CLINICAL TRIAL PROTOCOL

PROTOCOL TITLE:
EMPOWERing patients with diabetes using profiling and targeted feedbacks delivered through wearable device (EMPOWER)

PROTOCOL NUMBER:
202004-00158

PROTOCOL VERSION: 1.6
PROTOCOL DATE: 10th September 2021

PRINCIPAL INVESTIGATOR:
Low Lian Leng, Consultant, Singapore General Hospital

SITE PRINCIPAL INVESTIGATOR:
Quah Yan Ling, Family Physician, SingHealth Polyclinics
Tan Yan Ling Cynthia, Resident Physician, SingHealth Polyclinics
David Koot, Family Physician, SingHealth Polyclinics

CO-INVESTIGATORS:
Tan Ngiap Chuan, Senior Consultant, SingHealth Polyclinics – Head Office
Yoon Sungwon, Assistant Professor, Duke-NUS Medical School
Kwan Yu Heng, Senior Research Fellow, Duke-NUS Medical School
Tan Chuen Seng, Assistant Professor, NUS Saw Swee Hock School of Public Health
Tai Bee Choo, Associate Professor, NUS Saw Swee Hock School of Public Health
Teo Hock Hai, Provost's Chair Professor, NUS School of Computing
Stanley Kok, Assistant Professor, NUS School of Computing
Tan Swee Lin Sharon, Assistant Professor, NUS School of Computing

STUDY TEAM MEMBERS:
Dionne Loh Hui Fang, Research Coordinator, SingHealth Office of Regional Health
Phang Jie Kie, Research Associate, SingHealth Office of Regional Health

Table of Contents

PROTOCOL SIGNATURE PAGE

Protocol Title: EMPOWERing patients with diabetes using profiling and targeted feedbacks delivered through wearable device (EMPOWER)

Protocol Number: 202004-00158

Protocol Version/ Date: 1.6/ 10th September 2021

Sponsor Name: Ministry of Health

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: Dr Low Lian Leng

Principal Investigator Signature: _____

Date: _____

1 BACKGROUND AND RATIONALE

Chronic diseases are the leading cause of deaths in Singapore. The rising prevalence in chronic diseases with age and Singapore's rapidly aging population calls for new models of care to effectively prevent the onset and delay the progression of these diseases. Advancement in medical technology has offered new innovations that aid healthcare systems in coping with the rapid rising in healthcare needs. These include mobile applications, wearable technologies and machine learning-derived personalized behavorial interventions. Our overall goal is to improve health outcomes in chronic disease patients through delivering targeted nudges via mobile application and wearables to sustain behavioral change. Our objective is to design, develop and evaluate an adaptive interventional platform that is capable of delivering personalized behavioral nudges to promote and sustain healthy behavioral changes in senior patients with 3H (diabetes (hyperglycemia), hypertension and hyperlipidemia). Our aim is to assess the clinical effectiveness of real-time personalized educational and behavioral interventions delivered through wearable (FitBit) and an in-integrative mobile application in improving patient activation scores measured using the patient activation measure (PAM). Secondary outcome measures include cost-effectiveness, quality of life, medication adherence, healthcare cost, utilization and lab results. Together with the experts from the SingHealth Regional Health System and National University of Singapore, we will conduct a randomized controlled trial of 1,000 eligible 3H patients. This proposal aims to achieve sustainable and cost-effective behavioral change in 3H patients through patient-empowerment and targeted chronic disease care.

1.1 General Introduction

Wearables, despite being a fairly new area in healthcare research provides a potential approach to improve management of lifestyle factors in patients with chronic disease. Some notable trials done by Jakicic and McDermott et al, showed that wearable devices did not provide an improvement over usual care in weight loss and walking endurance respectively. This may be because wearable interventions were not personalised and largely only tracking the activity without personalised nudges. This therefore suggested that the potential of wearables and mobile application in improving health outcomes lies not just in the features of the technology but in the engagement strategies used when presenting these collected information back to the patient. Patel et al also proposed that the best way to build new habits is by using the collected information and presenting it back as frequent feedback with appropriate framing to the patients at moments when he or she is most likely to act.

1.2 Rationale and Justification for the Study

Traditional healthcare facility-based consultation model of episodic contact in managing chronic disease patients have limited exposure to monitor and intervene patients' lifestyle factors. These factors have been found to be more effective in managing 3H than medication. The proposed adaptive platform will utilize wearable and mobile application technologies which has the ability to continuous track several physiological and lifestyle factors data (e.g. moderate to vigorous active minutes, resting heart rate, sleep hours and quality and dietary habits)

Similarly, due to the limited exposure that healthcare workers have with patients under the current consultation model, current health education and intervention tends to be "one size fits all", passive and "top down" knowledge-loading. Patients are expected to change their behavior or to remember health education knowledge after a consultation session. The proposed adaptive platform will be built using educational and behavioral cues obtained from multiple stakeholders (including patients) and multiple data sources with the aim to gather more comprehensive and targeted feedback that is relevant to patients' needs in their management of their 3H condition. As changes in lifestyle factors and habits takes time,

the proposed platform can also provide timely and appropriate feedbacks and reminders to patients at a more constant interval as compared to current model of care when advice was only given during consultation follow-up.

