospital readmission, with the exception that the physician must provide feedback regarding their interventions to the telemonitoing centre. The patient's physician assumes responsibility for acting on the information.

Introducing the concept of PCC into the telemonitoring system to encourage adherence in participants

After hospital discharge, the patients and their family, especially among elderly persons, have a tendency to be

socially isolated, and that makes it difficult to practice self-management. In order to motivate the patients assigned to the telemonitoring group to maintain adherence to daily measurement of their body weight and blood pressure, the concept of PCC was proactively introduced into the telemonitoring system for the HOMES-HF study. Enhanced clinician–patient communication, patient empowerment and self-management are the elements of PCC.[22 23] To this end, professionals (typically nurses, although sometimes the patients' physicians) provide advice and education to the patients assigned to the telemonitoring group and create a care plan until the next visit referring to the patients' electronic health records acquired by daily monitoring on the website using a tablet computer in collaboration with the patients at every visit of theirs to the outpatient clinic. According to the protocol, the patients' physicians or nurses have to report to the monitoring centre what they performed for the patient according to the notice from the monitoring nurses. Moreover, we designed the monitoring system to be accessible to the patients' family in order for them to watch over their parents, spouse, siblings or relatives. In this way, we intend to enable the patients to recognise that all healthcare professionals around them and their family are not only monitoring on the website, but also communicating with each other. We believe that these efforts may help reassure patients and their family, as well as encourage them to participate in decision-making on their own treatment by collaborating with healthcare professionals and improve adherence to medical treatment.

Usual care

Patients assigned to the usual care group are treated by their physician in accordance with the Japanese Circulation Society Guidelines for treatment of chronic HF 2010. Clinicians provide discharge education and encourage the patients to measure their body weight by themselves every day.

Sample size calculation

We assumed that the HR of the primary endpoint (all-cause death and hospitalisation for worsening HF) of the telemonitoring group to the control group would be 0.60 and that the cumulative annual event rate in the usual care group would be 0.30, based on the result of previous studies.[10 13] This trial is designed to have 80% power to detect a 40% relative reduction in the risk of the primary outcome in the telemonitoring group within 12 months, as compared with the control group, based on an expected death rate at 12 months of 30% in the control group using a log-rank test with a two-sided α of 0·05. A total sample size of 420 patients is planned according to the Schoenfeld and Richter method,[24] with a 2-year period for patient enrolment and a follow-up period of 1 year.

Statistical analysis

All statistical analyses will be independently performed at the Chiba University Hospital Clinical Research Center (see online supplementary appendix 2). The analyses of the adjudicated primary and secondary outcomes will be conducted using data for all patients who had undergone randomisation, according to the intention-to-treat principle. For the baseline variables, summary statistics will be constructed employing frequencies and proportions for categorical data and means and SD for continuous variables. The patient characteristics will be compared using Fisher's exact test for categorical outcomes and t tests for continuous variables, as appropriate. The primary endpoint of a composite of all-cause death and rehospitalisation for worsening HF will be analysed using the stratified log-rank test for eligible patients with age (≥65 vs <65 years), LVEF (≥30% vs <30%) and history of ischaemic heart disease (IHD vs non-IHD) as stratification factors. Time to events will be estimated using the Kaplan-Meier method, and HRs and 95% CIs will be calculated using the Cox proportional hazards models with stratification factors. Sensitivity analyses will also be performed by means of the unadjusted Cox models.

All comparisons are planned, and all p values will be two-sided. A p value of less than 0.05 will be considered to be statistically significant. All statistical analyses will be performed using SAS software V.9.3 (SAS Institute, Cary, North Carolina, USA).

Data collection schedule

At the time each patient is enrolled into the study, investigators at each local site (see online supplementary appendix 6) perform a baseline history and physical examination and conduct a survey of the baseline scores of three types of questionnaires (PHQ-9, MMSE and GSES). The outcomes are assessed at 6 and 12 months after enrolment into the study. Clinicians at each local site submit a report to the data centre at these time points to assess psychosocial status, self-care skills, quality of life and rehospitalisations. We will evaluate the cost-effectiveness of the telemonitoring interventions, incorporating the costs associated with hospitalisations, outpatient visits, emergency department visits and home care services.

