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# "Predictive model-based decision support for diabetes patient empowerment"

# D5.2.2 Evaluation of Campaign Methodology

| | | |
|---|---|---|
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| **Task** | T5.2 | |
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| **Deliverable lead** | LUMC | |
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| Dissemination Level | | |
|---|---|---|
| PU | Public | X |
| PP | Restricted to other programme participants (including the Commission Services) | |
| RE | Restricted to a group specified by the consortium (including the Commission Services) | |
| CO | Confidential, only for members of the consortium (including the Commission Services) | |

**POWER2DM Consortium Partners**

| abbrev | Participant organization name | Country |
|---|---|---|
| LUMC | Leiden University Medical Center | Netherlands |
| IDK | Institute of Diabetes “Gerhardt Katsch” Karlsburg | Germany |
| SAS | SAS Servicio Andaluz de Salud | Spain |
| TNO | Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek | Netherlands |

**Change procedure and history**

This section contains the procedures for modifying the deliverable and maintaining a history of the changes.

| Version | Date | Changes | From | Review |
|---|---|---|---|---|
| V0.1 | April 25, 2017 | Outline Evaluation Campaign (EC) Protocol | LUMC | LUMC, SAS, TNO |
| V0.2 | April 28, 2017 | Outline EC Protocol revisions | LUMC | LUMC, SAS, TNO |
| V0.3 | April 30, 2017 | Outline EC Protocol revisions | LUMC | LUMC, SAS, TNO |
| V1.0 | May 24, 2017 | First draft of EC Protocol | SAS | LUMC, SAS, TNO |
| V1.1 | May 24, 2017 | Draft revision | LUMC | LUMC, SAS, TNO |
| V1.2 | June 16, 2017 | Draft revision | LUMC | LUMC, SAS, TNO |
| V1.3 | June 19, 2017 | Draft revision | LUMC | LUMC, SAS, TNO |
| V2.0 | June 28, 2017 | Draft Update | LUMC | LUMC, SAS, TNO |
| V2.1 | July 03, 2017 | Draft revision | TNO | LUMC, SAS, TNO |
| V2.2 | July 05, 2017 | Draft revision | LUMC | LUMC, SAS, TNO |
| V2.3 | July 07, 2017 | Draft revision | SAS | LUMC, SAS, TNO |
| V3.0 | July 12, 2017 | Draft Update | LUMC | LUMC, SAS, TNO |
| V3.1 | July 12, 2017 | Draft revision | SAS | LUMC, SAS, TNO |
| V3.2 | July 12, 2017 | Draft revision | LUMC | LUMC, SAS, TNO |
| V3.3 | July 20, 2017 | Draft Update | LUMC | LUMC, SAS, TNO |

**PROTOCOL TITLE: Evaluation of the POWER2DM Diabetes Self-Management Support System compared with usual care for patients with diabetes**

**Working Title: POWER2DM Evaluation Campaign**

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|---|---|
| **Protocol ID** | **Evaluation of the POWER2DM Diabetes Self-Management Support System compared with usual care for patients with diabetes** |
| **Short title** | **POWER2DM Evaluation Campaign** |
| **EudraCT number** | ***<only applicable for studies with an investigational medicinal product>***<br>***NA*** |
| **Version** | **3.3** |
| **Date** | **20-07-2017** |
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**TABLE OF CONTENTS**

## LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

| | |
|---|---|
| **(S)AE** | **(Serious) Adverse Event** |
| **ABR** | **ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)** |
| **ADDQoL** | **Audit of Diabetes Dependent QoL** |
| **AE** | **Adverse Event** |
| **APE** | **Action Plan Engine** |
| **AR** | **Adverse Reaction** |
| **ASQ** | **After-Scenario Questionnaire** |
| **BG5** | **iHealth Smart Wireless Gluco-Monitoring System BG5 and BG5+** |
| **BIPQ** | **Brief Illness Perceptions Questionnaire** |
| **BMI** | **Body mass index** |
| **BPM** | **Beats per minute** |
| **BU** | **Bread Exchange Unit/Bread Unit** |
| **CA** | **Competent Authority** |
| **CC** | **Calorie Counter by FatSecret** |
| **CCMO** | **Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek** |
| **CGM** | **Continuous Glucose Monitor** |
| **CV** | **Curriculum Vitae** |
| **DEPS-R** | **Diabetes Eating Problem Survey-Revised** |
| **D-FISQ** | **Diabetes Fear of Injecting and Self-Testing Questionnaire** |
| **DSMB** | **Data Safety Monitoring Board** |
| **DSMQ** | **Diabetes Self-Management Questionnaire** |
| **EU** | **European Union** |
| **EudraCT** | **European drug regulatory affairs Clinical Trials** |
| **EC** | **Evaluation Campaign** |
| **FCQ** | **Fear of Complications Questionnaire** |
| **FGM** | **Flash Glucose Monitoring** |
| **FSL** | **FreeStyle Libre Flash Glucose Monitor** |
| **FSL Pro** | **FreeStyle Libre Pro Flash Glucose Monitor** |
| **GAD-7** | **brief measure of Generalized Anxiety Disorder** |

| | |
|---|---|
| **GCP** | **Good Clinical Practice** |
| **HADS** | **Hospital Anxiety and Depression Scale** |
| **HbA1c** | **Glycated hemoglobin** |
| **HFS** | **Hypoglycemia Fear Survey** |
| **HRQoL** | **Health Related Quality of Life** |
| **IB** | **Investigator's Brochure** |
| **IC** | **Informed Consent** |
| **IMP** | **Investigational Medicinal Product** |
| **IMPD** | **Investigational Medicinal Product Dossier** |
| **JITAI** | **Just In Time Adaptive Intervention** |
| **KRIG** | **Klinische Researchunit Interne Geneeskunde** |
| **LUMC** | **Leiden University Medical Center** |
| **METC** | **Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)** |
| **mHealth** | **Mobile Health** |
| **NA** | **Not Applicable** |
| **PAID** | **Problem Areas in Diabetes** |
| **PHQ-9** | **Patient Health Questionnaire** |
| **PSS** | **Perceived Stress Scale** |
| **PWD** | **Patients with diabetes** |
| **QC** | **Quantification Campaign** |
| **QoL** | **Quality of Life** |
| **SDM** | **Shared Decision Making** |
| **SDMDB** | **Shared Decision Making Dashboard** |
| **SDSCA** | **Summary of Diabetes Self-Care Activities** |
| **SMBG** | **Self-Monitoring of Blood Glucose** |
| **SMSS** | **Self-Management Support System** |
| **SPC** | **Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)** |
| **Sponsor** | **The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.** |
| **SUSAR** | **Suspected Unexpected Serious Adverse Reaction** |
| **T1DM** | **Type 1 Diabetes Mellitus** |

| | |
|---|---|
| **T2DM** | **Type 2 Diabetes Mellitus** |
| **TAU** | **Treatment as usual** |
| **VAS** | **Visual Analogue Scale** |
| **Wbp** | **Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)** |
| **WHO-5** | **WHO-5 Well-Being Index** |
| **WMO** | **Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen** |

## SUMMARY

**Rationale:** Diabetes is a chronic condition that involves the inability of the body to maintain normoglycemia. A large investment of time and energy is required to properly manage diabetes. Inadequate self-management including healthy dietary habits and exercise, appropriate self-measurement of blood glucose (SMBG) and insulin administration based on food intake, exercise and other daily activities in patients on insulin therapy, usually underlies problems to maintain glycaemic control. Hyperglycaemia is an important cause of long-term macro-and microvascular complications in all patients with diabetes mellitus (PWD). And in patients on insulin therapy, (fear of) hypoglycaemia has an enormous impact on quality of life. Thus, optimization of self-management is one of the most important treatment goals in all types of diabetes. Patients need to be supported in order to reduce the burden and increase the effectiveness of their diabetes self-management. One way to do this is by using integrated technologies and personalized plans for care as a cornerstone in the modern scope of therapeutic approach current strategies in chronic diseases. For this purpose, the POWER2DM support system was developed to give patients insight into their condition and support diabetes patients and their health care professionals in setting and achieving self-management goals using predictive computer model simulations and behavioural action plans.

**Objective**: To evaluate and test the feasibility of POWER2DM in everyday use, and provide proof of concept that POWER2DM is safe and effective in improving glycaemic control and provide and an analysis of the cost-effectiveness of the approach to highlight any potential issues that may impede implementation.

**Study design:** The study is divided into two stages. In Stage 1 (Feasibility study), the prototype will be used by patients from each clinical center to generate two weeks of data regarding real-world system usage. Patients will be contacted after two and seven days of use, before returning at day 14 for a debriefing session to record the user-experience of the POWER2DM procedure. This data will be used to identify and resolve technical and usability issues prior to implementation in Stage 2. Stage 2 is a two-armed pragmatic randomised controlled trial lasting 9 months in which patients will be randomised to receive either POWER2DM Support (intervention) or usual care (control). There will be evaluation moments at baseline, after 3, 6 and 9 months.

**Study population:** For Stage 1, N=14 patients with either T1DM or T2DM (N=7 per clinical center). For Stage 2, N=280 patients with diabetes (N=140 T2DM, N=140 T1DM) recruited from out-patient clinics in the Netherlands (Leiden University Medical Centre and Primary Care Research Network) and Córdoba, Spain (Reina Sofia University Hospital)

with a total population of 140 in the POWER2DM support group (T1DM=70 and T2DM=70) and 140 in the usual care group.

**Intervention**: The POWER2DM support group will receive access to the prototype 2 of the POWER2DM system. This system consists of two components: 1) the Shared Decision Making Dashboard, used to set self-management goals together with a health care professional with the use of short-, medium-, and long-term predictive computer simulation models to, and 2) the POWER2DM Self-Management Support System, used to support behavioural change in DM self-management.

**Main study parameters/endpoints:** Change in glucose regulation as measured by %HbA1c before and after the intervention compared between the intervention and control groups.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** The risks associated with participation in the intervention group are limited as any changes to the patient's diabetes care plan will be done in cooperation with a healthcare professional. The primary potential foreseeable risk associated with participation in this study is negative feelings resulting from the increased attention to the patient's illness. As the purpose of the system is to assist the patient in successfully managing their diabetes by drawing attention to their disease and its management, this risk is acceptable as the potential benefits associated with better diabetes and glucose control include lowered chance of developing diabetes related complications or dying. There is an additional burden of time presented to the patient connected as they will need to track their diabetes self-management and there will be an increase in communication moments with the patient's healthcare provider. The POWER2DM Evaluation Campaign (EC) is the second stage of the POWER2DM Project, and is based on the results of the first stage POWER2DM Quantification Campaign (QC). In that stage, a very positive feedback was reported by the participants in the study in the two centers with patients reporting an average satisfaction of 8/10 for the system as a whole and 100% of participants who completed the study (18/20) reporting that they would like to participate in later stages of the study. Based on this feedback, the risk of the negative feelings seems low. Further, although there are no other predictable risks inherent to the EC, there are long-term risks associated with uncontrolled glucose levels caused by Diabetes Mellitus. These cardiovascular, renal and other metabolic systems risks associated with uncontrolled glucose levels should be reduced through participation in POWER2DM, meaning that the potential benefit of reduced long-term complications outweigh the slight risk of negative feelings and burden of time related to participation. Events occurred during the length of the study will be evaluated, and relationship with the POWER2DM will be also investigated.

## 1. INTRODUCTION AND RATIONALE

Diabetes is a chronic disease characterized by the bodies inability to maintain healthy levels of blood glucose (glycemic control) which is associated with long-term health problems such as retinopathy, nephropathy, peripheral and autonomic neuropathy, cardiovascular symptoms, and sexual dysfunction [1]. Diabetes was found to be directly responsible for 1.5 million deaths in 2012 with an estimated global prevalence of 9% in 2014 [2]. A majority of diabetes case fall under two categories, type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), with T1DM accounting for approximately 5-10% of cases and T2DM accounting for approximately 90-95% of cases [1]. Diabetes care is centered on the cornerstone of metabolic control; specifically keeping glucose levels as close to normal as possible through glucose monitoring, medication, a careful diet, and physical activity [3, 4]. Proper management of T1DM requires daily administration of insulin based on glucose concentrations and daily activities such as dietary intake and exercise, and other specific situations that can affect insulin requirement. T2DM management mainly involves oral glucose-lowering medication in the early stages of the disease along with lifestyle changes aimed at weight management, dietary modification, and increased physical activity [5]. Treatment plans for both T1DM and T2DM involve a significant investment of time and energy with some estimates exceeding two hours per day to comply with the minimum recommendation for diabetes specific care [6]. The high burden to the patient associated with recommended diabetes self-management often results in patient non-compliance with suggested self-care behaviors. Reports on time spent performing diabetes self-management actions found that patients spend on average 58 minutes per day on diabetes specific activities and even then often skip at least one aspect of their recommended care [7]. In addition to the burden of time needed for proper self-management, psychological issues related to diabetes outcomes and barriers to diabetes self-management resulting in poor self-management are commonly observed [8-10]. Further adding to issues surrounding successful diabetes management is the infrequency of contact between diabetes patients and their care provider. Patient reports of consultation frequency per year have found that in some countries patients only see their care provider twice a year indicating that patients often go months without professional guidance or advice on their DM self-management letting the burden of diabetes management fall completely on the shoulders of the patient [11, 12]. The combination of these issues surrounding proper diabetes management has resulted in almost half of diabetes patients showing either moderate or poor control of their blood glucose level [13]. There is a clear need to improve the burden of diabetes self-management and the support patients receive.