To be able to add healthy years to the life of the current and future seniors, behavioral interventions that are closely studied and carefully implemented without disruption to the daily activity of the seniors is needed to achieve a revolutionary improvement in current primary care management.

We will conduct a qualitative study to have a deep and enriched understanding of the types of nudges that are suited for patients with chronic diseases. Through modelling approach using the electronic medical records, the proposed adaptive platform will profile patients into groups and pre-set the nudges that are suitable for them. This allows us to identify patients that have a higher risk of complications of 3H and quickly match the desired nudges to change behavior.

The proposed adaptive platform also aims to empower patients by providing them with automated bite-sized knowledge of their health conditions. Coupled with real-time personalized feedback to their health behaviors, patients will be equipped with the knowledge to take charge of their health using far lesser healthcare manpower and resources.

The proposed adaptive platform will be integrated into common mobile wearables which are readily available devices that are widely used by many Singaporeans now. As such it can also be scaled up relatively easily with minimal resources and education.

Therefore, the proposed adaptive intervention will improve health outcomes and reduce healthcare utilization. An empowered patient will result in lesser complications and improve health outcomes, resulting in lower patient and caregiver burden, improving quality of life.

1.2.1 Rationale for the Study Purpose

A rapidly aging population is one of the greatest health challenges to Singapore and worldwide today and is associated with a higher prevalence of multiple chronic health conditions. Singapore has been rapidly ageing since 2012 and the percentage of individuals aged 65 years and above is projected to increase from 8.4% in 2005 to 18.7% in 2030 [6]. There is a strong imperative to prevent or slow the development of chronic diseases, and to provide ongoing, coordinated care to improve population health.

The challenge of a rapidly aging population is reflected in a rising chronic disease burden, as evidenced by increasing number of visits to the Accident and Emergency Department (A&E), high rates of public hospital bed occupancy, and escalating healthcare expenditure, which is predicted to exponentially increase from SGD $4 billion in 2011 to SGD $12 billion in 2020. To cope with the rising need for healthcare services, Ministry of Health (MOH) Singapore has called for a need to redesign current care models and tap on technology and automation to develop innovations that can improve efficiency and achieve significant healthcare manpower effectiveness[8].

Indeed, MOH have introduced several nation-wide campaigns in recent years such as ActiveSG, National Steps Challenge and Eat, Drink and Shop Healthy Challenge while tapping on mobile applications and wearables. However, these campaigns are mostly targeted at the general population and primarily focused on disease prevention by encouraging individuals to adopt a healthier lifestyle. Less been done to tap on these technologies on disease management and treatment despite the expectant rise in numbers in the near future.

The introduction of wearables and mobile applications in chronic disease management has several benefits. Firstly, the traditional healthcare facility-based consultation model of episodic contact in chronic disease management is ineffective to address lifestyle factors such as diet and exercise. It is well-established that lifestyle interventions have more impact in managing chronic diseases such as the 3H than medication. Lifestyle interventions are also the first line of treatment in chronic disease care.Traditionally, data of lifestyle factors can only be obtained from patients through surveys, interviews or diaries during clinic consultation and these data are often self-reported & periodic – susceptible to recall bias, require time for data collection and lack specificity in the data captured (i.e. weekly or monthly basis).

Wearables and mobile application provide a time-saving and more objective alternative in continuous tracking and recording several lifestyle factors data such as moderate to vigorous active minutes, heart rate, sleep hours, sleep quality and dietary logging. Data tracked by wearables are automatically recorded and synced periodically to users' phone and subsequently online servers via Bluetooth and internet. Data collected is free of recall bias, requires no time from patients or healthcare workers and is more detailed and precise than current methods.

Secondly, due to the limited episodic contact healthcare workers have with patients under the current consultation model of chronic disease management, traditional health education and intervention tends to be "one size fits all", passive and "top down" knowledge-loading. It is expected for patients to change their behavior or to remember health education knowledge after a consultation session. In contrast, mobile applications have the feature to deliver notifications to patients at any time and place and these notifications can also be synced in real-time to wearables via Bluetooth or Wifi. Being the country with the highest ranked globally in smartphone penetration; Singapore's healthcare institutions can use mobile applications as a medium to increase the exposure of health education and intervention to patients[31]. Coupled with the capture of more objective and precise lifestyle factors data, healthcare institutions can more accurately decide and tailor the appropriate health education and intervention feedbacks to each patient's lifestyle factors. For example, diabetic patients who just logged a meal that is high in carbohydrates are reminded of the possible need to inject more insulin and users are required to answer a yes/no question prompted by the mobile application on whether he/she has already inject the appropriate amount of insulin. Persistently logging of unhealthy meals can trigger a bite-sized educational message or video of the importance of healthy eating and proposed healthier meals alternatives (e.g. healthier dishes that users have previously consumed).