Study management

Data on the primary and secondary endpoints and adverse events are collected when the events occur. All data are collected by the independent data management centre established for the present study at the Chiba University Hospital Clinical Research Center (see online supplementary appendix 2). There will be no direct communication between HOMES-HF investigators and the Coordinating Data Center. The clinical data entry (double data entry), cording, data management and reporting will be performed by a data management system, HITCANDIS/DM (HITachi Computer Assisted

New Drug Information System/Data Management for clinical trial, Hitachi, Ltd Tokyo, Japan). Trained coding specialists will code the clinical data using standard coding dictionaries including MedDRA for adverse events and medical history and considering WHO-DD for concomitant medications. All the data management processes are tracked electronically, allowing regular updates on patient status, data receipt including missing segments or pages, data entry and verification, data query status and protocol deviations. In order to ensure consistency, integrity and accuracy for this study, these processes are based on the standard operating procedures.

An independent endpoint committee (see online supplementary appendix 3) consisting of three members, who are blinded to any information relating to the group allocations, evaluates each event and classifies the results. An independent data and safety monitoring board (see online supplementary appendix 4) composed of three members reviews all reports from the endpoint committee to advise early termination of the study for safety, scientific or ethical reasons. A steering committee (see online supplementary appendix 5) is responsible for the study design and scientific execution of the study.

Laboratory measurements

The plasma PTX3 levels are measured with a sandwich ELISA kit (Perseus Proteomics Inc, Tokyo, Japan) based on a previously described method.[25] The plasma HMW-adiponectin levels are measured using a sandwich ELISA kit (Fujirebio, Tokyo, Japan) based on a monoclonal antibody to human HMW-adiponectin, IH7.[26]

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Competing interests All authors have completed the ICMJE form for disclosure of potential conflicts of interest at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that NK is currently an endowed chair from Fukuda Denshi Co., Ltd, which is a medical equipment manufacturer. The company has no relation to the monitoring equipment used in this study. All authors have no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval All participants will provide their written informed consent, and the study protocol has been approved by the institutional review board of Saga University and each participating site.

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AROとして活動開始した千葉大学医学部附属病院臨床試験部

Activity of Chiba University Clinical Research Center as the leading Japanese ARO

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◎千葉大学は2012年，臨床研究中核病院に指定された．AROとして5つの試験のトラック，すなわち，先進医療，医師主導治験，ARO主導国際共同試験，創薬，製造販売後第Ⅳ相試験の4種類に関して試験を展開していくのであるが，明確なゴールをめざした試験が行われるためには研究者とAROチームの連携が重要である．本稿では，具体的な事例(サクセス研究とJ-POST)をあげてその取組みを示す．現在，本学では研究者と専門職員の教育育成として大学院などでの教育を開始するとともに，そのための組織の構築を行い，AROとして臨床試験の5つのトラックが実践可能となる体制を整備している．このような取組みにより千葉大学のみならず，多くの施設と連携したエビデンスの発信とその成果を社会へ還元することをめざす．

Key word：AROチーム，医師主導治験，先進医療，データセンター

2012年5月，千葉大学は厚生労働省の指定する臨床研究中核病院に選定された．これは，2007年に厚生労働省の治験中核病院に指定されてから5年間にわたり実績を積み重ねてきた成果でもあるが，一方でその5年間のacademic research organization(ARO)としての活動の準備期間においてひとつずつ整備をしてきたことにもよる．海外のAROを手本としてめざす方向性を明確にし，大学幹部の理解と強力な推進力のもと，本学の生き残りをかけて全学的な取組みを行ってきた結果が現在の本学の状況でもある．千葉大学医学部附属病院臨床試験部(Chiba University Clinical Research Center：CCRC)はつぎのステップに向けたスタートを切り，本学のみならず連携する多くの研究者とともに今後5年間，さらに臨床試験を推進していくものであり，本稿では，その取組みの一部を紹介する．

AROの定義と試験の5つのトラック

“Academic research organization(ARO)”とは，すなわち“アカデミア臨床研究機関”と訳されるが，その定義は一概ではない．本学では，「臨床研究を進めるための原動力となる機関として位置づけており，研究者とプロジェクトリーダーが中心となって臨床試験を進めるための組織である」と定義している．また，その目的は臨床研究の成果を患者に還元することであり，一般社会と対話を図りながら，基礎科学と臨床医学の間の架け橋を発展させる，現代の医学のまさに最先端に位置するものといえる．

さて，AROの役割は5つのトラックに分類することが可能である(図1)．

① **先進医療**：従来の高度医療を実施することにより，新しい医療技術のエビデンスを確立し，これを社会に還元することがその最終的なゴールとなる．すなわち，先進医療への承認や薬事法上の承認を得ることにより，その医療技術が広く使用可能となるのである．

