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

D5.2: Quantification Campaign Methodology

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Dissemination Level		
PU	Public	X
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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
TNO	Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Netherlands
IDK	Institute of Diabetes “Gerhardt Katsch” Karlsburg	Germany
SRDC	SRDC Yazilim Arastirma ve Gelistirme ve Danismanlik Ticaret Limited Sirketi	Turkey
LUMC	Leiden University Medical Center	Netherlands
SAS	SAS Servicio Andaluz de Salud	Spain
SRFG	Salzburg Research Forschungs Gesellschaft	Austria
PD	PrimeData	Netherlands
iHealth	iHealth EU	France

Abbreviations

This section contains the abbreviations used in this deliverable.

Abbreviation	*Definition*
(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**
AR	**Adverse Reaction**
ASQ	**After-Scenario Questionnaire**
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**
FCQ	**Fear of Complications Questionnaire**

FGM	**Flash Glucose Monitoring**
FSL	**FreeStyle Libre 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-II	**Hypoglycemia Fear Survey-II**
HRQoL	**Health Related Quality of Life**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
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**
QoL	**Quality of Life**
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**

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
V1.0	April 28, 2016	First concept of Pilot Design	LUMC	LUMC, SAS, SRFG, SRDC, IDK, TNO
V1.1	May 09, 2016	Major formatting revision	LUMC	LUMC
V1.2	June 23, 2016	Revised based on discussion in Munich, June 2016	LUMC	LUMC, SRDC
V1.3	June 30, 2016	Revised based on comments given by departmental science committees	LUMC	LUMC
V1.4	July 04, 2016	Revised based on discussion regarding outcome parameters	LUMC	LUMC, SAS, TNO, SRFG
V1.5	July 14, 2016	Wording revision	LUMC	SRDC
V1.6	July 26, 2016	Addition of appendix	LUMC	LUMC
V2.0	September, 01, 2016	Questionnaire and informed consent letter revision	LUMC	LUMC

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 unhealthy dietary habits, too little self-measurement of blood glucose (SMBG) and insulin administration based on food intake, too little exercise and other daily activities in patients on insulin therapy) usually underlies problems to maintain glycemic control. Hyperglycemia is an important cause of long-term macro-and micro-vascular complications in all patients with diabetes mellitus. And in patients on insulin therapy, (fear of) hypoglycemia 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. In order to reduce the burden and increase the effectiveness of diabetes self-management patients need to be supported in their self-management using integrated technologies and personalized plans for care.

Objective: The objective of the POWER2DM project is to develop and evaluate technologies that assist diabetes patients in their self-management using model based decision support and dynamic action plans. To this purpose we developed a three month observational quantification campaign to occur next to the patients' standard care in which we will use traditional means of data collection with integrated technologies as data input for new glucose simulation models in patients with diabetes. The predictive models of diabetes will be evaluated in their ability to predict specific glucose levels.

Study design: Observational study divided into two phases. Phase 1 involves one month of data collection using mobile health devices to monitor glucose levels, physical activity/sleep tracking, stress, eating behavior, and insulin and medication usage. In addition patient reported outcomes of quality of life, diabetes distress, emotional state and stress will be collected via questionnaire. Information gathered during this phase will be used to create an initial patient specific glucose metabolic model. Phase 2 is a follow-up phase of two weeks occurring in month 3 in order to assess whether the original glucose metabolic model is still accurate.

Study population: A total population of 60, age 20-70 years old, diagnosed T1DM or T2DM (N=30 T1DM, N=30 T2DM), from three clinical sites: Leiden, Cordoba, Karlsburg.

Intervention (if applicable): NA

Main study parameters/endpoints: This study is observational in nature with blood glucose and HbA1c levels as primary outcome. Secondary outcomes include actual and predicted frequency, timing, and magnitude of hyperglycemic episodes and hypoglycemic episodes; psychosocial measurements of affect, stress, distress, well-being, and self-management.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There is a limited burden to the patients in this observational study. This burden includes additional visits compared to usual care, becoming acquainted with e-health care device and filling out of questionnaires. In addition, blood samples need to be drawn and (more) frequent self-monitoring of glucose by finger-pricks is necessary on a number of days and a flash glucose monitoring device (FreeStyle Libre) should be worn on three occasions. Potential benefits for patients from participation in this 3-month study are more insight into their glucose levels and how specific lifestyle activities and behaviours can have an impact on these glucose levels.

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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 around 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]. These treatment plans involve a significant investment of time and energy with some estimates for diabetes two hours per day for the minimum of diabetes specific recommended care [6]. The high burden of proper 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 management letting the burden of diabetes management fall on the shoulders of the patient [11, 12]. The combination of all these issues surrounding proper diabetes management has resulted in almost half of diabetes patients either showing 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 they 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 in 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 an 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]. A highly personalized glucose simulation model based on a 'metabolic fingerprint' (KADIS system, Karlsburg) has 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 system is based on a mathematical model that describes the glucose metabolism in T1DM and T2DM patients. The inputs for KADIS are patients' data regarding blood glucose values, oral medication, insulin therapy, carbohydrate content of meals, and exercise as measured continuously over 72 hours. With this data, KADIS can build a personalized metabolic fingerprint of a patient's glucose system. The fingerprint can be used in clinical practice as an interactive simulation of a person's daily therapeutic regime in order to assist physicians in choosing individual diabetes management regimens for optimizing glycemic control based on calculated patient specific parameters. 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.

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 large 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].

In order to provide patients with the self-management support that they want and need, we need to develop a holistic mobile intervention platform that helps the patient in a variety of different ways. Our aim in this project is to develop a comprehensive self-management support system (POWER2DM) that helps patients with their diabetes by reducing the burden of diabetes through 1) automating input and tracking for daily monitoring or glucose, diet, and exercise; 2) offering tailored self-management action plans to help the patient overcome barriers to successful treatment goal accomplishment between consultations with their diabetes specialist; 3) provide online modules to help patients deal with diabetes related stress, depression, and anxiety; 4) use simulated glucose models to reduce uncertainty regarding hypoglycemic episodes, optimize medical regimens, and calculate insulin amounts. Our goal is to ensure that diabetes patients are receiving daily patient-centered care to help them control their chronic condition.

The POWER2DM project consists of two separate campaigns: quantification and evaluation. In this first campaign, the Quantification Campaign, we will lay the foundation for the development of the POWER2DM mobile application by grounding and calibrating currently available glucose models in order to operationalize them for patient use as predictive engines. Further, we will assess ways of integrating and connecting measures used in the daily monitoring of metabolic functioning with psychosocial measures in order to help guide the tailoring of the action plans.

2. OBJECTIVES

Primary Objective:

- To assess the stability of the KADIS model over time.
- To assess whether new technologies can improve the use of the KADIS model in guiding diabetes self-management.
- To assess whether the KADIS model can be translated into personalized predictive glucose model

Secondary Objective(s):

- To develop a set of questions used to establish psychosocial profiles of patients with diabetes which can be integrated in the Power2DM DSS and be used to tailor support and help them achieve their personal, psychological and medical goals.