Although research using wearables is a fairly new area in healthcare research and findings related to the efficacy of wearables in improving health have been inconsistent, these studies have mostly used wearables and mobile application as platform to track and monitor lifestyle factors data without any intervention to motivate change. Several researchers have suggested that the potential of wearables and mobile application in improving health outcomes lies not just in the features of the technology to but in the engagement strategies used when presenting these collected information back to the patient. Wearable devices should be used as facilitators and not drivers for health behavior change. Patel et al also proposed that best way to build new habits is by using the collected information and present back as frequent feedback with appropriate framing to the patients at moments when he or she is most likely to take action. Such personalized and timely feedbacks works by using gentleness rather than coercion and the threat of sanctions to encourage behavioral change. It works by system 1 of thinking whereby it is fast, effortless, uncontrolled, unconscious, and skilled rather than system 2 of thinking whereby it is slow, effort demanding, controlled, reflective and consists of deliberation.

1.2.2 Rationale for Doses Selected

N/A

1.2.3 Rationale for Study Population

One in three deaths in Singapore is due to chronic diseases. This figure is likely to rise as (1) the prevalence of these chronic diseases increases with age, and (2) Singapore has one of the most rapidly ageing populations in the world. Together with an increase in demand for healthcare workers, there is a need to redesign current care models and tap on technology and automation to develop innovations that can improve primary care management, reduce complications and healthcare utilizations and improving patients' quality of life.

1.2.4 Rationale for Study Design

Chronic diseases are the leading cause of deaths in Singapore. The rising prevalence in chronic diseases with age and Singapore's rapidly aging population calls for new models of care to effectively prevent the onset and delay the progression of these diseases. Advancement in medical technology has offered new innovations that aid healthcare systems in coping with the rapid rising in healthcare needs. These include mobile applications, wearable technologies and machine learning-derived personalized behavorial interventions. Our overall goal is to improve health outcomes in chronic disease patients through delivering targeted nudges via mobile application and wearables to sustain behavioral change. Our objective is to design, develop and evaluate an adaptive interventional platform that is capable of delivering personalized behavioral nudges to promote and sustain healthy behavioral changes in senior patients with diabetes. Our aim is to assess the clinical effectiveness of real-time personalized educational and behavioral interventions delivered through wearable (Fitbit) and an in-integrative mobile application in improving patient activation scores measured using the patient activation measure (PAM). Secondary outcome measures include cost-effectiveness, quality of life, medication adherence, healthcare cost, utilization and lab results. Together with the experts from the SingHealth Regional Health System and National University of Singapore, we will conduct a randomized controlled trial of 1,000 eligible diabetes patient. This proposal aims to achieve sustainable and cost-effective behavioral change in diabetes patients through patient-empowerment and targeted chronic disease care.

2 HYPOTHESIS AND OBJECTIVES

To achieve the overall objective of designing, developing and implementing an adaptive intervention platform on wearable device for current and future seniors with3H to sustain behavior change while minimising healthcare resources, the study team aim to:

1. Collating a list of relevant educational and behavioral feedback targeted at the management of 3H diseases through a multi-pronged approach of qualitative interviews, systematic reviews and modelling of retrospective electronic medical records data.
2. Designing and developing an adaptive intervention platform capable of delivering personalized educational and behavioral feedback through an iterative process of monitoring tracked physiological and dietary data and self-reported efficacy of feedback provided.
3. Demonstration of the clinical and cost-effectiveness of wearable technology with integrative mobile application in a large sample of primary care patients with 3H.

A successful execution of the above proposal will inculcate behavioral changes, hence revolutionize primary care management, retard complications of 3H, reduce hospital utilization through a cost effective and sustainable approach.

2.1 Hypothesis

There will be an improvement in patient activation scores for the intervention group - after-year adjusting of baseline patient activation scores between the intervention and control groups will be compared.

2.2 Primary Objectives

Our primary objective is to improve patient empowerment as measured by patient activation measure. The improvement in patient activation scores after-year adjusting of baseline patient activation scores between the intervention and control groups will be compared.