Recent developments in mobile technologies have led to promising innovations in current healthcare. The use of mobile interventions for chronic illness management in general has been found to be a cost-effective method of implementation but results have been mixed regarding the impact on metabolic outcomes [14-19]. Diabetes specific mobile interventions have been found to lower HbA1c levels in some cases although questions surround generalizability of these interventions have been raised [20-24]. Currently, most diabetes self-management mobile applications focus only on tracking of blood glucose, insulin usage, or carbohydrate intake (33%), often requiring manual input, with only a few offering teaching or training options regarding diabetes care (22%) [25]. While associations have been found between increases in frequency of self-monitoring of blood glucose levels (SMBG) and lower HbA1c levels [26], monitoring alone without any associated intervention has only been found to maintain current metabolic levels but not improve them [19]. Interactive diabetes diaries that give personalized advice on insulin usage, healthy eating, and that improve ease of contacting physicians have been found to be effective at lowering HbA1c levels and are desired and accepted by patients as a tool for self-management [27, 28]. Data collected in these diaries can be use in highly personalized glucose simulation models (KADIS system, Karlsburg) which have been shown to be successful in helping physicians to personalize the diabetes care of patient subjects, resulting in improved metabolic outcomes in diabetes care [29-32]. The KADIS simulation model describes the glucose metabolism in T1DM and T2DM patients based on patients' data regarding blood glucose values, oral medication, insulin therapy, carbohydrate content of meals, and exercise.

However, metabolic outcomes are only one area of importance in diabetes care. Diabetes related psychosocial problems (e.g. depression, anxiety, and stress) are prevalent and have a significant impact on the quality of life of diabetes patients and their ability to successfully manage their disease [10, 33-38]. Fortunately, these issues can all be improved upon using current forms of therapy and, in some cases, effective web-based interventions are already available for diabetes specific complaints [39, 40].

To provide patients with the self-management support that they want and need, we developed a holistic mobile intervention platform that helps the patient in a variety of different ways. This comprehensive self-management support system (POWER2DM) helps patients with their diabetes self-management by reducing the burden of diabetes through 1) automating input and tracking for daily monitoring or glucose, diet, and exercise; 2) assisted goal setting with regard to DM self-management making use of a Shared Decision Making Dashboard in consultation with a health care professional, including visualizations of predictive computer simulation models of DM risk scores and the KADIS model,

3) offering tailored self-management action plans to help the patient overcome barriers to successful treatment goal accomplishment between consultations with their diabetes specialist; 4) provide online and mobile psycho-education to help patients deal with potential barriers of diabetes self-management (diabetes related stress, depression, and anxiety); Our goal is to ensure that diabetes patients are receiving daily patient-centered care to help them control their chronic condition.

## 2. OBJECTIVES

Primary objectives

- To determine if the POWER2DM system improves glucose regulation and stability

Secondary objectives

- To evaluate the safety of the POWER2DM system
- To determine if the POWER2DM system improves (model based) risk scores of morbidity and mortality
- To determine if the POWER2DM system improves the chances of reaching pre-set self-management goals
- To determine if the POWER2DM system improves quality of life, mental health status, and psychological diabetes burden
- To determine technology acceptance and user satisfaction of the POWER2DM system and identify potential issues to the implementation of the system
- To assess the socio-economic and organizational impact of the POWER2DM system

## 3. STUDY DESIGN

The evaluation campaign is separated in two stages.

*Stage I*: A two-week observational “Feasibility” study in which the target population will use prototype 1 of the POWER2DM system in real-world settings. The purpose of this stage is to generate real-world functional usage information to be used to finalize the POWER2DM prototype 2 prior to its deployment in Stage II. Patients will initially attend the clinic for a demonstration of the system, and then be allowed to independently set up and use it, before trying it in real-world settings for a two-week period. During this period, they will assist in testing the SMSS by using it as instructed with direct access to the researchers by telephone or email for assistance and to provide feedback. Scheduled contact moments will occur after two and seven days of use, before returning for a debrief at day 14. During the debrief the patients will return any devices loaned to them for the study and undergo a one-to-one debriefing session to record the user-experience with the POWER2DM system. This stage will provide real-world system usage information which will be used to improve the POWER2DM system prior to Stage II.

*Stage II:* A 9 month, two-armed, pragmatic randomised control trial to test the effectiveness of the POWER2DM system. Patients will be randomised using stratified sampling to either Power2DM support as an adjunct to usual care (intervention group) or usual care alone (control group). There will be evaluation points consisting of clinical visits at baseline and after 3, 6 and 9 months.

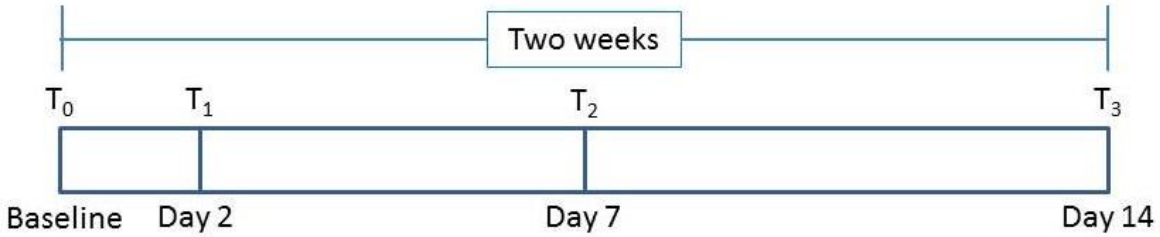



**Figure 1. Study schemes for Stage 1**

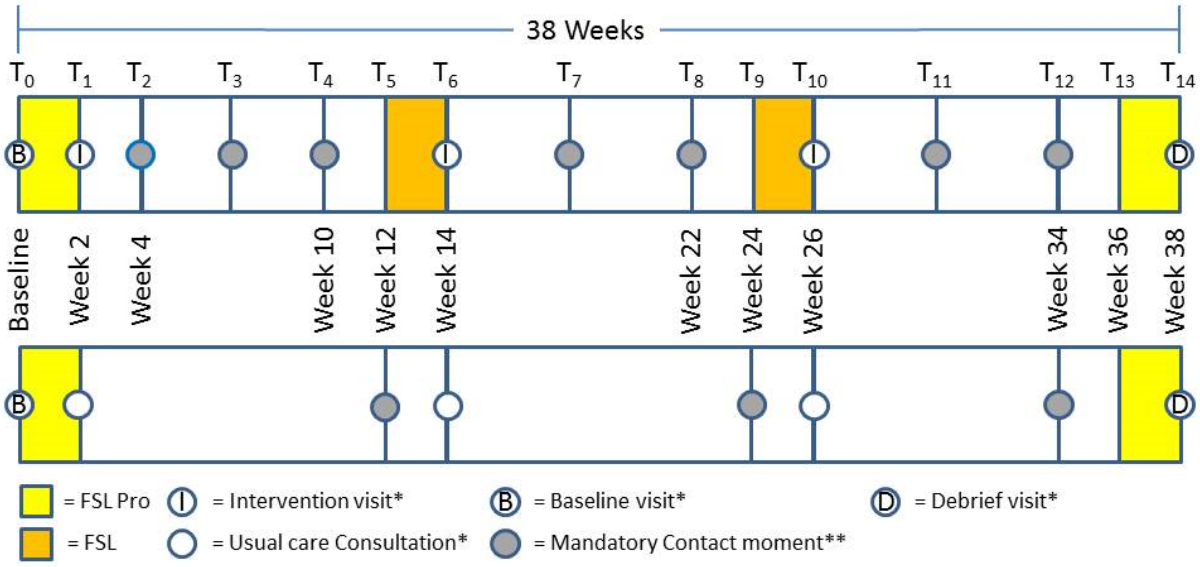



**Figure 2. Study schemes for Stage 2 (Intervention group: top; Control group: bottom)**

**Note: * Consultations and the start of the intervention are in person; ** Contact moments can be either in person or via telephone/email as desired**

## 4. STUDY POPULATION

### 4.1 Population

#### 4.1.1 Stage I, Feasibility study:

A total of N=14 patients with either T1DM or T2DM (N=7 per clinical center).

#### 4.1.2 Stage II, randomized control trial:

A total of N=280 patients with T2DM or T1DM (Leiden: T1DM= 105, T2DM= 37; Córdoba: T1DM= 35, T2DM=103) will be recruited from out-patient clinics in Leiden, the Netherlands (Leiden University Medical Centre and collaborating clinics) and Córdoba, Spain (Reina Sofia University Hospital). A total population of N=140 will be randomly selected to be in the POWER2DM intervention group using stratified sampling for an even patient distribution (T1DM=70 and T2DM=70) and 140 in the usual care group (T1DM=70

and T2DM=70). Patient distributions per site and per study group can be seen in Figure 3 and Table 1 below.

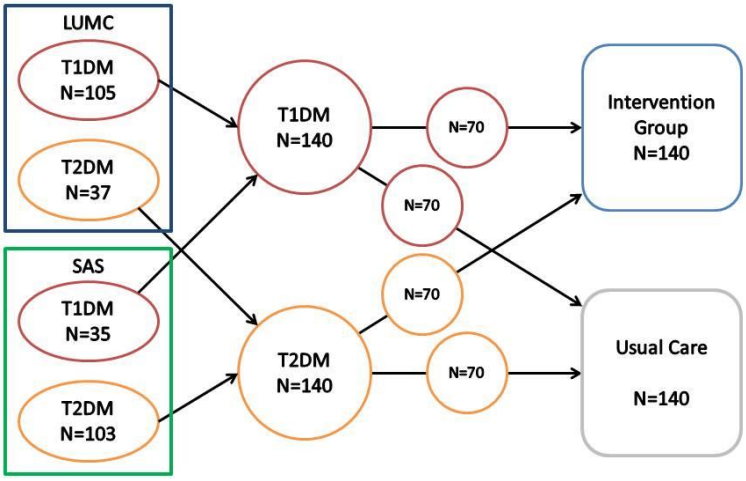



**Figure 3. Distribuition of patients over study sites and study groups**

| | T1DM | | T2DM | | |
|---|---|---|---|---|---|
| | Power2DM | Usual care | Power2DM | Usual care | Total |
| **LUMC** | 53 | 52 | 18 | 19 | 142 |
| **SAS** | 17 | 18 | 52 | 51 | 138 |
| **total** | 70 | 70 | 70 | 70 | **280** |

**Table 1. Distribution of patients over study sites, disease groups and intervention groups**

### 4.2 Inclusion criteria

To be eligible to participate in this study, a subject must meet all of the following criteria:

- Age 18 or older
- Diagnosed T2DM or T1DM
- Able to self-monitor and work with computer and smart phone with internet connections (as assessed by researcher)

### 4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Severe renal insufficiency (eGFR<30ml/min)
- Serious/severe comorbidity that interferes with diabetes outcomes or diabetes self-management including but not limited to: psychiatric diseases, chronic hepatopathy, active malignancy, COPD, diseases of the digestive tract, endocrine disorders, cerebrovascular disease with disability
- Pregnant or wanting/trying to become pregnant in the coming 9 months
- Concurrent participation in other clinical trials
- Any other situation in which the investigator identifies a potential risk of not being able to perform the study.

### 4.4 Sample size calculation for Stage 2

Sample size requirements were calculated based on the primary outcome variable of level of Hba1c% which has a minimum detectable difference= 0.35% (SD 1.0%). For an alpha error of 0.05 and a power of 80%, the minimum sample size needed is 129 subjects per group. The POWER2DM RCT will include 140 type 1 DM and 140 type 2 DM subjects, 280 patients in total, allowing us to face a loss to follow of 8.5%. In pre-specified subgroup analyses of patients with T1DM and T2DM we can detect a difference of 0.5% with a sample size of 63 subjects per treatment strategy per DM subtype (N=70 with 10% loss to follow-up). This number of patients will be recruited in the two cities participating (Cordoba and Leiden), resulting in a total sample size of N=280.

## 5. TREATMENT OF SUBJECTS

### 5.1 Investigational product/treatment

After informed consent is acquired and a participant is randomized in the POWER2DM support group, the patient will use a Free Style Libre Pro sensor (FSL Pro) for two week In order to generate the required data needed to use the POWER2DM system and create a metabolic fingerprint for the KADIS model. After these two weeks, the participant will set a self-management target together with a health care professional using the POWER2DM Shared Decision Making Dashboard and an instruction of the POWER2DM Self-Management Support System is given. Subsequently, the participant will use this system together with a fitness tracker and a supplied self-monitoring glucose meter for 9 months with two evaluation visits (3-months and 6-months after starting) and a final concluding

visit after 9 months. Before these visits, intervention group participants will wear a FreeStyle Libre (FSL) for two weeks in order to gain insight in their behaviour in relation to their blood glucose level and variability and to make a metabolic fingerprint for the KADIS model for use in the consultation. During these visits, self-management goals are evaluated and in some cases new goals are set together using the POWER2DM Shared Decision Making Dashboard.