3. STUDY DESIGN

The quantification campaign is an observational cohort study consisting of two data collection periods. The first period occurs from week 1-4 when the study participant will perform continuous glucose monitoring using a flash glucose monitor (FGM) and daily tracking of diet, physical activity, diabetes medication usage, sleep, mood, and stress. Additionally, during the first 72 hours the patient will conduct blood glucose monitoring using finger pricks (8/day). Currently, the KADIS model is based on data from an initial 72 hour period which is used to create a metabolic fingerprint. Data from the total period will be used to see to what extent additional parameters or new techniques for data collection or a 1-week basis of the model improve the accuracy of the KADIS model and assess the forecasting ability of updated models. the second period occurs from week 11-12 in which the study participant will again perform continuous glucose monitoring using an FGM along with daily tracking of diet, physical activity, diabetes medication usage, sleep, mood, and stress. The purpose of this repeated data collection is to check the stability of the KADIS models created from the data gather in period 1. The length of the quantification campaign is necessary to assess whether the metabolic fingerprints generated by the KADIS model remain stable for applied use later.

Participants will complete psychosocial evaluations related to quality of life, psychosocial barriers to self-management, emotional and disease related (dis)stress at baseline, end of week 4, and end of week 12 to identify psychosocial factors that may influence successful self-management, assess the relationship between continuous stress and glucose, and validate new translations of pre-existing questionnaires for use in the evaluation campaign. Psychological measurements will be collected at baseline (T_0: introduction visit), at the end of Phase 1 (T_2) and at the end of Phase 2 (T_3) as described below. The measurements schedule and frequency of measurement is summarized in Table 1.

In addition to these measurement periods, participants will be contacted by a healthcare provider at the end of week 1, 2, 3, and 11 to inquire as to patient problems or concerns related to study participation.

3.1 Table 1. Outcome parameter timeline

Measure Name or Type (# items)	Code	Introduction visit (Baseline)	Period 1 (Week 1-4)	Period 2 (Week 11-12)
Lifestyle and Daily Monitoring	LDM			
Blood glucose level	1	Once	Continuous	Continuous
Dietary intake	2	Once	Continuous	Continuous
Physical Activity	3	Once	Continuous	Continuous
Sleep- quantity	4	Once	Continuous	Continuous
Sleep- quality (1)	5	Once	Daily	Daily
Stress-physiological	6	Once	Continuous	Continuous
Stress-perceived (1)	7	Once	6/day	6/day
Mood (1)	8	Once	6/day	6/day
Diabetes medication treatment- type/dosage/ frequency	9	Once	Daily	Daily
Questionnaires (# items)	**Q**			
WHO-5 (5)	1	Once		Once
PHQ-9 (9)	2	Once		Once
GAD-7 (7)	3	Once		Once
PSS (10)	4	Once	End week 4	Once
PAID (20)	5	Once	End week 4	Once
DSMQ-R (20)	6	Once	End week 4	Once
HFS-II (33)*	7	Once		
DEPS-R (14)*	8	Once		
FCQ (15)*	9	Once		
D-FISQ (21)*	10	Once		
ASQ (3)	11		End of Week 1 and 4	

Measure Name or Type (# items)	Code	Introduction visit (Baseline)	Period 1 (Week 1-4)	Period 2 (Week 11-12)
Clinical/Lab Tests	**CLT**			
HbA1c	1	Once		Once
Fasting Glucose	2	Once		
Triglycerides	3	Once		
Cholesterol	4	Once		
HDL Cholesterol	5	Once		
LDL Cholesterol	6	Once		
Cholesterol Ratio	7	Once		
Urine-Albumin	8	Once		
Creatinine	9	Once		
Fasting insulin	10	Once		
Cortisol (hair sample)	11			Once
Patient Characteristics	**PC**			
Anamneses: Age/ Gender/Height/Type of Diabetes /Medical History (Time since diagnosis/ Complications/ Physical examination/Comorbidities)/ AS4	1	Once		
Weight	2	Once		Once
BMI (calculated from Weight and Height)	3	Once		Once
Waist	4	Once		Once
Blood pressure	5	Once		

Note: *indicates that this measure will only be used if a patient engages in an associated self-management task (e.g. only insulin users will be asked about anxiety related to using insulin) or they indicate associated problems in other questionnaires (e.g. DEPS-R will be administered if the patient indicates issues regarding eating)

4. STUDY POPULATION

4.1 Population (base)

Patients with T1DM (N=15) and T2DM (N=5) will be recruited from out-patient medical centers in the Netherlands (LUMC). Patients will be informed by their treating diabetes healthcare worker about the study with the option to talk with one of the researchers if further information is required.

4.2 Inclusion criteria

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

- Age 20-70
- Diagnosed T1DM or T2DM
- Able to self-monitor and work with a 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
- Concurrent participation in other clinical trials

4.4 Sample size calculation

Sample size requirements were calculated based on the daily correlation coefficients used to compare the predicted glucose model with continuous measurements using the STATA application sampsi_rho [41] and is based on a required significance level = 0.05 and null ρ = 0.80 to assess an improvement in the predictive accuracy of the regression model to ρ=0.90. A sample size of n=60 results in an associated power of 80.5% for a linear regression model which is generally accepted as sufficiently powerful for assessment of predictive accuracy. Similar data collection will also occur in research facilities in Cordoba, Spain and Karlsburg, Germany. Both of these facilities will each collect data from the same number of patients from a similar patient population resulting in a total sample size of N=60 for the quantification campaign.

5. METHODS

5.1 Data Collection, Study Parameters/Endpoints and Associated Devices

5.1.1Data Collection

The PatientCoach platform will be used to collect both physiological and questionnaire data, using either the mobile application or through the internet portal. PatientCoach is an online platform designed at the LUMC to support both the patient-physician communication and the tasks which support the patients in their daily life. It has a preexisting interface which allows for data collection across a variety of areas all relevant to successful self-management and patient based research. The PatientCoach application will be installed either on a mobile device owned by the patient or on an iPod provided by the researchers (as needed). The PatientCoach application will be linked to the associated Bluetooth and NFC (when applicable) connected devices via the associated applications from Spire, Fitbit, and Freestyle Libre (LibreLink) in order to gather data with a coded patient identifier for analysis. The mHealth technologies will be integrated into the current PatientCoach system to allow for automated data collection and logging. The data collected via the PatientCoach application will be regularly sent to and safely stored within the PatientCoach system.

All associated mobile applications will be (pre)installed on mobile devices by the POWER2DM research group or a research assistant who will help link the relevant apps and mHealth technologies to the PatientCoach platform. All questionnaires will be completed and registered through the PatientCoach internet application. As the baseline questionnaire packet is large, patients will have the option of starting the questionnaires prior to baseline through PatientCoach. Additionally, the baseline questionnaires will be made available to the patient in paper form at the introductory meeting (in which case a research associate will then log the answers to the patient profile within PatientCoach) with the option of completing these questionnaires later online via PatientCoach portal. Any questionnaires required after this baseline assessment will be collected via the PatientCoach mobile platform with the patients being notified when they have a questionnaire that requires completion via email. All questionnaires can be completed through the PatientCoach portal and will be required to be completed within one week of the patient starting the study or being notified that they have a questionnaire that requires their input. They will receive email reminders until the questionnaire is either completed or four weeks have elapsed.