2.3 Secondary Objectives

Our secondary objective is to assess for changes in health behaviors and health outcomes. Hence our main secondary outcomes includes, actual physical behaviors tracked by Fitbit (i.e. steps taken, active minutes, sleep quality and time and heart rate), self-reported lifestyle behaviors (i.e. dietary changes and medication adherence) and HbA1c. Other secondary outcome measures includes, self-reported Quality of Life (QoL) scores, participants' feedback on the intervention, healthcare utilisation, direct and indirect healthcare cost.
Medication adherence will be measured using Voils and Adherence to Refills and Medications Scale (ARMS). Healthcare cost and utilization and lab results will be extracted EHR. A qualitative interview with 30 patients and primary care physicians will be conducted to collect their feedback on the usefulness of the nudges in educating, motivating behavior change.

2.4 Potential Risks and Benefits:

2.4.1 Potential Risks

As this research used a very common platform (wearables) that is accepted by both current and future seniors, there is minimal safety risk involved in this research.

2.4.2 Potential Benefits

1. To be able to add healthy years to the life of the *current and future seniors - including participants*

2. To identify patients that have a higher risk of complications of 3H, and intervene to change behavior in attempt to lower their risk.

3. Patients will be equipped with the knowledge to take charge of their health using far lesser healthcare manpower and resources.

4. The proposed adaptive platform will be integrated into **common mobile wearables** which are readily available devices that are widely used by many Singaporeans now. As such it can also be **scaled up relatively easily with minimal resources and education**.

An ***empowered patient will result in lesser complications and improve health outcomes, resulting in lower patient and caregiver burden, improving quality of life***.

3 STUDY POPULATION

3.1 List The Number and Nature of Subjects to be Enrolled

Patients will be recruited from SHP sites (Bedok, Punggol, Tampines). These patients must not be cognitively impaired, and must be diagnosed with one or more 3H conditions at point of recruitment. A total of 1000 patients, with 500 patients per arm will be recruited.

3.2 Criteria for Recruitment and Recruitment Process

Patients will be screened and recruited for the RCT by research coordinators positioned in the SingHealth polyclinics. They will identify eligible patients according to the inclusion and exclusion criteria. Informed consent will be taken by the polyclinic research coordinators, before participants are randomly assign to the intervention or control arm. A Singhealth Polyclinic HQ staff and two Singhealth HQ research coordinators who are not involved in the recruitment or assessment of patients will keep custody of randomization lists. Patients will also be given the Fitbit wearables and an instruction manual for the appropriate use of Fitbit and adaptive intervention platform app upon recruitment. Patients will also answer a baseline survey administered by the research coordinator (data components of the survey elaborated in the survey section below). Patients will be followed up to 1 year on this RCT, and will have to complete the 1-year PRO Questionnaire upon completion of the RCT. At the 6-month mark, patients will be required to complete an interim EMPOWER PRO questionnaire as well. From a pragmatic trial standpoint, this reflects real world condition, hence, we will analyze as per intention to treat (ITT) protocol to minimize the potential bias associated with not following assigned treatment.

3.3 Inclusion Criteria

As this adaptive intervention platform is created for both *current and future seniors*, we will recruit (1) Aged 40 and above at time of recruitment (2) Have been diagnosed with diabetes at time of recruitment (3) Most Recent HbA1c $\geqslant$ 7.0% mmol/l (4) Physically able to exercise (5) Literate in English (6) Agreeable to be monitored by Fitbit and adaptive intervention platform (7) Able to conform to the Fitbit monitoring schedule

3.4 Exclusion Criteria

We will exclude patients who are (1) On insulin treatment (2) Require assistance with basic activities of daily living (BADL) (3) Have planned major operation or surgical procedure in the coming year at the time of recruitment (4) Cognitively impaired (scored < 6 on the Abbreviated Mental Test) from the RCT. Enrolled participants who fulfil any 1 of the exclusion criteria during the course of their 1 year participation in the study, will be withdrawn from the study but included in intention to treat.

3.5 Subject Replacement

No. We based our sample size calculation from a study by Solomon et al[53]. Although the commonly accepted MCID for PAM is 5[54], and this is the difference we hypothesize to see at follow-up for the intervention group. However, there have been some studies suggesting that a MCID of less than 5 may

be appropriate[55], and for this reason we have elected to use a conservative MCID of 2.5 in the sample size calculation.

With a conservative estimate of 2.5 point difference on a 100-point scale in patient activation scores between the two arms, and assuming a standard deviation of 14 for both arms, approximately 371 patients are needed for each arm to obtain a statistical power of 80% (two sided Type I error rate of 0.05) based on a 1:1 treatment allocation. After taking into account a dropout rate of approximately 20%, a total of 1000 patients with 500 patients per arm will be needed for this trial. This number is feasible to recruit on the ground because SingHealth polyclinics manages about 1.9 million attendances of patients a year with 9.2% of these patients diagnosed with diabetes[56].