The usual care group will not receive any interventions outside of their usual care. They will receive the blinded Free Style Libre Pro (FSL Pro) sensor at the first visit, which they will also wear for two weeks. At the 2 week visit, the FSL Pro is returned to the researchers and they receive a consultation as per their usual care. There are also two three-month evaluation visits combined with usual care visits for which the patient will need to complete questionnaires and blood samples will be taken. Before the last visit, again a FSL Pro is worn for two weeks.

### 5.2 Use of co-intervention (if applicable)

As the intervention is intended to be used as a part of regular care, there are no restrictions regarding use of a co-intervention. Participants in both the intervention and control group are allowed to adjust their self-care, self-management goals, and access healthcare as they would if they were not participating in the study as long as this would be acceptable as a part of their usual care. It is possible to schedule extra visits in both groups when desired by the researcher and/or participant. Participants are allowed to use their own continuous glucose measuring device or FSL during trial as long as the devices store glucose data as required by the study and make the glucose data available to the researchers at each consultation. In the event that the patient uses their own FSL, the study group will provide two sensors as they would for patients who do not have their own FSL, but will not provide a reader.

### 5.3 Escape medication (if applicable)

There are no restrictions on medication adjustments or changes to medical care for this study.

# 6. Investigational product

## 6.1 Name and description of investigational product(s)

The POWER2DM system is a personalized self-management support system (SMSS) for T1D and T2D patients that combines and integrates: 1) a decision support system (DSS) based on interlinked predictive computer simulation models for use with healthcare providers; 2) and a mobile SMSS for use by the patients. The POWER2DM integrates mobile health (mHealth) technologies and real-time data processing to help track and communicate the patient's self-management actions. The overall focus of the POWER2DM system lies in supporting individuals to achieve optimal self-management behaviour in order to obtain/maintain long–term optimal metabolic control, to prevent diabetes progression and complications.

### 6.1.1 The POWER2DM Shared Decision Making Dashboard

The POWER2DM DSS is a tool intended for use with a healthcare provider to review and facilitate shared decision making and goal setting for the patient's diabetes self-management. The DSS provides a visual overview of the patient's current care plan and presents data gathered by the SMSS alongside visualizations of short-, medium-, and long-term risk scores and computer simulations to assist in this process. Additionally, the DSS can be used to simulate the effect that changes to lifestyle and self-management plans can have in these short-, medium-, and long-term models.

#### 6.1.1.1 Predictive computer simulation models and risk scores

- KADIS: The KADIS simulation model is a short term prediction model based on 72 hours of patient data regarding blood glucose values, oral medication, insulin therapy, carbohydrate intake, and exercise [29, 32]. KADIS can visualize 24-h glucose absorption patterns based on bread exchange unit (BU) intake and insulin equivalents of exercise, as well as action profiles of exogenous insulin and, in the case of type 2 diabetes, also of endogenous insulin and of oral anti-diabetic drugs in relation to the diurnal insulin sensitivity. The model can be used in clinical practice with T1DM and T2DM patients as an interactive simulation of a person's daily therapeutic regime to assist physicians in choosing individual diabetes management regimens for optimizing glycemic control based on calculated patient specific parameters. In addition to this, the KADIS produces Q scores which assess risk of having uncontrolled blood glucose and HbA1c levels.

- MT2D Marvel: The MT2D-Marvel model is a medium-term prediction model that can be used for forecasts of T2DM progression in response to possible lifestyle therapies. The model combines measures of current metabolic status with assessments of eating, physical activity, sleep, and stress to predict medium term complications.
- ADVANCE risk scores: The ADVANCE risk scores are derived using the ADVANCE Cardiovascular risk engine and the ADVANCE Kidney risk engine which provide the risk of developing cardiac and kidney complications in PWD [41-43]. The ADVANCE risk engines combine aspects of the patient's current physical and clinical assessments with medical history and current care plan to give a risk percentage for developing cardiovascular disease, kidney disease, or dying due to either disease.
- Major Outcomes T1D: The Major Outcome T1D model uses the prognostic factors of age, glycated haemoglobin, waist-hip ratio, albumin/creatinine ratio, and HDL cholesterol to classify people according to risk groups for major outcomes including major coronary heart disease, stroke, end-stage renal failure, amputations, blindness and all-cause death [44].
- UKPDS Risk Score: The UKPDS is a risk engine used to calculate a risk score for T2DM patients developing coronary heart disease [45]. The engine uses a combination of demographic information, health information, and clinical lab values to calculate risk for developing coronary heart disease, stroke, or death resulting from either.

### 6.1.2 The POWER2DM Online and Mobile Self-Management Support system

The POWER2DM Online and Mobile Self-Management Support system (SMSS) supports the individual in achieving the personalized and specified self-management goals, by providing with feedback on goal progress and making use of behavioural change techniques. The system does this by integrating data collected directly from the patient along with data gathered via connected mHealth technologies to create a total picture of the patient's diabetes self-management experience. By combining these data points, the SMSS is able to target aid to the patient in the form of Just In Time Adaptive Interventions (JITAI), self-management barrier identification and targeted interventions to overcome these barriers, psychoeducation, and assistance in revision self-management action plans. Additionally, the SMSS communicates information to the DSS for use in the consultation room.

#### 6.1.2.1 **Patient generated data**

The SMSS will gather patient generated data regarding diet, exercise, insulin and medication usage, as well as have the ability to assess psychological states such as mood and stress. The SMSS does this via a mobile phone application and can be used by the patient as a diabetes diary or log book to help track their self-management.

#### 6.1.2.2 **JITAIs**

Just-In-Time-Adaptive-Interventions (JITAI) are interventions that are targeted to the specific needs of the patient by identifying problem areas that the patient experiences and the time context in which these issues often occur. JITAIs will be delivered to the patient on a schedule which they can adjust based on their personal preferences.

#### 6.1.2.3 **Action Plan Engine**

The SMSS contains an Action Plan Engine (APE) which will ask targeted questions regarding self-management and psychological health to patients based on a schedule that they decide and in conjunction with reviews of self-management. This process begins by asking the patient whether they are satisfied with their self-management goals/plans and whether they have reached their goals as planned. If the patient is unsatisfied, has not reached their goals, or wishes to change their goals or plans, the system will guide the patient through a barrier identification process to identify possible issues that may be preventing the patient from successfully self-managing. This process will end by offering the patient support in achieving their self-management goals using either motivational messaging, simple psychological exercise to help overcome barriers, psychoeducation related to the patients self-management plans and diabetes, or the ability to change the self-management plans.

#### 6.1.2.4 **Sensors**

The SMSS integrates information from connected mHealth devices to track the patients activity in two specific areas: physical activity and SMBG. mHealth devices integrated into POWER2DM are available on the commercial market. Data regarding the patient's physical activity includes steps taken, stairs climbed, heart rate, sleep duration will be done by connecting to commercially available products passively collect data related to the patient's physical activity. Data regarding SMBG include blood glucose levels and the frequency of checks. Information from

these devices is uploaded to secure servers via mobile phone applications and can then be used in the SMSS to help the patient track their self-management and be used by the APE.

### 6.2 Summary of findings from clinical and non-clinical studies

There is an abundance of literature on the use of mHealth technologies both in diabetes management and chronic illnesses in general [14-23, 25, 27, 28, 46-53]. The general consensus seems to be that interventions at the least do no harm and at the most have positive outcomes for the patient. More relevantly, in the previous QC study conducted with PWD here in the LUMC, all patients reported wanting a tool like this. Something that helps them track their diabetes, connect with their care giver, and provides support between the consultations. Patients reported that they liked having the activity tracker and that having objective measures like that helped to motivate them to be more active. The primary complaint from this early study was that the application was in such an early stage that they could not use it according to the final plans described for POWER2DM indicating that a system like this is something that patients want available to them.

### 6.3 Summary of known and potential risks and benefits

Since the POWER2DM system itself is software, electronic and microbiological safety is not an issue. The sensors used in the POWER2DM system are all CE marked and are available on the European market. Targets are only set in the SDM dashboard in consultation with a health care professional in a clinical setting and therefore entail no additional risk outside of that associated with a normal consultation. This is most important in regards to advice regarding glucose regulation as this is the area with the greatest potential for negative side-effects. The POWER2DM system does not provide participants with any specific advice regarding their medical care plan (e.g. “inject more insulin”). Changes in these areas are only done in consultation with a health care professional thus limiting the risk of inducing severe hypo- or hyperglycaemia due to inadequate advice by the system. The primary risk is that of negative affect associated with more attention being drawn to the patient’s illness. This is an issue that has been raised by patients, some of whom do not want to be over-burdened by thinking about having diabetes. Distress like this is not uncommon in people with chronic diseases and can present a real burden to the patient. The POWER2DM system is actually designed with these people in mind and allows for the patient to specify how often they want the system to interact with them. In this way, the patient can control how much

attention the POWER2DM system brings to their diabetes. Further, the APE can help the patient cope with these feelings through targeted interventions.

The primary benefit to the patient is support between the consultations, when they are usually left to manage their diabetes without professional support. POWER2DM provides support to PWD in these times, when the majority of diabetes management occurs. Further, the compiling of diabetes relevant information and passive communication of this information to the patient's health care provider will lead to better care for the patient, increasing satisfaction with their care and hopefully lead to better control of their blood glucose levels thus reducing the risk of long-term complications.

### 6.4 Description and justification of route of administration and dosage

Not applicable

### 6.5 Dosages, dosage modifications and method of administration

Not applicable

### 6.6 Preparation and labelling of Investigational Medicinal Product

Not applicable

### 6.7 Drug accountability

Not applicable

## 7. NON-INVESTIGATIONAL PRODUCT

Not applicable

## 8. METHODS

As there are two separate stages in this study with different study procedures, they will be described separately here.

### 8.1 Stage 1: Feasibility Study

#### 8.1.1 Study parameters

8.1.1.1 **Primary study endpoint:**

User Experience and Feedback when using prototype 1 of the SMSS

8.1.1.2 **Secondary study endpoint:**

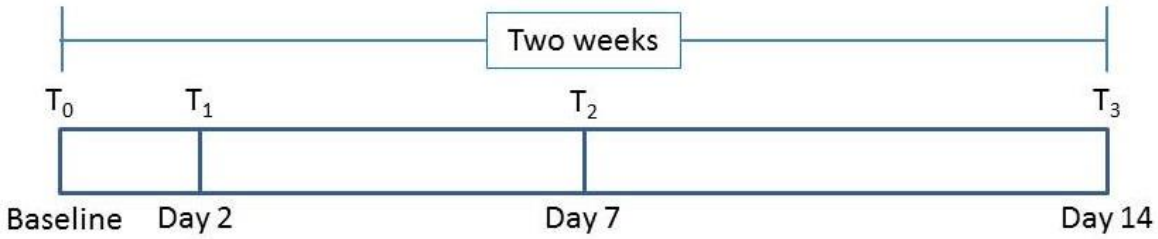
Technical review of the SMSS connectivity to POWER2DM System

### 8.1.2 Randomisation

N/A, this is an observational study meant to refine the prototype based on user feedback and real-world usage statistics

### 8.1.3 Study Procedure

The study consists of two visitations, set two weeks apart, with two contact points between the visitations occurring after the participants have been recruited and informed consent letters have been signed in accordance with Section 11.2. The study procedures for Stage 1 begin with contacting potential participants.




At the first visitation ($T_0$), the patient will be instructed on how to set up the SMSS on their phone with the assistance of the researcher. They will then receive instructions on operation of the devices that they will need to use (see section 8.1.4) and instruction on what they need to do during the two week period. During this period, the patient will be asked to test the SMSS by using it alongside their normal care. Two days ($T_1$) and seven days ($T_2$)after the patient's start date, they will be contacted by researchers and asked about any issues or feedback that they have regarding the SMSS. If there are serious technical issues, the researcher will attempt to resolve them on the phone. After 14 days ($T_3$), the patients will return any devices that they received and attend a debriefing session where they will give feedback on their user experience.

**Figure 4. Stage 1, Feasibility Study timeline**

Any technical issues resulting in non-usability of the system will result in an assessment regarding continuation of the study. Patients will be asked if they would be able and willing to resume testing the system once it has been fixed. If they are able and willing, the researcher and patient will agree upon a new study duration not longer than two weeks. If the participant is not able and/or willing then the study will stop.

### 8.1.4 Devices

The patients will be asked to install the SMSS on their personal mobile phone for the duration of the study. More information on the SMSS can be found in Section 6 of this protocol.