② **医師主導治験**：多くの場合，難病を対象としてあらたな適応追加の試験が実施される場合が

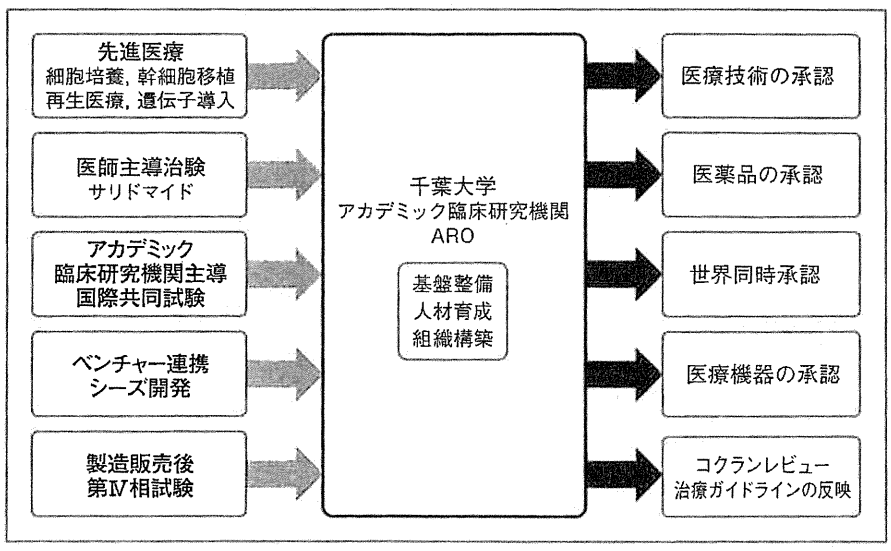

図 1　5つの臨床試験のトラック

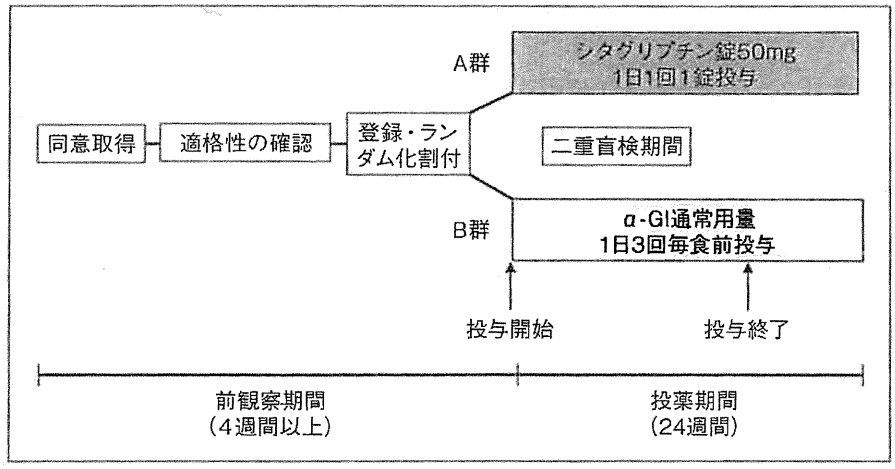

図 2　サクセス研究の試験デザイン

多いが，これにより，従来，保険適応とはならない患者の医療においてあらたな適応追加となる承認を得るための試験を，研究者が主導して実施することが可能である．

③　**ARO 主導型国際共同試験**：これは，医薬品の承認をめざした臨床試験を国内のみでなく海外の臨床研究機関と連携して実施するというものであり，医薬品の世界同時承認により日本での新薬のアクセスについて海外と差を減らすことが可能となる．

④　**ベンチャー連携シーズ開発**：創薬としてベンチャー企業と連携した新薬開発である．これにより日本からの新薬の創造と発信が可能となる．

⑤　**製造販売後第Ⅳ相試験**：ここではさまざまな使用方法や安全性に関するエビデンスの構築やガイドラインに反映することのできるイベントスタディをめざし，より一般化可能なデータを生むことが目的となる．

臨床試験の実践
――サクセス研究とJ-POSTの例から

つぎに，ARO ではどのように臨床試験の推進を行っているのか，具体的な事例をもとに示すこととする．

1. サクセス研究より

サクセス研究とは本学が中心となり，県内40の医療機関との多施設共同無作為ランダム化比較試験である(図 2)．本試験は千葉大学と関連施設の糖尿病専門医が連携してあらたなエビデンスの確立を目的として2010年に計画された試験である．