4 STUDY DESIGN

A pragmatic 2-arm (1:1) randomized controlled trial (RCT) on 1,000 eligible diabetes patients using the Pragmatic Explanatory Continuum Indicator Summary Framework-2 (PRECIS-2) criteria for pragmatic trials[52]. Patients with diabetes will be randomly allocated in a 1:1 ratio to either the intervention or control group. The intervention group will receive the personalized feedback intervention through the personalized and adaptive intervention platform app on a Fitbit wearable on top of their usual clinical care for their diabetes. The control group will receive the Fitbit wearable on top of their usual clinical care for their diabetes but will not receive the personalized and adaptive intervention platform.

Study Procedures:

Recruitment will be done by 2 methods: 1) Booth, 2) Referral from attending healthcare professional, 3) Pre-Screening by SingHealth Polyclinic Research Coordinators

1) Booth

The patient will initiate contact at the booth that is located at the SHP Sites (SHP Bedok, SHP Punggol, SHP Tampines). The SingHealth Polylinics Research Coordinators (RCs) will introduce the EMPOWER study and FitBit monitoring schedule to the patient.

2) Referral from attending healthcare professional

The patient's attending healthcare professional will refer the patient to the RCs. The RCs will introduce the EMPOWER study and FitBit monitoring schedule to the patient.

3) Pre-Screening by SingHealth Polyclinic Research Coordinators

The RCs will pre-screen potential participants from a pre-generated list, and proceed to contact eligible patients via phone call, or approach the patients in the waiting areas of the polyclinic sites. A copy of the phone call script has been uploaded under Other Attachments. The CRCs are only allowed to contact the patient if they have been granted permission by the patient's care team to do so. If permission is not granted, the first contact will still be via the care team even if the procedure is approved by IRB. This will be done in accordance to SingHealth Cluster PnP SHS-MI-204, Access to

Sunrise Clinical Manager (SCM) for Research Purpose, sections 6.4.1 and 6.4.2.For all 3 recruitment methods, the RCs will obtain informed consent from the patient before proceeding to screen for eligibility in cognitive impairment, BADL, planned operation/surgery, using the screening questionnaire (attached in section F10). If a patient fulfils all criteria, a unique trial ID will be assigned to the patient, and RCs will explain the details of the RCT along with the Fitbit monitoring schedule before enrolling them into the RCT.

Upon enrolment, participants will be informed if they are allocated to be in the intervention or control arm - polyclinic CRCs will contact a centralized Singhealth Polyclinic HQ staff or the Singhealth HQ research coordinator (Jie Kie, Wee Boon & SHP HQ Staff) who are not involved in the screening and assessment of participants for the randomization outcome. Only the centralized Singhealth Polyclinics HQ staff and the Singhealth HQ research coordinators (Jie Kie, Wee Boon & SHP HQ Staff) will have access to the randomization list that was pre-generated. The polyclinic research coordinators will be blinded in the randomization process and will only find out the randomization outcome upon being informed.
Participants will then be given the Fitbit along with instructions on the proper use and care of the device, and assistance with the necessary registration, installation and syncing of the Fitbit app, intervention platform app to the Fitbit wearable. Participants will be required to sign the Acknowledgement of FitBit form upon receiving the FitBit from the CRC to confirm that the FitBit is functioning as per normal. (Attached in section F10).

Lastly, RCs will administer the questionnaire to collect the remaining baseline data(data components of the survey elaborated in the survey section below). RCs will administer the PRO Questionnaire to patients 6 months after recruitment, followed by the final PRO Questionnaire 1 year after recruitment. The 6 months and 1 year follow-up questionnaire are to be conducted in-person if participants have an appointment at the recruitment site within 1 month from their follow-up date (i.e. 5-7 months for 6 months follow-up and 11-13 months for 1 year follow-up). If participants do not have an appointment at the recruitment site within the 1 month window from their respective follow-up date, the Singhealth Polyclinic (SHP) research coordinator will conduct the follow-up questionnaires via phone call.

In the case of participants withdrawing from the RCT, or being terminated from the RCT due to unforeseen circumstances prior to the 1-year mark, the individual will be required to sign the Acknowledgment of Withdrawal form, and the CRC will have to acknowledge on the same form as well as confirmation. (Attached in Section F10)

Intervention: Patients in the intervention arm will be given a FitBit device and will be encouraged to wear it as often as possible. Using FitBit built-in tracking technologies such as PurePulse and SmartTrack[54], patient's daily activities such as number of steps taken, sedentary time, heart rate, sleep time and exercise will be captured and synced to the adaptive intervention platform as developed in Phase 2 for real-time tracking. Behavioral nudges will be delivered to patients' FitBit device through adaptive intervention platform via notification syncing. To ensure the delivered nudges are timely and personalized, predictive nudges will be developed based on patterns in patients' sociodemographic, clinical and baseline activity tracking. These nudges will be sent automatically to patients upon specific triggers. The nudges will also be assessed for its effectiveness in behavior change. For example, a predictive nudge to encourage patients to take a short walk after detecting long periods of sedentary time will be assessed for its effects by step counts data after delivery of nudge. An iterative approach will be used to generate an effective set of nudges and its most appropriate delivery times for specific activity patterns.