The patients will be provided with a Fitbit Charge 2 activity tracker and an iHealth BG5+ Bluetooth connected blood glucose monitor. These devices will only be used to assess the technical aspects of connecting mHealth devices to the POWER2DM system in real-world settings; no data collected will be used for patient specific analysis.

## **8.2** Stage 2

### **8.2.1** Study Endpoints

#### 8.2.1.1 **Primary study endpoint**

Difference in glucose regulation as measured by HbA1c% before and after treatment

#### 8.2.1.2 **Secondary study endpoints**

##### 8.2.1.2.1 *Safety:*

As measured by:

- amount of hypoglycaemia measured by time spent in hypoglycaemia before and after treatment in the Power2DM group compared to the usual care control group,
- hypo unawareness as measured by Clarke's hypo unawareness questionnaire, before and after treatment in the Power2DM group compared to the usual care control group and
- other adverse events occurring during the study period to include serious hypoglycemic events among others

##### 8.2.1.2.2 *Glucose variability:*

As derived from continuous measurements and defined as measured by:

- Mean blood glucose (MBG)
- Standard deviation of MBG (SDBG)
- Largest amplitude of glycemic excursions (LAGE)
- Mean amplitude of glycemic excursions (MAGE)
- Absolute means of daily differences (MODD)
- Time spent in range

8.2.1.2.3 *Change in Model based risk scores including:*

- ADVANCE Cardiovascular risk
- ADVANCE Kidney disease Risk
- Major outcomes T1D
- UKPDS risk score
- MT2D-Marvel model
- KADIS-based Q score

8.2.1.2.4 *Behavioural change (self-management)*

- Exercise
- Frequency of SMBG measurements
- Adherence to medication plan
- Amount of goals reached
- Weight (and BMI)
- Diabetes Self-Management Questionnaire score

8.2.1.2.5 *Psycho-social changes*

- Quality of life
- Diabetes burden
- Mental health
- Diabetes knowledge
- Diabetes self-efficacy

8.2.1.2.6 *User satisfaction*

- Satisfaction with diabetes care
- Communication with healthcare provider
- User feedback on SMSS
- Goal Progress
- Usage of app
- Usage of features

8.2.1.2.7 *Cost-effectiveness (socio-economic impact)*

8.2.1.3 **Other study parameters (if applicable)**

- Patient characteristics
  - Age
  - Gender
  - Weight
  - Height
  - Medical history
  - Diabetic complications

### 8.2.2 Randomisation

A stratified randomisation procedure will be used to assign participants to either the POWER2DM self-management support as an adjunct to usual care group (Power2DM group) or to usual care alone (control group). The stratification will be done using a computerised algorithm with two stratification classes: disease type and clinical center. This method will ensure that there is a 1:1 ratio for both stratification classes in both study groups. A full breakdown of the stratification blocks can be found in Table 1.

### 8.2.3 Study procedures

Stage 2 of the study consists of consultations and self-management periods spread across 38 weeks. The study starts with a Baseline Consultation followed by a short data collection period and before participants either receive a consultation as a part of their usual care or an intervention consultation. Consultations follow every three months with self-management periods between. The study finishes with a Debrief Consultation after 38 weeks. The timeline for the study can be seen in Figure 8.2.3F below

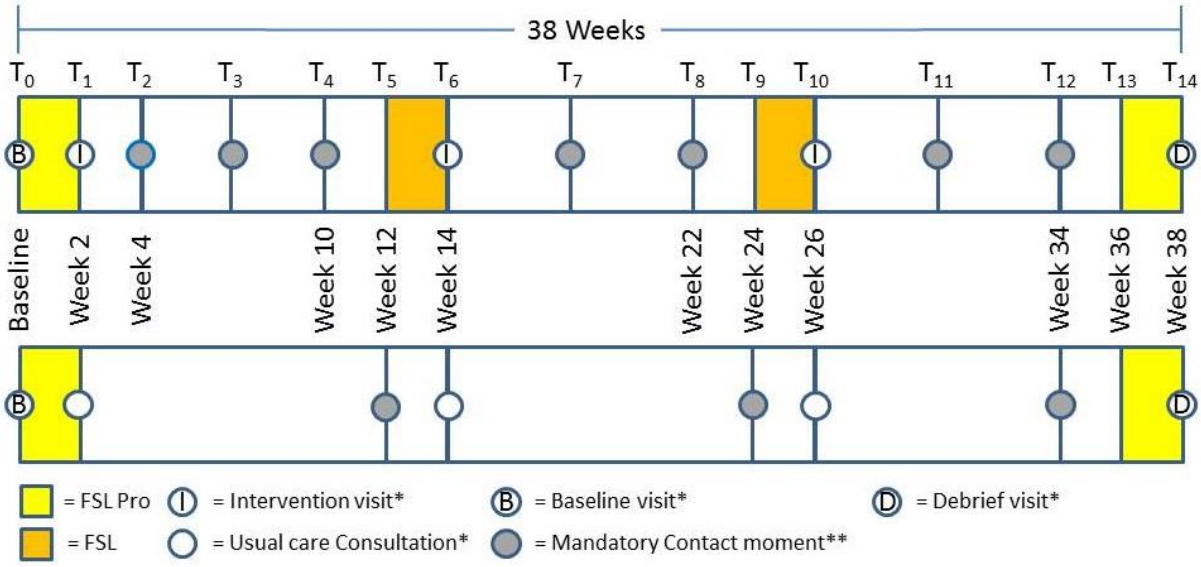



**Figure 5. Timeline of Stage 2, Evaluation Campaign: Top- schedule for intervention group; Bottom: schedule for control group. * Consultations and the start of the intervention are in person; ** Contact moments can be either in person or via telephone/email as desired;**

#### 8.2.3.2 Baseline Procedures

After patients have been recruited according to the recruitment procedures found in Section 11.2 of this protocol, a Baseline Consultation will be planned during which baseline measurements will be taken for all participants in the study regardless of whether they are receiving the intervention or are in the control group. These measurements will be recorded in an eCRF The Baseline Measurements consist of personal demographic information, body measurements and vital signs, a medical history, and a set of questionnaires, For more information on the questionnaires, body measurements and vital signs, see the Data Collection Methods Section below.

A medical history including concomitant illnesses and medication will be recorded for each participant. A Medical history is a list of medical events that the subject has experienced in past. Only relevant medical history, as judged by the investigator, should be reported. A concomitant illness is any illness other than diabetes that is present at the start of the trial or found as a result of the screening procedure. A clinically significant worsening of the concomitant illness during the trial must be reported as an adverse event. Concomitant medication is any medication that is taken during the trial.

After all Baseline Measurements have been taken a FSL Pro sensor will be applied. If the patient is randomized to the intervention group, an appointment will be made for them to return to the clinical center after two weeks for the first intervention consultation. If the patient is randomized to the control group, they will return the sensor two weeks later at their next regular appointment, and an appointment will be made for over three months to submit blood samples, complete questionnaires, and receive another FSL Pro for data collection.

#### 8.2.3.3 **Shared Decision-Making Consultation Procedures**

For the intervention group, three intervention consultations will occur between the patient and their healthcare provider during the study. The first will occur two weeks after the Baseline Measurements are taken. This initial consultation will involve the setting up and first usage of the POWER2DM system (including all monitoring devices and the installation of required apps) for use in monitoring and making of care plans. The doctor will discuss the patient's current care plans and any ways in which the patient would like to revise these. They will then discuss and review different options using the dashboard before agreeing on two diabetes self-management goals to aim for in the coming months. Based on these goals, the doctor and the patient will create SMART goals as described in the POWR2DM Dashboard training manual.

The next two consultations will occur 3 and 6 months after the start of the intervention. Each of these consultations will be preceded by a two week period in which the patient will be provided with a FSL both for their self-management and to gather data to feed the predictive models used in the SDM consultations. The primary focus of these consultations is to discuss how the patient has been managing their diabetes including (as in usual care), but with the added insight that the POWER2DM system can give into their self-management experience. Prior to starting this procedure, the healthcare provider and the patient will discuss the patient's healthcare usage in the previous period, changes to concomitant medication, and report and adverse events that the patient has experienced in accordance with the guidelines laid out in the section *Safety Reporting: AEs, SAEs and SUSARs* of this protocol. Additionally, the patient will be required to complete any questionnaires related to this visit that they were unable to complete prior to the consultation, body measurements and vital signs will be noted, and blood samples will be drawn.

The healthcare provider and patient will use this information along with the predictive models provided in the SDMDB to help adjust the care plan (where necessary) finishing by agreeing on two goals to strive for regarding the patient's management of their diabetes in the coming self-management period. The doctor and patient will then agree upon a specific action plan to achieve these plans according to SMART guidelines for goal setting. The doctor will then input these goals and action plans into the POWER2DM system and a new period of self-management will begin.

For the control group, no additional consultations in connection with the POWER2DM study will occur between the Baseline and Final/Debrief consultations. During this time, the patients assigned to the control group will follow their normal diabetes consultation schedule.

#### 8.2.3.4 Self-Management Period Procedures

There are three planned Self-Management periods start after the SDM consultations have occurred and end with another consultation. These periods consist of the patient managing their diabetes according to the agreed upon self-management plan created with their healthcare provider. During this period, the patient will attempt to reach their self-management goals using the POWER2DM SMSS which will be connected to a wireless blood glucose monitor and a wristband activity tracker. At the end of each period, the patient will be given a FSL (Pro) to use to collect data related to their glucose variability.

In addition to the self-management of diabetes that the patients need to conduct during these periods, there are mandatory contact points scheduled for researchers to inquire as to the patient's use of the SMSS and any (technical) issues that they may be having regarding use of the system. These contact points can be done using any medium agreed upon by the research team and the participant (e.g. telephone, email, WhatsApp, etc.). The first of these contact moments occurs two weeks after the initial consultation to enquire as to the use of the SMSS. Additional contact moments will occur two weeks prior to the start of a new FSL (Pro) to ensure that the patient wishes to remain active in the POWER2DM study prior to sending out materials. Additional the patient will be contacted at least once between weeks 4-10, 14-22, and 26-12 at a time agreed upon by the contact person and the patient. These contact points are intended to be used to maintain motivation in the study and prevent drop-outs. These contact points will be restricted to discussions surrounding the use of the SMSS for diabetes self-management any non-urgent issues that the patient wishes to discuss during these moments will be noted and discussed in the next following consultation.

Additional contact moments can occur as desired by the researcher upon indication that there is an issue related to protocol non-compliance or technical problems. These are optional, non-scheduled moments which will not occur more often than once per week except in the case of a follow-up regarding technical problems and their solutions.

For the control group, no additional self-management actions will occur in connection with the POWER2DM study will occur between the Baseline and Final/Debrief consultations other than completing questionnaires sent by email and wearing an FSL Pro prior to the debrief consultation. During this time, the patients assigned to the control group will follow their normal diabetes consultation schedule. Optional contact moments can occur between weeks 2-8, 14-20, and 26-32 and be used to follow-up on questionnaires or issues the control group participants may have had. All control group patients will be contacted one week prior to being sent questionnaires of FSL Pro. They will then have to apply the sensor on weeks 12, 24, 36 and return this to the researchers via post two weeks later.

#### 8.2.3.5 Final Consultation/Debrief Procedure

The final consultation will occur 38 weeks after the baseline measurement and will consist of a debrief in which the patients will return any equipment not be given as incentives and the experiences that the patient had during the study will be discussed. In addition, the patient will be asked about changes in their personal demographic information and any adverse events will be recorded. Their body measurements and vital signs will be noted and a blood sample will be taken. The researcher will also ask them to complete any required questionnaires in accordance with the data collection schedule below. For more detailed information on the questionnaires, body measurements and vital signs being recorded at this time point, see the Data Collection Methods Section below.

#### 8.2.3.6 Post participant data points

Information about patient medication usage during the study period will be gathered from pharmacy databases to be used for economic analysis.

### 8.2.4 Data Collection Methods

Due to the length of the study and the different requirements for data collection, this section will be limited to only a description of the data being gathered. For information regarding of the timing of the data collection see Table 2.

#### 8.2.4.1 Body measurements and vital signs

All values of the body measurements will be recorded in the eCRF. Height (without shoes) will be measured by the Investigator at screening (Visit 1) only. Body weight will be measured at each visit should be measured without overcoat and shoes, wearing only light clothing. The body weight should be assessed on the same calibrated weighing scale equipment throughout the trial, if possible. Blood pressure and pulse will also be measuring at all study visits. Blood pressure should be assessed while the subject is in a sitting position after five minutes of rest. If the Subject is using antihypertensive medication to control the blood pressure, then the medication should be taken as usual prior to assessing vital signs.

#### 8.2.4.2 Questionnaires

The following questionnaires will be filled in by the participant at different moment during the study.