5.1.2Lifestyle and Daily Monitoring (LDM) parameters/endpoints

1. Blood Glucose Level (Primary outcome):

   FGM (T1DM, T2DM) and 2/day fingerpricks

   Maintaining healthy blood glucose levels is the primary goal of all diabetes care and monitoring these levels is the basis for guiding actions to maintain these levels and prevent both short-term and long-term complications [42, 43]. Flash glucose monitoring (FGM) is used in this project as blood glucose levels are one of the primary input measures used in the KADIS model and will be used as the outcome for assessing the use of this model and whether the simulations can be used for glucose prediction [29-32, 44].

   Glucose monitoring will be done using the FreeStyle Libre (FSL) Flash Glucose Monitoring System which measures interstitial fluid glucose levels. The FSL system consists of a small FSL Sensor and a wireless FSL Reader. The FSL Sensor allows for 8 hours of continuous measurement and storing of interstitial fluid glucose levels. Each sensor is valid for a period of two weeks and can be installed by the patient. The stored information can be retrieved using either the FSL Reader or with an NFC enabled Android device. When either the FSL Reader r NFC enabled Android device are held over the FSL Sensor they retrieve the previous eight hours of blood glucose level data wirelessly. The FSL has been tested and found to be at least 85.2% accurate over a 14 day period [45]. The FSL Reader will also be used for the 8/day blood glucose checks using finger-pricks during the first 72 hours and all subsequent blood glucose checks. Patients will perform the finger-pricks at least twice a day (morning and evening) or as frequently as they do in their current diabetes treatment plan, whichever is more.

   The patients will perform FGM during weeks 1-4 and weeks 11-12. All glucose readings will be uploaded to the patient's profile in PatientCoach over the internet either automatically as is the case with the FSL with NFC connected devices or through manual uploading the collected data as is the case with the FSL Reader.

2. Eating behavior: Sort/Type, Amount (weight volume), Quality/Nutritional Value, Time of consumption

   Tracking dietary habits and food intake (specifically carbohydrate intake) is critical for calculation of blood glucose levels, maintaining healthy body weights, and is used as the basis for insulin dosage. However, the amount of time required to accurately monitor and record eating behaviors is restrictive to many patients. Therefore, three options for logging eating behavior will be given.

The first, and simplest, of these options is a bread units logger in the PatientCoach platform. Bread units (BU) are calculated as the amount of foodstuff containing carbohydrates with 1 BU = 12g Carbohydrates [46]. The patient will log into the PatientCoach app and record the time of consumption and the estimated BU content of the meal. PatientCoach will convert these into BU levels for use in the KADIS model. The KADIS model input requires meal ratings based on the level of carbohydrates consumed (Low = 0-2BU, Medium = 3-4BU, High = 5-6BU, Very High >7BU). This has been validated as an acceptable and low burden method of data collection by the KADIS developers but relies on the patient perceptions of amount of carbohydrates in a meal which gives little insight into the actual amounts and type of carbohydrates consumed.

The second option given to patients will be to record patient's calculations of calorie (in kcal) and carbohydrate (in grams) content directly into the PatientCoach platform. This option increases the accuracy of the data logged as well as increases the applicability of the food tracking to those patients not on insulin therapy who may not be required to closely monitor their carbohydrate intake but are recommended to monitor their caloric intake. Again this relies on the patient's ability to calculate these values properly.

The final option available within POWER2DM is the integration of the mobile application Calorie Counter by FatSecret. CC can be used to track specific dietary intake by logging the consumption amounts of foodstuffs found within the CC database. CC is an easy to use, web-based food diary which allows the user to track what they eat with from anywhere with an internet connection [47]. CC contains a location based searchable food database and has been used over 10,000,000 globally. Additionally, CC allows the user to create their own personal food database, adding their own foods and recipes at any time and accessing them from anywhere with an internet connection. Users can make a personalized diet profile, customized to their unique weight loss goals, and is flexible enough to support many different diet plans. CC is available in many different languages (including Dutch, German, and Spanish) which automatically change based on the phone settings that the user chooses. For comparison to the original KADIS model, carbohydrates as measured in grams in CC will be converted into KADIS ratings of meals using the previously states definitions of carbohydrate content.

3. Exercise and energy expenditure: Steps taken, Distance, Duration, Intensity, Calories burned

The Fitbit HR Charge is a wristband activity tracker that counts steps, tracks physical activity and sleep, allows for monitoring of pulse rate and tracks calorie burn [45]. It has a non-intrusive design, can automatically upload tracked information to connected devices, and can easily integrate with MyFitnessPal. Further, the five day battery life reduces the burden of maintenance for the patients as they will not need to load the battery every day and is already integrated into PatientCoach.

4. Sleep: Duration, Frequency, Quality/Disturbances

   The Fitbit HR Charge will be used to measure sleep duration, frequency, and quality/disturbances. The Fitbit HR Charge automatically begins to track sleep based on user movement thus decreasing the risk that the patient will forget to turn on their sleep tracker.

5. Sleep: VAS

   A one item Visual Analogue Scale (VAS) ("On a scale from 0 to 10 where 0 is the worst possible sleep ever and 10 is the best quality sleep ever, how would you rate your sleep the previous night?") will be filled in daily during the monitoring periods. This question will be integrated into the PatientCoach app and asks about sleep quality with the first data input for the day. A modified version asking about the previous month will be included in the introduction visit to assess baseline perceptions of sleep quality. One item questions about sleep quality have been validated in fibromyalgia patients [48] and VASs represent an easy and low-impact method of data collection that have been found to be valid for use in the context of eHealth research [49].

6. Stress/relaxation: Respiratory and heart rate

   The FitbitHR Charge will measure relaxation as a product of resting heart rate and inactivity. Additionally, the Spire will be used to measure respiratory rate. The Spire is a small eHealth device that is clipped on to the waistband of a participant and records continuous measurements of inhalation and exhalation times, breath rate, deep breaths, apnoeic events [50]. It analyses breathing patterns to infer state of mind (tense, calm, focus) and has been validated as a reliable and non-invasive index of emotion regulation abilities in times of stress [51].

7. Stress: VAS

A visual analogue color scale will be integrated into the PatientCoach app for completion six times a day. On this scale cooler (blue) colors represent lower stress and hotter (red) colors represent more stress. Additionally, the patient has the option of making a note about their current status beneath this VAS. The patient will be asked to fill these in when they inject insulin or conduct a finger-prick blood glucose measurement and will be automatically sent after 90 minutes of inactivity in the application.