Control: Patients in control arm will have FitBit. However, there are no personalised nudges given to the patients in the control arm. Occasional reminders to encourage adherence to wearing of the FitBit will be sent. Patients in the control group will still be receiving usual care as per standardized guidelines[58].

4.1 Randomisation and Blinding

Stratified block randomisation will be implemented with participating centre as the stratification factor to ensure balance between the treatment arms, based on a 1:1 allocation ratio.

Upon enrolment, participants will be informed if they are allocated to be in the intervention or control arm - polyclinic CRCs will contact a centralized Singhealth Polyclinic HQ staff or the Singhealth HQ research coordinator (Jie Kie, Wee Boon & SHP HQ Staff) who are not involved in the screening and assessment of participants for the randomization outcome. Only the centralized Singhealth Polyclinics HQ staff and the Singhealth HQ research coordinators (Jie Kie & Wee Boon) will have access to the randomization list that was pre-generated.

4.2 Contraception and Pregnancy Testing

Patients to be recruited have to be aged 40 and above at time of recruitment. Pregnant patients will be excluded from this RCT.

4.3 Study Visits and Procedures

Patients under the control arm will be given a FitBit with in-built technologies for daily use, and their HbA1c readings will be recorded at every routine clinical visit by the research coordinators. The direct healthcare costs (i.e. costs in consultation, lab tests, medication, admissions) will be calculated on a unit cost basis for each RCT participant.

4.3.1 Screening Visits and Procedures

Patients will be screened prior to recruitment based on the inclusion-exclusion criteria. After which, they will be approached by the research coordinators and asked if they would like to participate in the RCT. If they consent to participating in the RCT, these patients will then be randomized to the intervention arm or control arm.

4.3.2 Study Visits and Procedures

Patients under the intervention arm will be given a FitBit with the intervention platform on top of in-built technologies for daily use, and those under the control arm will be given a Fitbit without the additional intervention platform. Both groups will have their HbA1c readings taken at every routine clinical visit. Patients will complete the EMPOWER PROs questionnaire during the enrolment, and during the visit on the 52nd Week (Day 0 is the day they receive the Fitbit). At the 6-month mark, patients will complete an interim EMPOWER PROs questionnaire as well.
The 6 months and 1 year follow-up questionnaire are to be conducted in-person if participants have an appointment at the recruitment site within 1 month from their follow-up date (i.e. 5-7 months for 6 months follow-up and 11-13 months for 1 year follow-up). If participants do not have an appointment at the recruitment site within the 1 month window from their respective follow-up date, the Singhealth Polyclinic (SHP) research coordinator will conduct the follow-up questionnaires via phone call.

Patients in the intervention arm will be asked to complete a System Usability Survey to find out the feasibility and acceptability of the intervention platform during their 3-month routine clinical visit, or the CRC will contact them via phone (i.e. if first clinical routine visit after recruitment is > 3 months later - CRC will have to call the participant 3-4 months post-recruitment).

4.3.3 Final Study Visit:

During the final study visit, 1 year from the start date of FitBit usage, patients will be asked to fill in a final PRO questionnaire.

4.3.4 Post Study Follow up and Procedures

None

4.4 Discontinuation/Withdrawal

4.4.1 Discontinuation Criteria

Discontinuation criteria includes:

1. Patient's condition worsening due to other factor (i.e. other conditions, terminal illness)
2. New diagnosis which would affect patient's physical and/or mental stability
3. When patient has lost the wearable device ≥2 times and is unable to replace it
4. When patient requests to withdraw from RCT

4.4.2 Discontinuation Visit and Procedures

The participant who is no longer suitable to be part of the RCT will be asked to sign a withdrawal form to confirm his/her withdrawal from the RCT, and that they have indeed been informed that reimbursement will not be given due to incompletion of the 1-year period. The Fitbit will then be handed back to the RC after the confirmation and the data collected will no longer be used for the analysis. The RC will then inform the person holding on to the master list of RCT participants of the name of the participant who has withdrawn from the project. The name will be removed from the list and kept for data-entry purposes.

5 TRIAL MATERIALS

For placebo/control arm, patients will be given the Fitbit Versa 2, but will be using the default application that is linked to the wearable – no personalized reminders will be given.

5.1 Trial Product (s)

EMPOWER Application on patient's mobile phone, which is synced with the Fitbit Versa 2. Patients will be asked to follow the schedule set by Fitbit for duration of wearing the wearable. Patients will also need to complete the daily logs stated in the EMPOWER application. Personalized nudges and reminders will be given to the patients under the Intervention arm.