##### 8.2.4.2.1 *Quality of Life: SF-36, WHO-5*

Quality of life has been described as the ultimate goal of all health interventions [54]. Assessment of quality of life in the EC is necessary to understand the health status of the patients being assessed in order to evaluate specific areas that may need additional attention in the POWER2DM intervention. To measure QoL we will administer the WHO-5 Well-Being Index (WHO-5) at baseline. The WHO-5 was chosen over diabetes-specific measures of quality of life for its applicability to both T1DM and T2DM patients and to reduce the amount of overlap with other diabetes specific questionnaires that will also be used in this study. The WHO-5 is one of the most widely used questionnaires assessing well-being and consists of five simple, non-invasive questions [55]. The five items are assessed on a 6-point Likert scale ranging from 0 to 5 and the individual item scores are added together and transformed into a 100 point scale with lower scores indicating worse well-being [56]. The WHO-5 has been found to correlate moderately to strongly with diabetes specific measures of distress and depression in both T1DM and T2DM [57]. To assess health related quality of life (HRQL), the MOS Short Form 36 (SF-36) will be used. The SF-36 is a 36 item questionnaire used to evaluate the functional health status and well-being of an individual across an 8-dimension profile [54]. This questionnaire was developed as a shorter version of the original 116 item MOS HRQOL survey to assesses three overarching dimensions of quality of life: physical, psychological, and general health. These three dimensions can be divided into eight health dimensions: Physical Functioning

(PF), Vitality (VT), Bodily Pain (BP), General Health Perceptions (GH), Mental Health (MH), Physical Role Functioning (RP), Emotional Role Functioning (RE), and Social Role Functioning (SF). The use of the SF-36 allows for detailed analyses of what is impacting a patients HRQL.

#### 8.2.4.2.2 ***Depression: PHQ-9***

Comorbid depression and mood related problems is a common issue amongst diabetes patients and is associated with poor glycemic control, hyperglycemia and other associated complications [54]. Therefore all patients will be assessed for symptoms of depression at baseline. The Patient Health Questionnaire (PHQ-9) is a nine-item, self-administered questionnaire which measures each of the 9 DSM-IV criteria for depression on a four point scale [55]. These scores range from 0 to 3 with three indicating near daily frequency. The sum of these scores (range= 0-27) is then used to assess the level of depression with cut-off points of 5, 10, 15, and 20 representing mild, moderate, moderately severe, and severe symptoms of depression respectively. The PHQ-9 has been assessed in diabetes patient populations and was found to be an efficient screening instrument for major depressive disorder with a cut-off of 12 representing the best combination of sensitivity and specificity for use in assessing the presence of depression [56].

#### 8.2.4.2.3 ***Anxiety: GAD-7***

Generalized anxiety disorder has been found to present in 14% of diabetic patients with 40% of all diabetes patients reporting elevated symptoms of anxiety in clinical studies [38] and is associated with poor glycemic control [36]. For this reason all patients will be assessed for symptoms of anxiety at baseline. The brief measure of Generalized Anxiety Disorder (GAD-7) is a seven item anxiety scale that measures how often the patient has been bothered by specific symptoms of anxiety over the previous two weeks [57, 58]. These scores range from 0 to 3 with three indicating near daily frequency. The sum of these scores (range= 0-21) is then used as an assessment of the presence of anxiety with cut-off points of 5, 10, and 15 interpreted as representing mild, moderate, and severe levels of anxiety respectively. The GAD-7 has been validated for use in the general population [59] and has been previously used in two large scale studies of diabetes patients [60, 61].

#### 8.2.4.2.4 ***Stress: PSS***

Perceived Stress Scale (PSS): The PSS is a 10 item scale designed to measure the degree to which situations' in one's life are appraised as stressful [66]. The participant

rates each item based on their recall of the past month and the degree to which they perceived events as being stressful on a 5 point scale (never –almost never – sometimes – fairly often – very often). Four positively stated items are the reverse scored and then all scores are summed for an overall perceived stress score with higher score representing more perceived stress. A validated Spanish version is available [67], as well as Dutch and German translations. All participants will be required to complete this questionnaire at baseline, and at the ends of Phase 1 and Phase 2.

#### 8.2.4.2.5 ***Diabetes Distress: PAID***

The Problem Areas in Diabetes (PAID) questionnaire is a 20-item measure of psychosocial adjustment to diabetes developed by Polonksy et al. [68]. Each of the 20 items represents a unique area of diabetes-related distress which are rated on a 5 point Likert scale (range = 0-4). These individual items are then added together and multiplied by 1.25 to transform the raw score into a 0-100 scale with higher scores representing increased emotional distress [69]. The PAID was developed for routine clinical usage in both T1DM and T2DM and there are validated versions in Dutch [70], German [71], and Spanish [72]. All participants will be required to complete this questionnaire at baseline, and at the ends of Phase 1 and Phase 2.

#### 8.2.4.2.6 ***Diabetes Self-Management: DSMQ-R***

The Diabetes Self-Management Questionnaire-Revised (DSMQ-R) questionnaire is a revision of the original Diabetes Self-Management Questionnaire and contains 20- items that asks the patient about their self-management based on the previous [73, 74]. These items can be grouped into four factors (Glucose management, dietary control, physical activity, and physician contact) from which a sum score can be calculated for overall glycemic control. All subscales are highly correlated with levels of HbA1c. Additionally, the revised version has an additional 7-item subscale containing questions specific to insulin usage intended for patients using insulin. All participants will be required to complete this questionnaire at baseline, and at the ends of Phase 1 and Phase 2.

#### 8.2.4.2.7 ***Hypoglycemic related Distress-Behaviour: HFS-II***

Hypoglycemia Fear Survey-II (HFS-II): The HFS-II is a 33 item revision of a survey designed to quantify the fear associated with hypoglycemia in diabetes patients [75, 76]. The survey is divided into two sections assessing specific behaviors used to avoid low blood sugar and worry associated with low blood sugar. We will use the section which assesses behavior to identify target areas for behavior change interventions. Patients report on the frequency of these behaviors or feelings on a five point scale ranging from

never to almost always. A score can then be calculated for overall hypoglycemia fear or scale specific values. Only participants who use insulin, medication associated with hypoglycemic episodes, or those indicated as potentially having hypoglycemic related distress based on their responses on the PAID will be required to complete this questionnaire

#### 8.2.4.2.8 ***Diabetes related eating problems: DEPS-R***

Diabetes Eating Problem Survey-Revised (DEPS-R): The DEPS-R is a 16 items instrument developed to assess the presence of eating related problems in T1DM patients [77]. Patients report on eating behavior items using a 6-point Likert scale (0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = usually, 5 = always) with higher scores representing greater pathology. The DEPS-R was later validated with T2DM patients [78] and has been found to be highly correlated with the EAT-12, a generic measure of pathologic eating attitudes and behaviors [79].

#### 8.2.4.2.9 ***Hyperglycemia related Distress: FCQ***

Fear of Complications Questionnaire (FCQ): The FCQ is a 15 item questionnaire that evaluates patient fear surrounding long-term complications of diabetes [80]. It uses simple language to assess how much or how frequently someone worries or is afraid of developing these complications on a four point scale. A sum score of all the items can be used to calculate overall fear of complications.

#### 8.2.4.2.10 ***Fear of injections and Self-Monitoring: D-FISQ***

Diabetes Fear of Injecting and Self-Testing Questionnaire (D-FISQ): The D-FISQ is a 21 item questionnaire designed to assess fear of injecting insulin and fear of self-testing blood glucose in diabetes patients [62]. The patient reports on the frequency of given actions on a 4 point scale (range: almost never-sometimes- often-almost always). The questionnaire can be split into specific scales to measure the two individual factors of fear of injecting insulin and fear of self-testing blood glucose. Patients who indicate on the PAID that they may have anxiety related to self-testing will be required to complete the fear of self-testing blood glucose scale, and only those on insulin therapy or who indicate on the PAID anxiety related to insulin injections will be required to fill in the fear of injecting insulin scale.

#### 8.2.4.2.11 ***Clarke's Hypoglycemia Awareness Questionnaire***

Hypoglycemia awareness will be measured using a question developed by Clarke et al. to assess the frequency and severity of hypoglycemic episodes [62]. The instrument consists of 8 items and has been found to be a good measure of whether a person has reduced

awareness of hypoglycaemia. Validated versions are available in Spanish and Dutch [63, 64].

#### 8.2.4.2.12 *Whitehall II Study Stress and Sleep Quality Questions*

Thirteen questions from the Whitehall II study questionnaire are used to feed the MARVEL model. These questions relate to lost sleep and restless nights, and feelings related to chronic stress assessed on a four point scale.

#### 8.2.4.2.13 *Health Literacy Scale*

Patient health literacy will be measured using a short, three question health literacy questionnaire developed for use in the general population to assess whether patients are able to perform basic reading and numerical tasks required to function in the health care environment [65]. The short version has been found to be valid in assessing health literacy in both Dutch and Spanish speaking populations [66, 67].

#### 8.2.4.2.14 *Patient Assessment of Chronic Illness Care*

To understand how the POWER2DM system improves the patient's perception of the care that they receive, the Patient Assessment of Chronic Illness Care Scale will be used. This is a brief instrument based on the Chronic Care Model which assesses whether the care received was patient-centered, proactive, planned and includes collaborative goal setting; problem-solving and follow-up support.

#### 8.2.4.2.15 *Technology acceptance and user satisfaction (only applicable for the Power2DM group)*

Technology acceptance and user satisfaction will be assessed via a semi-structured interview conducted by a researcher at each clinical site.

#### 8.2.4.2.16 *Health care consumption:*

For economic assessments, healthcare consumption during the study will be assessed using a short questionnaire asking about the occurrence of non-study related healthcare contact moments including but not limited to: regular/planned contact moments, irregular/non-planned contact moments, emergency contact moments, and all other times that the patient was in contact or used healthcare services, medication usage, and other healthcare related costs incurred during the study

#### 8.2.4.2.17 *Medications usage:*

Medication usage as a part of healthcare costs will be assessed by checking the medical records of the patient at their local hospitals and pharmacies.

#### 8.2.4.3 Laboratory tests

The following laboratory parameters will be assessed at points $T_0$, $T_5$, $T_9$, $T_{13}$ during the study.

Blood test for:

- HbA1c: Glycated hemoglobin (HbA1C) is the standard measure used for diagnosis and assessment of glycemic control [82]..
- Lipid profile (including total cholesterol, HDL-C, LDL-C, Triglycerides, VLDL-C, Non-HDL-C, Cholesterol/HDL Ratio)
- Fasting glucose (only for T2D without insulin treatment)
- Fasting insulin (only for T2D without insulin treatment)
- Albumin
- Creatinine

Urine test for:

- Urine-albumin
- Urine-creatinin

#### 8.2.4.4 mHealth Devices

##### 8.2.4.4.1 *SMBG measurement device*

Self-monitoring of blood glucose levels will occur using the iHealth Smart Wireless Gluco-Monitoring System BG5 and BG5+ (BG5). The BG5 is a wireless blood glucose monitor that measures blood glucose and automatically uploads the values to a Bluetooth connected device with the POWER2DM mobile application installed, allowing for the storage and tracking on blood glucose values on mobile devices and uploading to secure cloud databases. The BG5 is CE marked and meets the newest ISO standards (ISO 15197:2013)[68] The connection of the BG5 device with the POWER2DM system, allows us to gather data of all SMBG measurements done by the participants. Since the control group will not be receiving a connected device, they will be asked to bring the own SMBG device to the final consultation for data to be downloaded by researchers.

##### 8.2.4.4.2 *FreeStyle Libre/FreeStyle Libre pro*

Continuous monitoring of glucose levels will be done using the FreeStyle Libre (FSL) or the FreeStyle Libre Pro (FSL Pro) Flash Glucose Monitoring System which continually measure interstitial fluid glucose levels. The systems consists of a small FSL Sensor and a wireless FSL Reader. The FSL Sensor stores the

previous 8 hours of continuous glucose levels in 15 minute increments and is not blinded. The FSL Pro stores 14 days' worth of continuous measurement of interstitial fluid glucose levels in 15 minute increments and is blind to the patient. Sensors in both systems are valid for a period of two weeks and can be installed by the patient. When the FSL is scanned using either the associated system reader or an NFC enabled Android devices with the LibreLink app installed, the latest glucose measurement is displayed and stored information is uploaded to the reader or Android device. The FSL Pro is blind to the patient and is only scanned once wirelessly by the treating physician after 14 days using the associated system reader. The FSL has been tested and found to be at least 85.2% accurate over a 14 day period [69].

FSL Pros will be used at baseline and prior to the final consultation/debrief for both intervention and control groups so that . At weeks 12 and 24, intervention group participants will receive a FSL while the control group will receive the FSL Pro. This data will be used for the measurement of glucose variation, time in range, time in hypo and mean glucose concentration.