8. Mood: VAS

Due to the commonly accepted two-dimensional model of mood [52], a cartoon based pictorial will be used to assess affect. In this pictorial, different mood states are displayed on two axis with the y axis representing the valence and the x axis representing the arousal of the mood. Scales like this are easy to understand and require little effort for participants to complete making this an ideal tool to use in repeated daily measurements [53]. Understanding the mood state of the person throughout the day can help to refine action plans and identify possible psychosocial barriers that may exist to self-management. Additionally, the patient has the option of logging written notations about their current mood state beneath this pictorial. The Mood VAS will be filled in on the same schedule as the Stress VAS.

9. Diabetes Medical treatment: Type (oral/insulin), Dosage/Frequency

The frequency and dose of anti-hyperglycemic agents will be recorded at baseline and daily logging of frequency, dose, and timing will be recorded in weeks 1-4 and weeks11-12 in the PatientCoach app.

5.1.3 Questionnaires (Q) parameters/endpoints

1. Quality of Life: WHO-5

Quality of life has been described as the ultimate goal of all health interventions [54]. Assessment of quality of life in the quantification campaign 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].

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 [58]. 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 [59]. 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 [60].

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 [61, 62]. 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 [63] and has been previously used in two large scale studies of diabetes patients [64, 65].

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.

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.

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.

Questionnaires 7 through 11 are conditional and will only to be given to patients that indicate a specific need for further screening regarding psychosocial issues related to their diabetes care. The needs assessment will be based on the answers given in the PAID, DSMQ-R, and anamneses.

7. Hypoglycemic related Distress-Behavior: 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. 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].

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.

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.

11. ASQ

After-Scenario Questionnaire (ASQ): The ASQ is a three item questionnaire designed to assess computer user satisfaction directly after scenario completion [81]. The user rates their agreement with three satisfaction statements assessing ease, time, and support of use on a 7 point scale ranging from strongly agree (1) to strongly disagree (7) with the option of choosing not applicable. All patients will be required to complete this questionnaire at the end of the first month as a means of assessing acceptance of the POWER2DM system as a part of their diabetes self-management.

5.1.4 Clinical/Lab Tests (CLT) parameters/endpoints

1. HbA1C: lab

   Glycated hemoglobin (HbA1C) is the standard measure used for diagnosis and assessment of glycemic control [82]. Lab measurements of HbA1c will be done at baseline and at the end of week 12.

2. Fasting Glucose: FGM

   Fasting glucose will be assessed based on blood glucose levels observed during FGM.

3. Triglycerides: lab

4. Cholesterol: lab
5. HDL Cholesterol: lab
6. LDL Cholesterol: lab
7. Cholesterol Ratio: lab
8. Urine-Albumin: lab
9. Creatinine: lab
10. Fasting insulin: lab
11. Cortisol (hair sample): lab

Cortisol as derived from a hair sample will be used as a measure of chronic stress based on a sample taken at the end of the first month (sample size ≥ 7cm). Cortisol derived from hair samples is validated and a commonly used biomarker of systemic stress exposure and will be used as a measure of chronic stress [83-93].

5.1.5 Patient Characteristics (PC) parameters/endpoints

1. Anamnesis: Age, Gender, Height, Type of Diabetes, Medical History (Time since diagnosis/ Complications/ Physical examination/Comorbidities), AS4
2. Weight
3. Waist
4. BMI
5. Blood Pressure

All patient characteristics will be recorded at baseline by the diabetes healthcare provider or researcher. Weight and BMI (calculated from Weight) will be reassessed at the end of week 4 and 12.

The AS4 is a brief set of questions intended to assist in understanding the psychosocial and environmental problems that may affect the diagnosis, treatment, and prognosis of mental disorders and helps the clinician to understand the life events and circumstances that are impacting the patient and their ability to self-manage their health. The core of the AS 4 is based on identifying problems commonly classified under Axis 4 of the DSM-IV-TR as a part of a comprehensive psychological diagnosis [94].

5.2 Randomisation, blinding and treatment allocation

As blinding of the FGM devices is not possible, patients will be instructed to not adjust their frequency of SMBG or change their other usual self-management based on the FGM readings without first consulting with their diabetes healthcare provider unless otherwise required during the study.

5.3 Study procedures (codes for measures are drawn from Table 1)

Phase 1.

Pre-Baseline

Steps:

1. Eligible participants are identified and contacted by their local care provider regarding whether they would like to participate in POWER2DM quantification campaign
2. Patients who agree will sign an informed consent form.
3. Patients who have signed an informed consent form will be given the option of creating a PatientCoach profile in order to begin filling in the baseline questionnaires in the week prior to introduction visit.

Introduction visit (Baseline)

Steps:

1. At the introductory meeting the patient is told about research, what the goal of research project is and what they can expect by a researcher or diabetes healthcare provider.
2. All participants who have not signed an informed consent will be asked to sign an informed consent form.
3. The researcher or diabetes healthcare provider will install, help set-up, and link all necessary mobile applications to their respective devices (PatientCoach, Spire, Fitbit, FreeStyle Libre)
4. The researcher or diabetes healthcare provider will describe each device to the patient and demonstrate how each device should be used
5. The patient will be instructed on how they should measure glucose and record/submit data by researcher or diabetes healthcare provider
6. The researcher or diabetes healthcare provider will ensure that the patient is aware that this is an observational study intended to take place next to the patient's usual care and they are not supposed to adjust their normal diabetes care activities based on information gathered during the monitoring period without first consulting with their diabetes healthcare provider.

7. The researcher or diabetes healthcare provider will record and log baseline measurements of LDM_1-9 and PC_1-5
8. The researcher or diabetes healthcare provider will ensure that Q_4-6 have been completed prior to the completion of the intake. Patient will complete any other unfinished baseline questionnaires within the next 7 days
9. Blood sample taken for lab testing of CLT_1-10
10. Patient demonstrates understanding of how to use PatientCoach and mobile devices by logging first entry of continuous monitoring with researcher or diabetes healthcare provider and starts continuous tracking.

Week 1

Steps:

1. Patient conducts 3 days of 8/day blood glucose level monitoring using finger-pricks according to KADIS schedule.
2. Patient continually monitors glucose level along with time-stamped records of eating behavior, exercise, medication usage, and insulin usage for one week
3. Patient completes ASQ
4. Individual metabolic fingerprint created by researcher based on 72 hour continuous measurements of glucose, eating behavior, exercise, medication usage, and insulin usage; report sent to treating diabetes healthcare provider along with interactive model
5. Diabetes healthcare provider assess KADIS model and, if the provider feels that it is necessary, contacts patient by telephone to discuss KADIS model findings and possible ways to improve diabetes self-management
6. Healthcare provider contacts participant to inquire as to problems and concerns regarding study participation at end of week 1.