5.2 Storage and Drug Accountability

N/A

6 TREATMENT

6.1 Rationale for Selection of Dose

N/A

6.2 Study Drug Formulations

N/A

6.3 Study Drug Administration

N/A

6.4 Specific Restrictions / Requirements

N/A

6.5 Blinding

Only the centralized Singhealth Polyclinics HQ staff and the Singhealth HQ research coordinators (Jie Kie & Wee Boon) will have access to the randomization list that was pre-generated. The polyclinic research coordinators will be blinded in the randomization process and will only find out the randomization outcome upon being informed - polyclinic CRCs to contact the centralized Singhealth Polyclinic HQ staff or the Singhealth HQ research coordinator (Jie Kie & Wee Boon) who are not involved in the screening and assessment of participants for the randomization outcome upon subject enrolment.
Only the polyclinic CRCs, Site-PIs and Co-I will have access to identifiable data. The Site-PIs and Co-I are involved in reporting of SAE, but they will be unable to link the intervention/control arm to the individual. The identifiable data will not be shared with any other study team members (including the Singhealth HQ research coordinator).

6.6 Concomitant therapy

N/A

7 SAFETY MEASUREMENTS

7.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally

associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

7.2 Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to CIRB

Only related SAEs (definitely/ probably/ possibly) will be reported to CIRB. Related means there is a reasonable possibility that the event may have been caused by participation in the clinical trial. Please refer to the CIRB website for more information on Reporting Requirement and Timeline for Serious Adverse Events.

The investigator is responsible for informing CIRB after first knowledge that the case qualifies for reporting. Follow-up information will be actively sought and submitted as it becomes available.

Unrelated AEs will not be reported to CIRB. However, the investigator is responsible to keep record of such AEs cases at the Study Site File.

7.3 Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to the Health Science Authority (HSA)

All SAEs that are unexpected and related to the study drug will be reported to HSA. Please refer to the HSA website for more information on Safety Reporting Requirements for Clinical Trials.

7.4 Safety Monitoring Plan

All research data will be stored within the institution. The completed questionnaires and informed consent forms will be kept in a locked cabinet in the respective recruitment sites, where only authorized staff are allowed access, for a maximum of 7 years. After which, the documents will be destroyed. All identifiable data will not be available on any of the documents that are handled by the study team.

Only authorized study staff (PI, Co-I and study coordinators) will have access to the research data. This is to ensure that all study information remains safe and secure.

RedCAP will be used for the uploading of questionnaire results, and only authorized study staff will be able to access their institution's RedCAP for this specific study.

7.5 Complaint Handling

Patients can contact the study coordinators (contact number and names written down on information sheet) when they have complaints. As for complaints that are technical, patients will be directed to technical support (contact number given on product booklet when wearable is handed over).

8 DATA ANALYSIS

8.1 Data Quality Assurance

Patients will all be given the same model for the wearable (Fitbit Versa 2), and the 365 day period starts from the day that they receive the wearable. Information obtained from the questionnaires will be digitalized according to the answers that were filled in, without a need for interpretation of the results prior to data entry.

The applications used for the control arm will be a commercially available product that has passed quality checks and usability testing. The intervention platform used has passed usability testing and load testing prior to being introduced to the RCT. This ensures that the data collected is uniform throughout all the participants for the control arm and the intervention arm. The data is synced from their wearable device, without any human interference.

8.2 Data Entry and Storage

Data obtained from the wearable will be stored on a secured cloud platform and is synced via Bluetooth function. The data obtained from the questionnaires will be uploaded into RedCAP. All hardcopy documents will be stored under lock and key in a specific locked cabinet in SingHealth Polyclinics (Site specific for SHP Bedok, SHP Punggol, SHP Tampines), where only authorized staff will have access. After 7 years, the hardcopy documents will be destroyed.

9 SAMPLE SIZE AND STATISTICAL METHODS

9.1 Determination of Sample Size

We based our sample size calculation from a study by Solomon et al[53]. Although the commonly accepted MCID for PAM is 5[54], and this is the difference we hypothesize to see at follow-up for the intervention group (refer to KPI 1 – page 23). However, there have been some studies suggesting that a MCID of less than 5 may be appropriate[55], and for this reason we have elected to use a conservative MCID of 2.5 in the sample size calculation.

With a conservative estimate of 2.5 point difference on a 100-point scale in patient activation scores between the two arms, and assuming a standard deviation of 14 for both arms, approximately 371 patients are needed for each arm to obtain a statistical power of 80% (two sided Type I error rate of 0.05) based on a 1:1 treatment allocation. After taking into account a dropout rate of approximately 20%, a total of 1000 patients with 500 patients per arm will be needed for this trial.