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#### 8.2.4.4.3 *Activity tracker*

The Fitbit Charge 2 is a wristband activity tracker that tracks physical activity. When the wearer has the tracker on it passively collects data on physical activity (counts steps, duration and intensity of physical activity, and calculates calories burned), sleep (duration, frequency, and quality/disturbances), and heart rate [45]. It has a non-intrusive design, can automatically upload tracked information to connected devices, and has a five day battery life and can store seven days' worth of data memory which reduces the daily burden of maintenance for the patients. The Fitbit Charge 2 automatically uploads data to the users mobile device when the associated mobile application is installed, and this data can then be accessed by the POWER2DM system, allowing for seamless, real-time tracking and analysis for patient feedback.

#### 8.2.4.4.4 *Parameter tracking by the POWER2DM SMSS*

The POWER2DM SMSS is will also be used to track data through its mobile application. The SMSS can collect patient generated data related to medication and insulin usage, diet, exercise, mood, and stress.

- Medication and insulin usage: Users are able to track the type, dosage, and time of usage for all medications and insulins used in connection with their diabetes self-management. Using this information, the SMSS can help the patient track their diabetes self-management and the patient's adherence to their treatment plan.
- Diet: Food intake plays a critical role in diabetes management both in terms of maintaining a healthy body weight and in how carbohydrate intake is directly related to blood glucose concentration. For PWD using insulin, carbohydrate intake is also important when determining the insulin dosage necessary to maintain blood glucose levels. Therefore, three options are given for logging eating behaviour. 1) Carbohydrate intake in categories (low: 0-24g, medium: 24-48g, high: 48-72 and very high: 72g or more) 2) amount of carbohydrates in grams and amount of total food intake in kilocalories and 3) using a food library (in categories of low, medium, high and very high or in grams) in the system, this data can be used as outcome parameter.
- A 5 point stress score will be integrated into the POWER2DM mobile application.. On this scale 1 means absolutely no stress and 5 maximum stress.
- The system is designed to set goals and support the user in reaching them, so goal progress is another parameter which can be extracted from the POWER2DM system.
- A pictorial mood scale is also available in the app for use in tracking the how mood impacts diabetes and its management, and vice versa.
- In addition, the system can gather data on the usage of the app and its different functionalities.

### 8.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons or failure to follow the protocol. In that case, investigator may replace that patient in order to achieve the stablished number of subjects needed for the EC.

**Table 2. Study Parameters Timeline**

| STUDY PARAMETERS | $T_0$ | $T_1$ | $T_2$ | $T_3$ | $T_4$ | $T_5$ | $T_6$ | $T_7$ | $T_8$ | $T_9$ | $T_{10}$ | $T_{11}$ | $T_{12}$ | $T_{13}$ | $T_{14}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Personal info** | | | | | | | | | | | | | | | |
| Date of birth, Gender, Ethnicity, Education level, Age of completion formal education | X | | | | | | | | | | | | | | |
| Substance usage (smoking, drugs, alcohol) | X | | | | | X | | | | X | | | | X | |
| Psycho-social living situation (AS4) | X | | | | | | X | | | | X | | | | X |
| | | | | | | | | | | | | | | | |
| **Body Measurements and Vital Signs** | | | | | | | | | | | | | | | |
| Weight | X | | | | | | X | | | | X | | | | X |
| Height | X | | | | | | X | | | | X | | | | X |
| Waist | X | | | | | | X | | | | X | | | | X |
| Hip | X | | | | | | X | | | | X | | | | X |
| Blood pressure | X | | | | | | X | | | | X | | | | X |
| | | | | | | | | | | | | | | | |
| **Medical Anamnesis** | | | | | | | | | | | | | | | |
| Type diabetes | X | | | | | | | | | | | | | | |
| Age diabetes diagnosis | X | | | | | | | | | | | | | | |
| Diabetes duration | X | | | | | | | | | | | | | | |
| Diabetes complications | X | | | | | | | | | | | | | | |
| Medical History (including concomitant medications and other illnesses including atrial fibrilation, or changes since last visit and adverse events) | X | | | | | | X | | | | X | | | | X |
| | | | | | | | | | | | | | | | |
| **Lab values** | | | | | | | | | | | | | | | |
| HbA1c | X | | | | | X | | | | X | | | | X | |
| Lipid profile (total cholesterol, HDL-C, LDL-C, Triglycerides, VLDL-C, Non-HDL-C, Cholesterol/HDL Ratio) | X | | | | | X | | | | X | | | | X | |
| Fasting Glucose and insulin (only for type 2 without insulin treament) | X | | | | | X | | | | X | | | | X | |
| Albumin | X | | | | | X | | | | X | | | | X | |
| Creatinine | X | | | | | X | | | | X | | | | X | |
| Urine-albumin | X | | | | | X | | | | X | | | | X | |
| Urine-creatinin | X | | | | | X | | | | X | | | | X | |
| | | | | | | | | | | | | | | | |
| **Glucose variables** | | | | | | | | | | | | | | | |
| Two week continuous glucose measurement via FSL/FSL Pro | X | | | | | X | | | | X | | | | X | |
| Reported hypoglycemeic events | | | | | | | X | | | | X | | | | X |
| | | | | | | | | | | | | | | | |
| **Questionnaires** | | | | | | | | | | | | | | | |
| QoL: SF36, WHO-5 | X | | | | | | | | | | | | | | |
| Depression: PHQ-9 | X | | | | | | | | | | | | | | |
| Anxiety: GAD-7 | X | | | | | | | | | | | | | | |
| Stress: PSS | X | | | | | | | | | | | | | | |
| Diabetes Self-Management: DSMQ-R | X | | | | | X | | | | X | | | | X | |
| Diabetes Distress: PAID | X | | | | | X | | | | X | | | | X | |

| STUDY PARAMETERS (CONT'D) | $T_0$ | $T_1$ | $T_2$ | $T_3$ | $T_4$ | $T_5$ | $T_6$ | $T_7$ | $T_8$ | $T_9$ | $T_{10}$ | $T_{11}$ | $T_{12}$ | $T_{13}$ | $T_{14}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Questionnaires (cont'd)** | | | | | | | | | | | | | | | |
| Hypo Awareness: Clarke's | X | | | | | X | | | | X | | | | X | |
| Hypo Distress-Behavior: HFS-II | X | | | | | X | | | | X | | | | X | |
| Hyper Distress: FCQ | X | | | | | X | | | | X | | | | X | |
| Fear of Injecting and SMBG: D-FISQ | X | | | | | X | | | | X | | | | X | |
| Diabetes Eating Problems: DEPS-R | X | | | | | | | | | | | | | | |
| Whitehall II Study Sleep Quality Questions | X | | | | | X | | | | X | | | | X | |
| Whitehall II Study Stress Questions | X | | | | | X | | | | X | | | | X | |
| Health Literacy Questionnaire | X | | | | | | | | | | | | | | |
| Patient Assessment of Chronic Illness Care Scale | X | | | | | | X | | | | X | | | | X |
| Healthcare usage | | | | | | | | | | | | | | | X |
| Medication usage | | | | | | | | | | | | | | | X |
| | | | | | | | | | | | | | | | |
| **Other** | | | | | | | | | | | | | | | |
| Technology acceptance and User feedback on SMSS | | | X | X | | | | X | | | | X | | | X |
| | | | | | | | | | | | | | | | |
| **(Semi-)Continuous data collection paramters during self-management periods** | | | | | | | | | | | | | | | |
| SMBG (time, frequency, glucose value) | | | | | | | | | | | | | | | |
| Reported hypoglycemeic events | | | | | | | | | | | | | | | |
| Medication/Insulin usage (time/date, type, dose) | | | | | | | | | | | | | | | |
| Dietary intake | | | | | | | | | | | | | | | |
| Physical activity (steps, time active, heart rate) | | | | | | | | | | | | | | | |
| Sleep (duration, restlessness) | | | | | | | | | | | | | | | |
| Mood | | | | | | | | | | | | | | | |
| Stress | | | | | | | | | | | | | | | |
| Treatment goals reached or progress towards | | | | | | | | | | | | | | | |
| SMSS app open time and feature usage | | | | | | | | | | | | | | | |

# 9. SAFETY REPORTING

## 9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

## 9.2 AEs, SAEs and SUSARs

All Adverse Events (AEs), Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be recorded according to the following guidelines and tracked via electronic forms. Each AE, SAE, or SUSAR will be evaluated at the patient's host center by a medical committee composed of the physician who reported the event and lead physician responsible at that center (Dr. Javier Delgado-Lista at Spain and Dr. Eelco De Koning at LUMC). If it occurs that that the reporting physician is the lead physician, they will discuss the issue with another physician on the research team. The two lead physicians will share any AEs, SAEs, or SUSARs received at each center, and reports will be sent to the Ethical Committees.

### 9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to POWER2DM. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. Since this study is intended to be conducted next to normal treatment, no AEs are expected. However, At each visit following the initial visit, the participant will be asked whether they experienced any unwanted medical occurrence from the last visit. If an adverse event has taken place, the severity and causality of this event is assessed using the following definitions:

Severity:

- Mild: No or transient symptoms, no interference with the Subject's daily activities; acceptable
- Moderate: Marked symptoms, moderate interference with the Subject's daily activities;
- Severe: Considerable interference with the Subject's daily activities; unacceptable

Causality:

- Probable - good reason and sufficient documentation to assume a causal
- relationship
- Possible - a causal relationship is conceivable and cannot be dismissed
- Unlikely - the event is most likely related to etiology other than the POWER2DM system

The adverse event will be followed-up to assess the outcome. The final outcome will be described as followed:

- Recovered/resolved - the Subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the Subject signed the informed consent
- Recovering/resolving - the condition is improving and the Subject is expected to recover from the event. This term is only applicable if the Subject has completed the trial or has died from another AE
- Recovered/resolved with sequelae - the Subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE
- Not recovered/not resolved - the condition of the Subject has not improved and the symptoms are unchanged, or the outcome is not known
- Fatal - this term is only applicable if the Subject died from a condition related to the reported AE. Outcomes of other reported AEs in a Subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE
  Unknown - this term is only applicable if the Subject is lost to follow-up

### 9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- is a serious hypoglycaemic episode that requires external assistance;
- is a ketoacidosis
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission or pre-set clinical intervention or surgery will not be considered as a serious adverse event.

The principal investigator will report the SAEs through the web portal ToetsingOnline in the LUMC, or through an email to <cetico.hrs.sspa@juntadeandalucia.es> in the SAS center to the accredited METC that approved the protocol, within 15 days after the principal investigator has first knowledge of the serious adverse events.
SAEs that result in death or are life threatening will be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report. Since this study is intended to be conducted next to normal treatment, no SAEs are expected.

### 9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
    - Summary of Product Characteristics (SPC) for an authorised medicinal product;
    - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;

- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

### 9.3 Follow-up of adverse events.

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

## 10. STATISTICAL ANALYSIS

All Lifestyle and Daily Monitoring, Clinical Lab Test, and Patient Characteristic data (excluding Medical History and AS4) are considered quantitative in nature and will be presented as such. We will use the statistical software package Stata version 14 for all analyses [StataCorp, College Station, TX, USA]. Missing data will be handled through multiple imputation within Stata. Multiple imputation is a relatively flexible, general purpose approach to dealing with missing data that reduces the risk of bias associated with excluding or including incomplete data sets in analysis [70].

### 10.1 Primary study parameter(s).

The primary study outcome parameters of glucose regulation as measured by HbA1c and average glucose variability (Intraday: MBG, SDBG, LAGE, MAGE; Interday: MODD) will be used to asses group differences between the intervention and control group using a pretest-posttest Analysis of Covariance to assess whether the POWER2DM intervention was effective in helping glucose regulation.

### 10.2 Secondary study parameter(s)

The secondary study outcome analysis of safety will be derived via of reports of hypoglycemic events, and the occurrence and causality of the AEs, SAEs, and SUSARs in the intervention group. Independent samples T-test will be used to see whether the intervention group experience more hypoglycemic events, AEs, SAEs, and SUSARs than the control group on average. Additional pretest-posttest ANCOVAs assessing change in scores on measures of diabetes self-management, distress, depression, anxiety , QoL, assessments of chronic illness care, risk scores will be done to assess the impact that the POWER2DM system has on PWD. Usage statistics will be analyzed to see which aspects of the POWER2DM system was most utilized by patients to be utilized for guiding further development of the POWER2DM system and other eHealth interventions.

### 10.3 Interim analysis (if applicable)

None planned

# 11. ETHICAL CONSIDERATIONS

## 11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki, Finland, June 1964, amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. This study will be sent to the Medical Ethics Committee of the participating clinical centers for consideration and approval. This approval will have to be received prior to the start of the study. The subjects are required to give informed consent for participation in the study and confirm this by signing an informed consent letter.

## 11.2 Recruitment and Consent

Stage 1. Patients will be identified from a pool of patients who participated previously in the QC of the POWER2DM project and expressed interest in further involvement with POWER2DM. They will be contacted by researchers regarding participation in the Feasibility Study. Those who agree will arrange a time to come to the clinical center for a brief informational session where any questions can be answered. If the participant understands the requirements, has no further questions, and wants to participate, they will sign an informed consent letter and the study will begin either at that time or at a later date.