Week 2-4

Steps:

1. Patient continually monitors glucose level along with time-stamped records of eating behavior, exercise, medication usage, and insulin usage
2. Healthcare provider contacts participant to inquire as to problems and concerns regarding study participation at end of week 2
3. Healthcare provider contacts participant to inquire as to problems and concerns regarding study participation at end of week 3
4. Patient completes ASQ at end of week 4
5. Patient debriefed on findings and experience by researcher or diabetes healthcare provider

6. Patient debriefed that they may continue using profile in PatientCoach along with the Fitbit, Spire, and FreeStyle Libre devices for personal tracking during weeks 5 through 10 but must purchase their own sensors/fingerprick strips and allow the data collected using these means to be used for further research purposes
7. Patient stops continuous glucose monitoring and returns to TAU or opts to continue monitoring using PatientCoach and devices for their self-management as they want during weeks 5 through 10.

Period 2.

Week 11-12

Steps:

1. Patient is sent new sensors/strips two weeks prior to regular check-up.
2. Patient is contacted via telephone to verify receipt of new sensors/strips and to ensure that they still have all necessary devices and that all necessary mobile applications are installed, set-up, and linked to their respective devices (Fitbit, Spire, FreeStyle Libre)
3. Patient begins new round of continual glucose level monitoring along with time-stamped records of eating behavior, exercise, medication usage, and insulin usage for 14 days
4. Healthcare provider contacts participant to inquire as to problems and concerns regarding study participation at end of week 11.
5. Patient returns to diabetes healthcare provider for quarterly check-up, stops FGM and returns to TAU (patient retains the option to continue using profiles in PatientCoach, Spire, Fitbit for personal tracking of diet/exercise/diabetes care but must provide their own devices).
6. Patient returns all devices provided during project
7. Patient completes project exit questionnaires
8. Blood sample taken for testing of CLT_1
9. Hair sample taken for testing of CLT_11.
10. Patient debriefed on project and user experience by researcher or diabetes healthcare provider

5.4 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,.

6. SAFETY REPORTING

6.1 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.

6.2 AEs, SAEs and SUSARs

6.2.1 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, not AEs are expected.

6.2.2 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 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 will not be considered as a serious adverse event.

The principal investigator will report the SAEs through the web portal ToetsingOnline 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.

6.2.3 Suspected unexpected serious adverse reactions (SUSARs)

<This c*hapter is only applicable for studies with an investigational medicinal product*>

NA

6.3 Annual safety report

<This c*hapter is only applicable for studies with an investigational medicinal product*>

< The annual safety report may be combined with the annual progress report (see chapter 12.4).>

NA

6.4 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

7. STATISTICAL ANALYSIS

All Lifestyle and Daily Monitoring, Questionnaire, 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 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 [95].

7.1 Primary study parameter(s)

Blood glucose Level is the primary study parameter of the quantification campaign with the intended purpose of grounding and calibrating the KADIS model and assessing whether it can be transformed into a glucose prediction application. Daily individual correlation coefficients comparing the predicted glucose levels using the input parameters of previous glucose level, insulin dosage and time, oral medication dosage and time, carbohydrate amount and time of consumption, and measurement of duration and intensity of physical exercise with the actual glucose levels as measures with the FSL will be generated for each patient for each day of Phase 1 and Phase 2. Potential improvements to the model will be assessed by creating different versions of KADIS using different input parameters and length of monitoring used to build the fingerprints and comparing the correlation coefficients generated when the input parameters are done using the original form of paper-based data collection and input versus input from continuous and automated mHealth data collection devices. Additionally, the predictor of continuous stress measurement will be added to the model to see if adding this parameter increases the accuracy of the predictive glucose model significantly. Further, the average and individual correlation coefficients will be plotted over time to assess the stability of the predictive model from baseline until the end of Phase 2. During the quantification campaign we will obtain 2340 correlation coefficients for analysis [60 patients*(25-day-Phase1+14-day-Phase2)] per model.

In order to assess whether correlation coefficients improve by updating the KADIS model with data from eHealth technologies will be analysed by a mixed model with KADIS version, time and their interaction as fixed effects and patient identifier as random effect (intercept).

7.2 Secondary study parameter(s)

The anonymized dataset will be input for the development of prediction services and the recommender engine in order to generate a spatial – temporal model using artificial intelligence methods and data related to user activity, responses to psychological measures, and physiological measures. Probabilistic techniques, i.e. Bayesian network, will be applied on a provided set of parameters to give probabilistic prediction of specific indicators. Different soft computing, probabilistic and data mining techniques will be applied on the sensors' signals/data to provide least error prone analysis and decision support.

7.3 Interim analysis (if applicable)

None planned < *Please describe when the interim analysis will be done, which statistical methods will be used, who will perform the interim analysis and the stopping rules (if applicable). Also refer to the DSMB Charter in case a Data Safety Monitoring Board will be established to advice on stopping, see also chapter 9.5*>

8. ETHICAL CONSIDERATIONS

8.1 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.

8.2 Recruitment and consent

In the region of Leiden a total of 20 patients will be recruited, N= 15 T1DM and N= 5 T2DM, from the patient population of the Diabetes Out-patient clinic in the Leiden University Medical Center. Eligible patients from the LUMC will be selected if they are currently in treatment in the Diabetes department at the LUMC. Initially, potential participants will be identified by their health care provider and will be given information outlining the study procedures (Appendix 1: Informatiebrief voor deelnemers). Also permission will be asked to be contacted by a POWER2DM study researcher. After at least one week the study researcher will contact the potential participant as to whether they are interested to participate and a visit will be scheduled if that is the case. During this first visit patients will be further informed about the study and informed consent will be signed if patients agree to participate.

This study is approved by the Medical Ethics Committee of the Leiden University Medical Center in the Netherlands. The subjects are required to give signed informed consent (Appendix 2: Toestemmingsformulier).

8.3 Benefits and risks assessment, group relatedness

We do not consider this study to have any significant risk to the participants.
There is limited burden for the patient. This burden is due to the use of a Free Style Libre flash monitor which requires some skills and piercing of the skin to place the device. There are also additional fingerpricks compared to usual care and blood samples taken at the beginning and end of the study. There may be some distress related to frequent glucose monitoring. There is also baseline psychological assessment with questionnaires. To limit the burden of these assessment, patients will be informed that they can complete all required questionnaires at any time during the first week excluding the PAID, DSMQ-R, and the PSS. The PAID, DSMQ-R, and PSS questionnaires will be required to be completed before or during the introduction meeting as they will be used for the as the pre-test in the initial week assessment of distress.

To manage this concern 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 weekly during the intensive periods to see if there was a significant increase in distress compared to baseline or any other problems related to participation in the study. If this is found then the patient will be contacted and asked if they wish to continue in the study.

Potential benefits for the patient in this study is the metabolic fingerprint that will be created for each patient and more insight into glucose levels using the flash glucose monitor. 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.

8.4 Compensation for injury

The sponsor/investigator has 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.

8.5 Incentives

Participants will receive the FreeStyle Libre Reader, 3 FreeStyle Libre Sensors, and 50 FreeStyle Precision testing strips for use during the study representing a significant amount of savings that is normally a part of their diabetes care (€200.00). At the end of the study, they will be allowed to keep the FreeStyle Libre Reader for their own personal use. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

8.6 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 PatientCoach database. The PatientCoach platform is hosted by the LUMC. 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 PatientCoach via (already existing) connections with the proprietary servers. All questionnaires and VASs and dietary input will be logged manually by the patient in the PatientCoach system. All patient characteristics and clinical lab measurements will be manually entered into the PatientCoach 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 in the Klinische Researchunit Interne Geneeskunde (KRIG) at the Leiden University Medical Center.