9.2 Statistical and Analytical Plans

All patients will be analyzed using intention-to-treat approach. The primary outcome of interest is the difference in patient activation score at 1-year between the interventional and control arms. Patient's characteristics will be summarized using mean and standard deviation (or median and interquartile range where adequate) for continuous variables, and count and percentage for categorical variables. Primary outcome of patient activation at 1-year will be analyzed using Student's t-test to obtain the crude estimate of difference and its associated 95% confidence interval, between the intervention and control. Further adjustment will be made with baseline patient activation score and other confounding variables (e.g. participation in other ongoing health programmes) using ANCOVA.

For secondary outcomes with repeated measurements, we will use the linear mixed model to account for within-individual correlation among measurements and the sandwich estimator to obtain robust standard error estimates. The intervention indicator and time factor will be included into the linear predictors adjusting for baseline covariates. All evaluations will be made assuming a two-sided type I error rate set at 0.05.

The economic evaluation will be conducted from the health care system and societal perspectives. Both a cost-effectiveness analysis (i.e. cost of reduction in 1 patient activation point) and a cost-utility analysis (cost of reduction in 1 quality-adjusted life year saved) will be performed. Effectiveness will be measured as the improvement in patient activation scores at 1-year for the cost-effectiveness analysis. For the cost-utility analysis, utility will be measured at all observed time points using the EQ-5D. Effectiveness will be measured exclusively through improvements in quality of life. We will regress the effectiveness on follow-up time in order to assess the time profile of the effectiveness of the intervention. In case of residual effectiveness at 1-year, we will extrapolate using the estimated effectiveness profile in order to assess additional effectiveness arising beyond study completion. Utility weights from Singapore will be applied to determine the corresponding societal preferences[50]. All diabetes-related and non-diabetes-related health care use (secondary economic outcomes) will be used for the health care system perspective. Non-health care financial consequences (secondary economic outcomes) will be added for the societal perspective. All costs will be adjusted to 2017 values using consumer price index health care component. The incremental cost- effectiveness ratio will be calculated in which the difference in total costs between intervention arm and control arm is divided by the difference in the improvement in patient activation score between the two arms. Sensitivity analysis will be conducted to evaluate the influence of uncertainties in the variables and assumptions employed on the analysis results.

An interim review will be done at the 6-month mark of the RCT, and the statistical data will be used to generate the trial report to calculate: a) safety issues, if any, b) the efficacy end-point of the intervention, and c) recruitment issues and how to resolve these issues if any.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The collaborators (NUS Computing) will be analysing the data collected from the wearable devices, and patients will be instructed to adhere to the schedule given by Fitbit in order to ensure that data collection is optimal. Patients will be asked prior to being enrolled in the RCT if they can adhere to the given schedule. Those who are unable to will be eliminated from the RCT at screening stage.

12 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Clinical Trial Protocol, including the final version of the Participant Information Sheet and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB) and regulatory approval from Health Sciences Authority (HSA), prior to enrolment of any patient into the study.

The principle investigator is responsible for informing the CIRB and HSA of any amendments to the protocol or other study-related documents, as per local requirement.

12.1 Informed Consent

Patients will be approached by the Research Coordinator at the polyclinic, and briefed about the study project. The RC will then obtain informed consent, and the patient will need to sign on the consent form. The original copy of the signed consent form will be kept under lock and key by the RC, and a photocopy will be kept in the patient's medical records for reference. A copy of the signed consent form would be given to the patient as well.

12.2 Confidentiality of Data and Patient Records

All identifiable information will only be known to the polyclinic CRCs, Site-PIs and Co-I of the project, the Site-PIs and Co-I are involved in SAE reporting, and will not be able to link the individual to intervention/control arm. The randomization list will only be with the HQ RC (Jie Kie, Wee Boon & SHP HQ Staff). All other study team members will only have access to the patients' demographics, but none of the identifiable information (i.e. NRIC, full name).

Doctors will not be able to identify the participants involved in the project based on their EMRs.

Identifiable information would be kept at SHP only.

13 PUBLICATIONS

Data collected via the interactive platform, and findings obtained based on both arms of the study will be published. The PI, Co-PI and Site PIs will have co-authorship of the published works, and NUS School of Computing will also be involved in the authorship of published works for this study.

14 RETENTION OF TRIAL DOCUMENTS

Consent will be taken at the respective Polyclinics (i.e. recruitment sites). The hard copy research data (i.e. signed informed consent forms) will be kept in locked cabinet at the respective recruitment sites. The documents will be kept for 7 years, after which they will be destroyed.

15 FUNDING and INSURANCE

This project is funded by the NMRC National Innovation Challenge (NIC) on Active and Confident Ageing (Chronic Diseases Management) Grant.