Stage 2. Potentially eligible participants will be identified by their healthcare providers and informed about the study. If the potential participant expresses interest in taking part in the study, they will be given an information letter (Appendix. XX) about the study to consider for one week. The potential participant will then be contacted after one week by a researcher to further discuss the study and answer any questions the participant may have. If the participant is satisfied with the information that they have received, they will be invited to a clinical center for a final information and question session regarding the study along with a final check for eligibility. If the participant understands the requirements, has no further questions, meets all eligibility criteria, and wants to participate, they will sign an informed consent letter and the study will begin either at that time or an appointment will be made for a Baseline Consultation at a later date.

### 11.3 Benefits and risks assessment, group relatedness

We do not consider this study to have any significant risk to the participants. The risks associated with participation in the intervention group are limited as any changes to the patient's diabetes care plan will be done in cooperation with a healthcare professional. The primary potential foreseeable risk associated with participation in this study is negative feelings resulting from the increased attention to the patient's illness. As the purpose of the system is to assist the patient in successfully managing their diabetes by drawing attention to their disease and its management, this risk is acceptable as the potential benefits associated with better diabetes and glucose control include lowered chance of developing diabetes related complications or dying.

Participation in this study entails a limited burden. The main burden associated with participation is that of time as participants will need to complete multiple questionnaire packets and track their diabetes self-management and there will be an increase in communication moments with the patient's healthcare provider. Additionanlly, there is an additional burden of having to apply an FSL which requires some skills and piercing of the skin to place the device. The FSL provides easy access to glucose measurements which many patients find beneficial, but some patients experience distress due to increased insight and attention to their glucose levels. The POWER2DM Evaluation Campaign (EC) is the second stage of the POWER2DM Project, and is based on the results of the first stage POWER2DM Quantification Campaign (QC). In that stage, a very positive feedback was reported by the participants in the study in the two centers with patients reporting an average satisfaction of 8/10 for the system as a whole and 100% of participants who completed the study (18/20) reporting that they would like to participate in later stages of the study. Based on this feedback, the risk of the negative feelings seems low. Further, although there are no other predictable risks inherent to the EC, there are long-term risks associated with uncontrolled glucose levels caused by Diabetes Mellitus. These cardiovascular, renal and other metabolic systems risks associated with uncontrolled glucose levels should be reduced through participation in POWER2DM, meaning that the potential benefit of reduced long-term complications outweigh the slight risk of negative feelings and burden of time related to participation.

Additional benefits for the patient in this study include access to a FSL sensor which allows for easy assessment of fluid glucose levels. Also, a metabolic fingerprint will be created for each patient. Having a metabolic fingerprint available will allow for the

patient to adjust their diabetes management routine with a speed and accuracy not available outside of this study, a task that is currently done through trial and error. Quickly improving this routine will help to reduce the risk of both short- and long-term diabetes complications in the most expedient manner possible. Additionally, the insight gained from the continuous glucose monitoring as to the impact that specific health behaviours have on glucose level management is something that most diabetes patients will never have access to. Further, the patients can increase their awareness of current mHealth available, to assist the self-management of diabetes. In the long term, the results will assist in the development and design of the patient-centered POWER2Dm diabetes self-management system, that will help diabetes patients manage their chronic conditions which thus be of help to the participants as well.

To manage and risks or potential issues we have taken several steps:

- Patients will be informed upon the purpose of the research at several stages of the process, including; the study advert, the participant information sheet, during the consent process and at the start of the study.
- Patient distress will be monitored after two weeks to see if there was a significant increase in distress compared to baseline. If this is found then the patient will be contacted and asked if they wish to continue in the study.
- Adverse events occurred during the length of the study will be evaluated, and relationship with the POWER2DM will be also investigated to identify courses of action to resolve these events and prevent their future occurrence.

### 11.4 Compensation for injury

Each clinical center will be responsible for assessing whether they will arrange an insurance policy for participants in the study.
They will either opt out of arranging their insurance due to the following reasons:
*Some medical studies need to have an insurance policy. This part of the study POWER2DM does not, because the risks of participating in this study are similar to normal follow-up care during their illness, or normal procedures / products already on the market. Due to that the risks of this study are minimal, there is no need for an specific insurance.*

Or will arrange the following:

*a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.*

### 11.5 Incentives (if applicable)

Incentives for participation are center specific and to be decided upon by the researchers responsible at each center. Possible incentives include:

- a “healthy food packet “ and dietary advice from a nutritionist
- FSL sensors
- FSL readers
- iHealth BG5/BG5+ Smart Wireless Gluco-Monitoring Systems

# 12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

## 12.1 Handling and storage of data and documents

Participants will be anonymised using patient ID numbers. Patient measurements will be uploaded either automatically or manually to the POWER2DM database. The POWER2DM platform is hosted by iHealthlabs Europe. All glucose measurements, and physical measurements of exercise, stress, sleep will be collected with devices via proprietary apps with a coded patient identifier. Data will automatically be transferred to POWER2DM via (already existing) connections with the proprietary servers. All questionnaires and VASs and dietary input will be logged manually by the patient in the POWER2DM system. All patient characteristics and clinical lab measurements will be manually entered into the POWER2DM database. Only the principal investigators have access to original patient details. Paper copies of consent forms, clinical research files and paper questionnaires will be stored securely in a locked cabinet either in the Internal Medicine Unit at the Reina Sofia University Hospital or the Leiden University Medical Center.

## 12.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. These amendment would have to have at least:

1. Covering letter, including the reasons for the amendment in one or two sentences, a brief description of the changes that are included in the amendment and the name of the documents that are modified;

2. An extract of the modified documents, where applicable, showing both the previous and new wording, where applicable.

3. The new version of the modified documents, where applicable, identified with updated number of version and date.

## 12.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have

completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

### 12.4 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

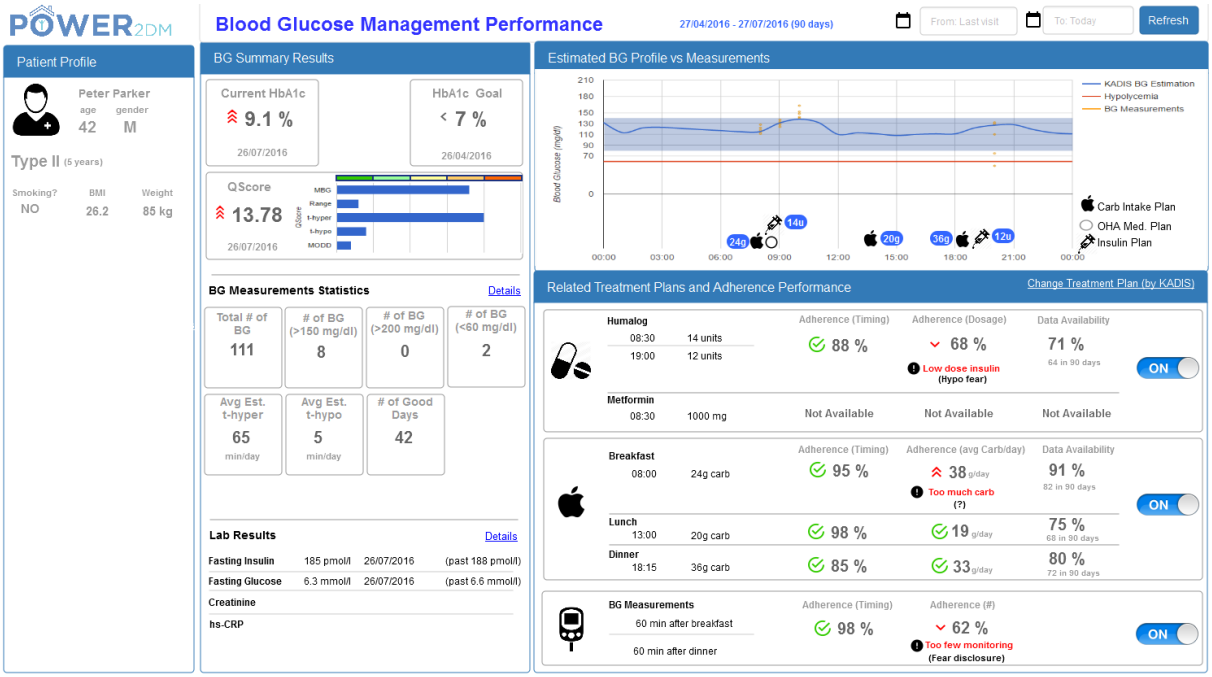
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

### 12.5 Public disclosure and publication policy

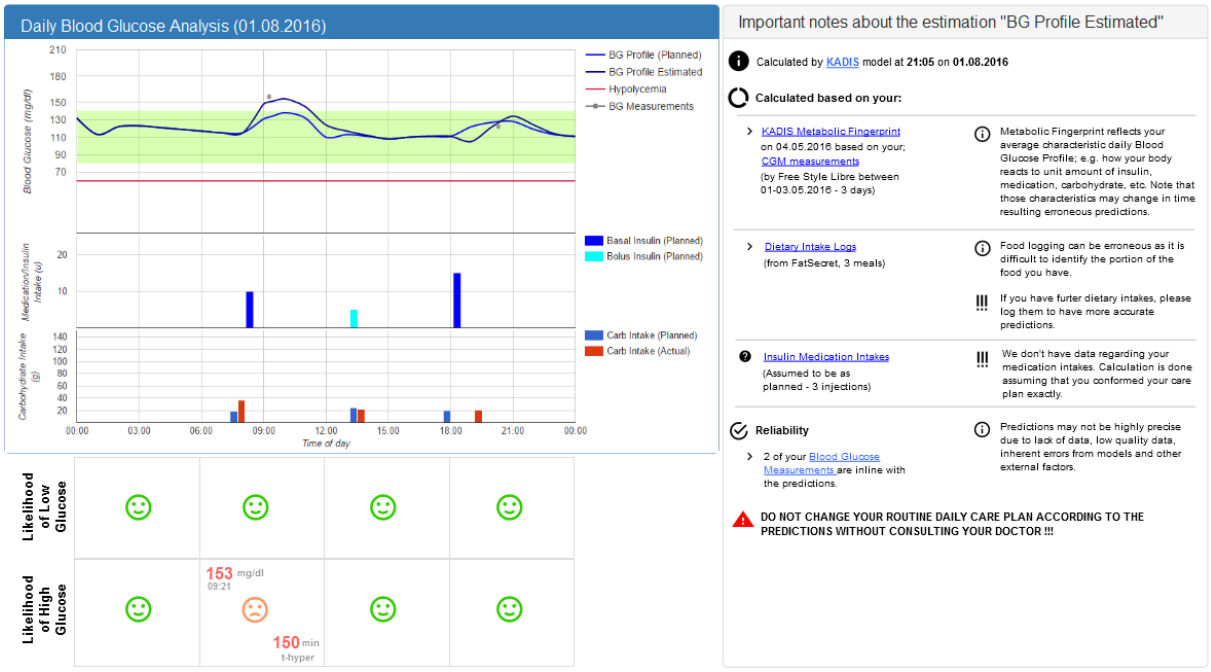
The research will be registered on ClinicalTrials.gov, a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