8.7 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.

8.8 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.

8.9 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.

8.10 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.

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10. Appendix

10.1 Informatiebrief voor deelnemers

mHealth ter ondersteuning van mensen met Diabetes Mellitus: welke sensoren en glucose modellen helpen in zelfmanagement?

Inleiding

Geachte heer/mevrouw,

Via deze brief willen wij u vragen of u mee wilt doen aan een onderdeel van het medisch-wetenschappelijk onderzoek 'POWER2DM' naar het gebruik van 'mHealth' bij zelfmanagement van diabetes. U kunt zelf beslissen of u aan dit onderzoek wilt meedoen. Voordat u deze beslissing neemt, is het belangrijk om meer te weten over het onderzoek, vandaar deze informatiebrief. Leest u deze informatiebrief rustig door en bespreek de brief zo nodig met partner, vrienden of familie. Hebt u na het lezen van de informatie nog vragen? Dan kunt u terecht bij de onderzoeker. In de bijlage vindt u de contactgegevens.

1. Wat is het doel van dit project?

Diabetes is een chronische aandoening die ontstaat wanneer er onvoldoende insuline door de alvleesklier wordt aangemaakt of wanneer insuline in het lichaam niet goed werkt. In beide gevallen leidt het tekort aan insuline tot een verhoogde hoeveelheid glucose (suiker) in het bloed. Om hoge bloedglucosewaarden te verlagen gebruiken mensen met diabetes insuline of andere medicatie, en/of maken zij aanpassingen in hun leefstijl.

Het zelf reguleren van bloedglucosewaarden middels insuline/medicatie, voeding en beweging noemen we diabetes zelfmanagement. Diabetes zelfmanagement is niet (altijd) eenvoudig. Om bloedglucosewaarden zo goed mogelijk te reguleren is het nuttig om informatie bij te houden over uw bloedglucose, insuline/medicatie, voeding en beweging. Veel mensen vinden het lastig om dat consequent te doen.

Om diabetes zelfmanagement te vergemakkelijken, maken veel mensen gebruik van technologische hulpmiddelen, zoals sensoren, apps of online programma's. Het gebruik van 'apps' en online toepassingen noemen we 'mobiele gezondheid' of

mHealth. Helaas zijn niet alle hulpmiddelen altijd voor iedereen beschikbaar of goed ingebed in bestaande diabeteszorg.
Met deze 'POWER2DM' studie doen we onderzoek naar de mogelijkheden van een nieuw mHealth systeem dat diabetes zelfmanagement eenvoudiger maakt. Het uiteindelijke doel van het POWER2DM project is een gebruiksvriendelijk, nieuw mHealth systeem op te zetten, dat gebruikt kan worden door mensen met diabetes en hun zorgverleners. Dit nieuwe mHealth systeem zal gebruik maken van meerdere technologische hulpmiddelen, zoals sensoren, computer simulaties en persoonlijke boodschappen op een SmartPhone. Voordat we dit uiteindelijke doel kunnen bereiken, zijn er een aantal tussenstappen nodig. De eerste stap is te leren welke informatie en sensoren nuttig zijn om in het mHealth systeem te gebruiken. Om deze vraag te beantwoorden verzamelen we in dit eerste deel van het project informatie middels verschillende soorten sensoren en via vragenlijsten.

2. Wat wordt onderzocht?

In dit onderzoek bekijken we welke sensoren en computersimulaties nuttig zijn om mensen met diabetes te helpen bij hun zelfmanagement. Ook kijken we, middels de vragenlijsten, naar hoe mensen met diabetes hun zelfmanagement ervaren en hoe ze zich voelen.

3. Hoe wordt het onderzoek uitgevoerd?

In totaal zullen 60 patiënten met diabetes deelnemen aan het onderzoek: 20 uit Nederland, 20 uit Spanje, en 20 uit Duitsland. De studie zal gedurende 3 maanden gegevens over diabetes zelfmanagement verzamelen via de verschillende sensoren en vragenlijsten. De periode van drie maanden in deze studie bestaat uit drie verschillende delen:

- Een intensieve periode van vier weken aan het begin van de studie (week 1-4)
- Een optionele, niet-intensieve periode van zes weken (week 5-10)
- Een intensieve periode van twee weken aan het einde van de studie (week 11-12)

Het verschil tussen de drie delen is dat u in de intensieve periodes dagelijks wordt gevraagd om uw diabetes zelfmanagement bij te houden, uw voeding te noteren en een aantal vragen te beantwoorden. In de optionele periode kunt u kiezen wat u wilt bijhouden en hoe vaak.

In dit onderzoek zullen alle gegevens alleen verzameld worden voor onderzoeksdoeleinden, en het opzetten van het mHealth systeem. Het verzamelen van de gegevens heeft niet het doel om uw zelfmanagement te veranderen. Tijdens dit onderdeel van de studie ontvangt u dus geen nieuwe/aanvullende behandeladviezen. Als u meedoet aan de studie, blijft u gewoon onder behandeling van uw eigen arts en verandert er niets aan de wijze waarop die behandeling plaatsvindt.

4. Wat wordt er van u verwacht?

Het onderzoek duurt drie maanden. Het begint met een kennismakingsbezoek, daarna volgen twee periodes van thuismetingen, verdeeld over twee intensieve perioden en een niet-intensieve periode.

Introductie bezoek

Het kennismakingsbezoek vindt plaats in het LUMC en duurt ongeveer anderhalf uur. Tijdens dit bezoek zal het onderzoek uitgebreid worden toegelicht. Als u wilt deelnemen aan de studie dan tekent u een deelname toestemmingsformulier. Vervolgens wordt u gevraagd om een aantal initiële metingen uit te voeren, vragenlijsten in te vullen, en wordt er een bloedmonster afgenomen. Deze metingen worden hieronder toegelicht:

Initiële Metingen

Tijdens het kennismakingsbezoek noteren we uw gewicht, lengte, buikomvangen bloeddruk, samen met een korte medische voorgeschiedenis en uw huidige diabetes behandelplan.

Vragenlijsten

Aan het begin van de studie wordt u gevraagd om een set vragenlijsten in te vullen over uw diabetes zelfmanagement, problemen die u kunt hebben in verband met diabetes, en de kwaliteit van leven.

Bloedmonster

Het bloedmonster wordt afgenomen om te zien hoe uw HbA1c en cholesterol zijn aan het begin van de studie. Daarnaast wordt met dit bloedmonster gekeken naar

andere belangrijke bloedwaarden bij diabetes. Een volledige lijst van alle bloedwaarden die worden bekeken is beschikbaar op uw verzoek.

Nadat de eerste metingen, vragenlijsten, en bloedmonster zijn voltooid krijgt u instructies over hoe u de verschillende apparaten zult gebruiken tijdens de studie. Onder begeleiding van de onderzoeker zult u ervaren hoe de apparaten werken in de praktijk, en heeft u de mogelijkheid te oefenen en vragen te stellen.

Thuismetingen

Het onderzoek begint met een intensieve periode van vier weken waarin u wordt gevraagd om zorgvuldig uw bloedglucose, voeding, lichaamsbeweging, medicatie en stress bij te houden. Het hoofddoel van deze studie is om te zien of we dit proces gemakkelijker kunnen maken. Daarvoor gebruiken we drie apparaten die gegevens verzamelen over uw bloedglucose, lichaamsbeweging en stress. Dit gebeurt automatisch. Daar hoeft u zelf weinig voor te doen. Wel willen we u vragen bij te houden wat u eet, welke/hoeveel medicijnen en insuline u neemt en op welke tijdstippen. Om dit makkelijker te maken, krijgt elke deelnemer een iPod Touch 6^{e} generatie gedurende het onderzoek. Op deze iPod installeert de onderzoeker vooraf alle noodzakelijke apps. Als u een mobiele telefoon heeft waarop al de apps kunnen worden geïnstalleerd, dan is dat ook een mogelijkheid. Dit zal echter wat extra tijd kosten tijdens het kennismakingsgesprek. Een uitleg over de verschillende thuismetingen vindt u hieronder.

Glucosewaarden

Uw glucosewaarden worden bijgehouden met behulp van het FreeStyle Libre Flash Glucose Monitoring Systeem. Het FreeStyle Libre Flash Glucose Monitoring Systeem bestaat uit een sensor en een Reader (hieronder afgebeeld). U kunt de sensor aanbrengen op uw arm, waar deze gedurende 14 dagen kan blijven zitten. U kunt met de sensor sporten en de sensor is waterbestendig. De FreeStyle Libre Sensor meet automatisch uw bloedglucosewaarden in de afgelopen 8 uur. Deze waarden en uw huidige bloedglucosewaarde kunnen worden verzameld met een pijnloze, 1 seconde scan met behulp van de FreeStyle Libre Reader.

Tijdens de eerste drie dagen van de studie, wordt u gevraagd om uw bloedglucosewaarde 8 keer per dag te meten met een vingerpriktest en elke 8 uur de

sensor te scannen om te zorgen dat de sensor nauwkeurig is. De FreeStyle Libre Reader kan worden gebruikt voor zowel de automatische bloedglucose scan met de sensor, als de vingerprik meting.

Na deze drie dagen is het voor de studie niet nodig om uw bloedglucose te meten via een vingerprik, en hoeft u de sensor slechts één keer in de 8 uur te scannen (als u wakker wordt ‘s ochtend, 's middags,' s avonds en voordat u gaat slapen). We raden u aan wel een vingerprik uit te voeren wanneer uw sensor aangeeft aan dat uw bloedglucose onder de 3 mmol/L of boven de 20 mmol/L is, of wanneer u symptomen van hoge of lage bloedglucose ervaart die niet lijken te kloppen met de meting van het Flash Glucose Monitoring Systeem. Aan het einde van het onderzoek zullen de gegevens van de Reader worden gedownload en opgeslagen op een onderzoekscomputer. Meer informatie over de FreeStyle Libre Flash Glucose Monitoring Systeem is te vinden op deze website: http://www.freestylelibre.nl/.

Stress (gemeten door middel van ademhaling)

Om stress te meten krijgt u een kleine sensor die kan worden gedragen op uw broekriem of BH-band. Deze sensor heet de Spire en meet de frequentie van uw ademhaling. Tijdens de intensieve periodes vragen wij u de Spire te dragen op uw broekriem of BH-band gedurende de dag. De Spire kan 6 uur van de metingen opslaan en maakt automatisch

een verbinding met de iPod als deze in de buurt is om stress-gegevens op te slaan. U hoeft dus niets anders te doen dan de sensor te dragen. Meer informatie is te vinden op deze website: www.spire.io (Engelse website).

Lichamelijke activiteit, slaap, ontspanning en hartslag

Om uw lichamelijke activiteit te meten geven wij u een Fitbit Charge HR polsbandje. Tijdens de intensieve periode vragen wij u de Fitbit continu te dragen om uw pols, behalve wanneer u in het water gaat (bijvoorbeeld bij het douchen of zwemmen) of wanneer u de Fitbit moet opladen. We vragen u de Fitbit verder continu te dragen, zelfs wanneer u slaapt! Wanneer u de Fitbit Charge HR draagt, verzamelt het automatisch gegevens over uw lichamelijke activiteit door het tellen van hoeveel stappen u heeft gezet, hoe lang u heeft geslapen, en geeft een overzicht van uw hartslag. Deze gegevens worden automatisch verzonden naar de iPod. U hoeft dus niets anders te doen dan de Fitbit te dragen! U vindt meer
informatie op deze website:
https://www.fitbit.com/nl/chargehr (Engels site).

Voeding

We begrijpen dat het bijhouden van wat u eet veel werk is. Daarom hebben we er in deze studie voor gekozen om deelnemers de keuze te geven uit drie verschillende manieren voor het noteren van voeding. U kunt kiezen welke manier u wilt gebruiken en wanneer. De eerste manier is met behulp van de app Calorie Counter van FatSecret. Calorie Counter heeft een grote database van verschillende soorten voedingsmiddelen die u via de app kunt selecteren, en zo online uw eetgedrag bij kunt houden over de dag. Het leuke van deze app is dat wanneer u een

voedingsmiddel kiest, alle voedingswaarde-informatie automatisch wordt opgeslagen. Zo krijgt u een goed inzicht in de kwaliteit van uw voeding, ten aanzien van bijvoorbeeld de hoeveelheid koolhydraten, calorieën of bijvoorbeeld zout en transvetten. De tweede optie is zelf te berekenen hoeveel koolhydraten en calorieën u at en dit noteren in de app PatiëntCoach. De derde en laatste optie is een schatting te maken van hoe koolhydraatrijk uw maaltijd of tussendoortje was met behulp van zogenaamde ‘’brood eenheden’’. ‘’Brood eenheden’’zijn een makkelijke manier om te schatten hoeveel koolhydraten er in een maaltijd zitten. Een korte uitleg over het noteren van ‘’brood eenheden’’ kunt u vinden in PatiëntCoach. U kunt kiezen op welke manier u uw voeding wilt noteren en kunt eventueel wisselen tussen methoden.

Medicatiegebruik

Elke dag wordt u gevraagd te noteren welke medicijnen u heeft gebruikt in de PatientCoach app. Bij gebruik van insuline vragen wij u wat voor soort, hoeveel eenheden, en wanneer u de insuline heeft ingespoten.