## 13. POWER2DM APP PANELS

## 13.1 Blood glucose management Performance.

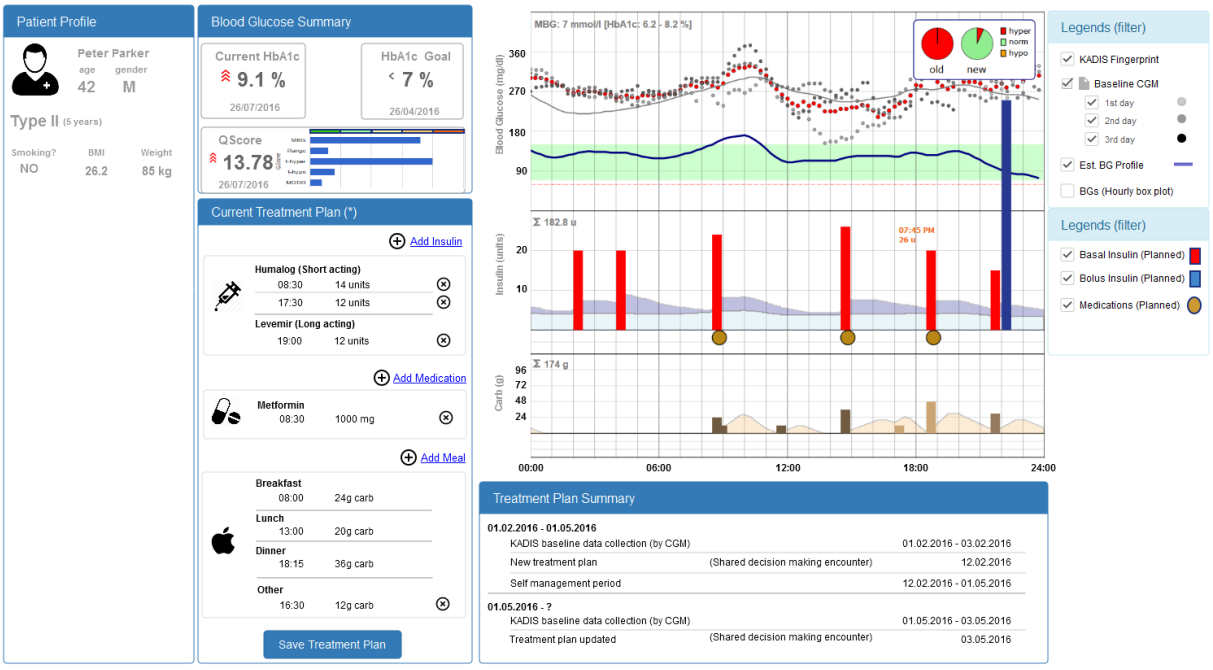



## 13.2 DailyBlood Glucosa Analysis.

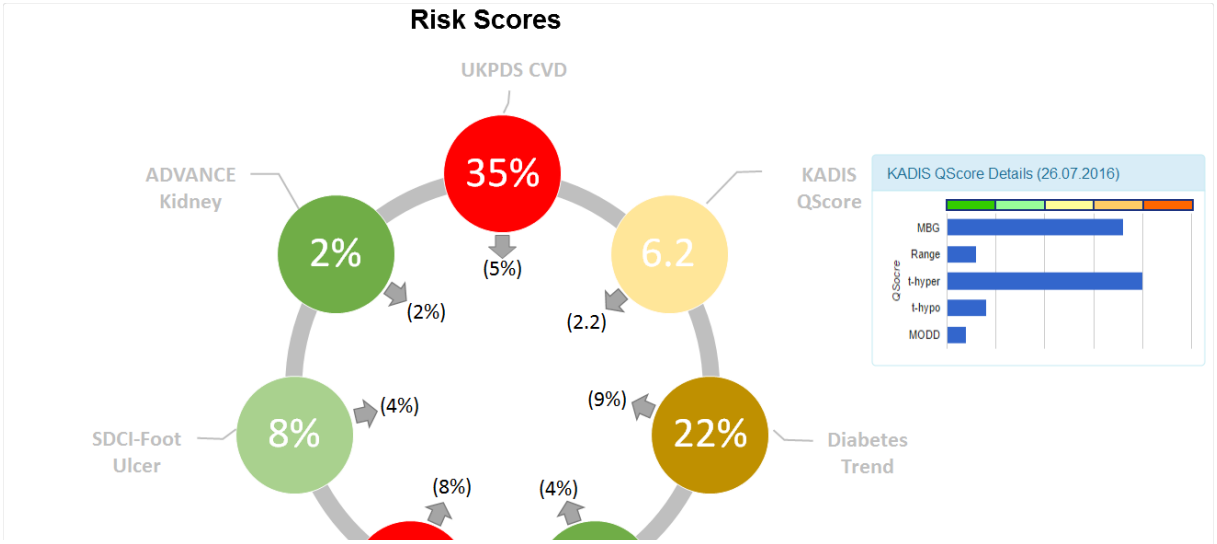


## 13.3 Blood glucose summary.

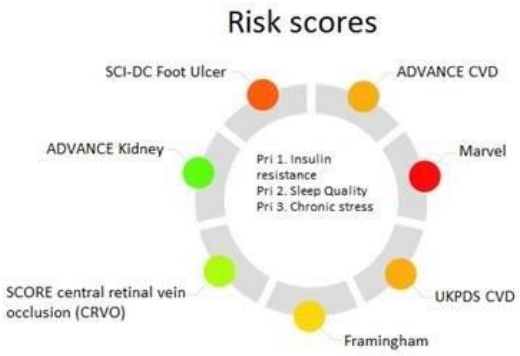

## 13.4 Treatment planning with KADIS



## 13.5 Risk scores.

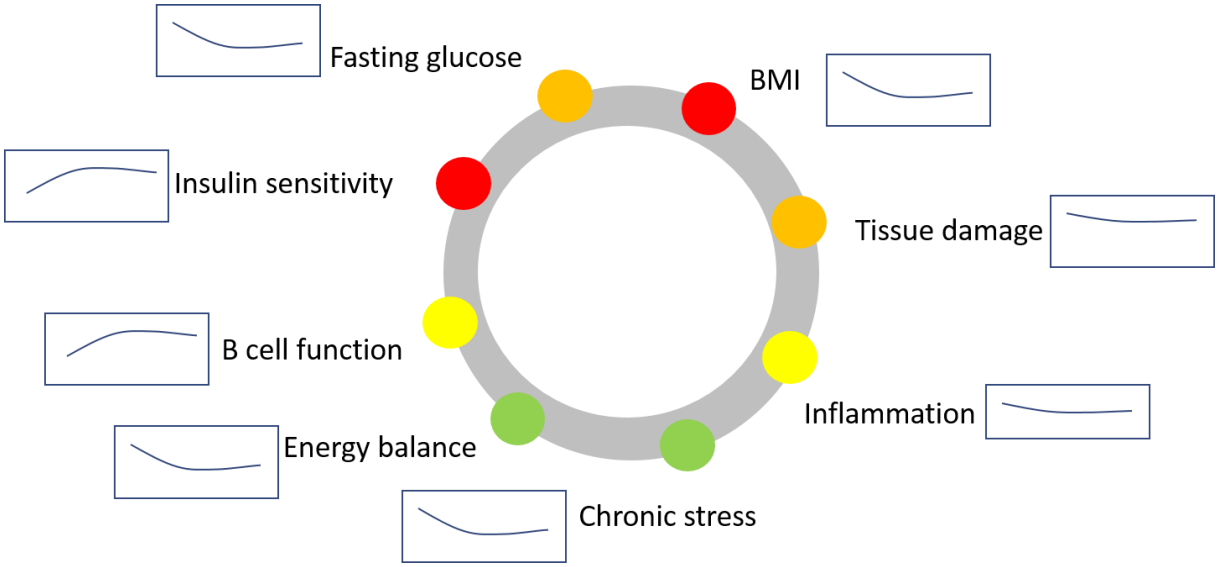




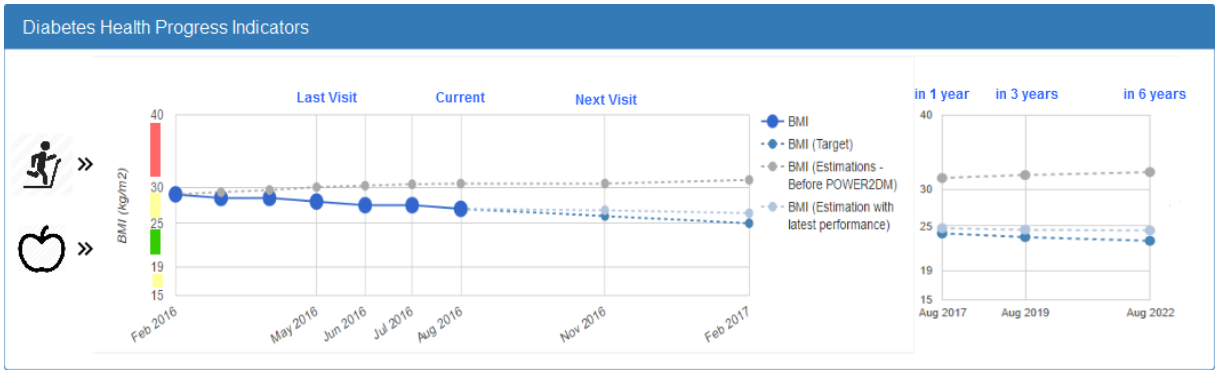



## 13.6 POWER2DM main compass

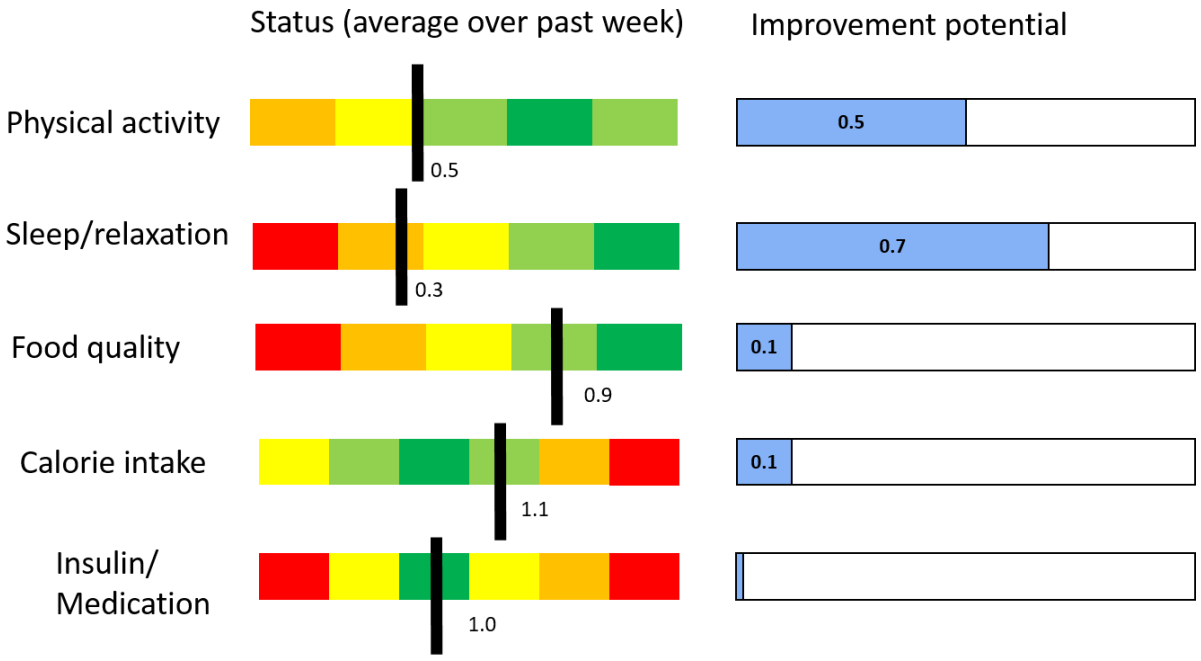
### 13.7 Health progress.



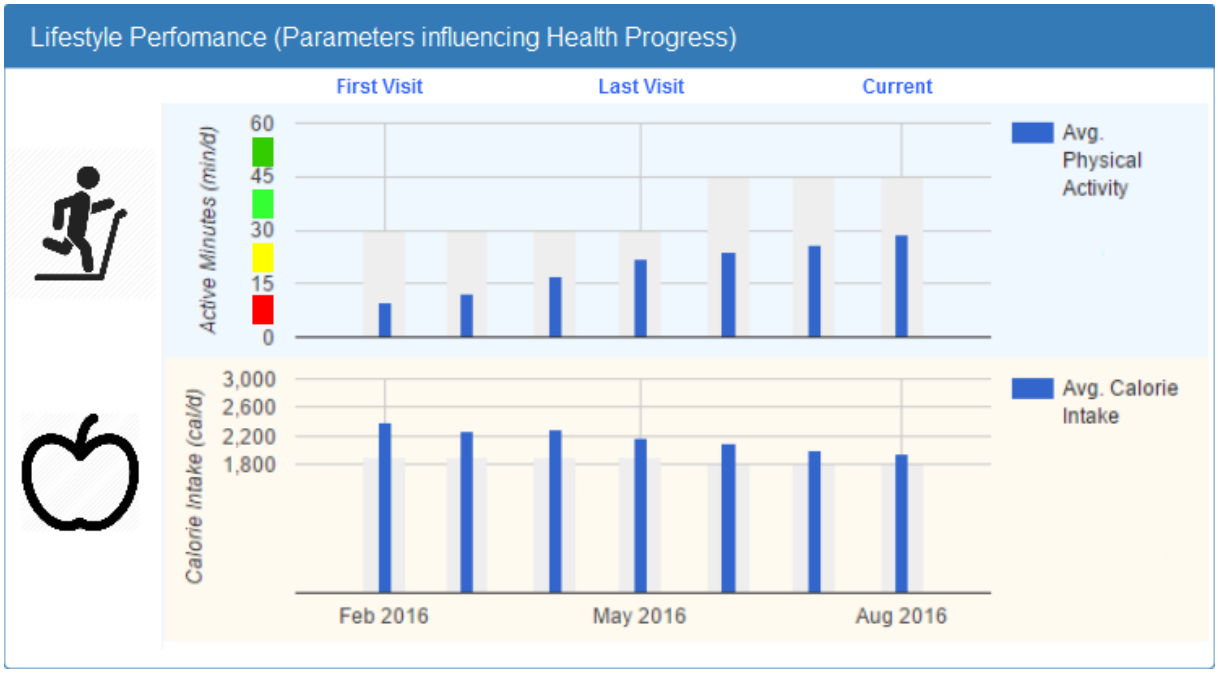
## 13.8 Diabetes Health Progress Indicators.




## 13.9 Lifestyle feedback



### 13.10 Lifestyle performance.

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