Vragenlijsten

Graag willen we weten hoe u zich gedurende het onderzoek voelt, en in het bijzonder met betrekking tot uw diabetes. Hiervoor vragen wij u om dagelijkse vragen over uw stress, stemming, en kwaliteit van de slaap te beantwoorden. Bovendien vragen wij u tweemaal een vragenlijst in te vullen over stress en uw diabetes: aan het einde van de eerste intensieve periode en tijdens de tweede intensieve periode. Deze vragen worden verzonden via de PatiëntCoach app op de iPod (www.patientcoach.nl). De dagelijkse vragen nemen minder dan een minuut in beslag en de vragenlijsten die twee keer in drie maanden worden verstuurd, nemen minder dan 15 minuten in beslag.

Aan het einde

Aan het einde van de studie vragen wij u om naar het LUMC te komen voor een consult. Gedurende dit consult vragen wij u om alle apparaten te retourneren, behalve de Reader van de FreeStyle Libre. Deze mag u behouden. Verder vragen we u een aantal vragenlijsten in te vullen, en uw ervaring in de studie met een onderzoeker te bespreken. Daarnaast wordt een bloedmonster afgenomen om uw

HbA1c te meten en een haarmonster om uw stress in de afgelopen paar maanden te meten. Ook geeft dit consult de mogelijkheid om uw eventuele vragen te beantwoorden.

Privacy

Alle apparatuur wordt verstrekt aan de deelnemers bij de start van de studie. Deze apparatuur is voorgeprogrammeerd door de onderzoekers met een unieke code voor elke deelnemer. Dit zorgt ervoor dat alle gegevens anoniem worden verzameld. Buiten het onderzoeksproject is het niet mogelijk om gegevens te koppelen aan een specifieke patiënt.

Vergoeding

Tijdens het onderzoek worden alle glucose meetinstrumenten waaronder de FreeStyle Libre Reader, 3 FreeStyle Libre Sensoren en 50 FreeStyle Precision teststrips aan u verstrekt. Hieraan zijn voor u geen kosten verbonden. Aan het einde van de studie, mag u de FreeStyle Libre Reader houden voor uw eigen gebruik .

5. Wat zijn de mogelijke voor en nadelen van deelname aan het onderzoek

Mogelijke voordelen van deelname aan de studie zijn dat u meer leert over het thuis monitoren van diabetes en over mHealth mogelijkheden die er op dit moment zijn. Het onderzoek zal helpen om een nieuw mHealth systeem te creëren dat mensen met diabetes, inclusief uzelf, kunnen gebruiken voor ondersteuning van diabetes zelfmanagement in de toekomst.

Nadelen van de studie zijn dat u in de eerste dagen van de studie vaker een vingerprik moet uitvoeren en dat bloedmonsters moeten worden afgenomen aan het begin en het einde van de studie. Bovendien, deelname aan het onderzoek kost tijd, vooral in de intensieve perioden en wanneer u in het LUMC komt aan het begin en het einde van de studie.

6. Wat gebeurt er als u niet wenst deel te nemen aan dit onderzoek?

U beslist zelf of u meedoet aan het onderzoek. Deelname is vrijwillig. Als u besluit niet mee te doen, hoeft u verder niets te doen. U hoeft dan niets te tekenen. U hoeft ook niet te zeggen waarom u niet wilt meedoen als u dat niet wilt. Als patiënt van de diabetespoli krijgt u gewoon de behandeling die u anders ook zou krijgen. Als u wel

meedoet aan het onderzoek, kunt u zich altijd bedenken en toch stoppen. Ook tijdens het onderzoek, en zonder opgaaf van reden. De relatie met uw behandelend arts zal niet veranderen, onafhankelijk van of u wel of niet meedoet.

7. Heeft deze studie een verzekering?

Sommige medische studies moeten een verzekering afsluiten. Voor dit onderdeel van de POWER2DM studie hoeft dat niet. De Medisch Ethische Commissie van het Leids Universitair Medisch Centrum (LUMC) heeft bepaald dat de risico's van meedoen aan dit onderzoek minimaal zijn. Omdat de risico's van dit onderzoek minimaal zijn, is er geen verzekering nodig.

8. Wat gebeurt er met uw gegevens?

Al uw gegevens worden vertrouwelijk verwerkt en opgeslagen. Alleen de onderzoeker, IT-medewerker en de onderzoeksleider kennen uw persoonlijke code, waarmee onderzoeksgegevens kunnen worden gekoppeld aan uw naam. Alleen daarvoor erkende en geregistreerde mensen mogen uw medische en persoonsgegevens inzien. Dit is om te controleren of het onderzoek goed en betrouwbaar is. Algemene informatie hierover vindt u in de brochure 'Medisch-wetenschappelijk onderzoek'. Mensen die uw gegevens kunnen inzien zijn: het onderzoeksteam en de Inspectie voor de Gezondheidszorg. Zij houden uw gegevens geheim. Als u de toestemmingsverklaring ondertekent, geeft u toestemming voor het verzamelen, bewaren en inzien van uw medische en persoonsgegevens. De onderzoeker bewaart uw gegevens 15 jaar.

9. Welke medisch-ethische toetsingscommissie heeft dit onderzoek goedgekeurd?

De Medisch Ethische Toetsingscommissie van het LUMC heeft dit onderzoek goedgekeurd.

10. Wie betaalt dit onderzoek en wie voert het uit?

Dit onderzoek wordt betaald vanuit een Europese subsidie (European Commision Horizon 2020 Framework Programme for Research and Innovation, nummer 689444). Het onderzoek is een samenwerkingsverband tussen de afdelingen Medisch Besliskunde, Endocrinologie, en Public health en Eerstelijnsgeneeskunde in

het LUMC. Het onderzoek in het LUMC wordt geleid door Dr. Jaap Sont (associate professor afdeling Medische Besliskunde) en uitgevoerd door, onder anderen, Ian Smith (onderzoeker), Dr. Sasja Huisman (psycholoog en senior onderzoeker), Prof. Dr. Eelco de Koning (internist en hoogleraar diabetologie), Dr. Jiska Snoeck-Stroband (huisarts en senior onderzoeker), Dr. Persijn Honkoop (huisarts en senior onderzoeker), en Dr. Niels Chavannes (arts en hoogleraar eHealth). Daarnaast zal het onderzoek ook plaatsvinden in Cordoba, Spanje, onder leiding van Dr. Javier Delgado-Lista en in Karlsburg, Duitsland, onder leiding van Dr. Eckhard Salzseider.

11. Wilt u verder nog iets weten?

Als u nog iets wilt weten, kunt u dit vragen via de coördinerend onderzoeker. Ook heeft dit onderzoek een onafhankelijke arts. U kunt deze arts raadplegen voor onafhankelijk advies over de studie.

12. Contact gegevens

Coördinerend onderzoeker

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Onafhankelijk arts

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m.a.schroijen@lumc.nl of telefoon: 071-5299701.

13. bijlage

- Algemene brochure medisch-wetenschappelijk onderzoek met mensen

10.2 Toestemmingsformulier

Toestemmingsformulier POWER2DM studie

Ik heb de informatiebrief voor deelnemen aan het onderzoek gelezen. Ik heb de mogelijkheid gehad aanvullende vragen te stellen. Mijn vragen zijn afdoende beantwoord. Ik heb voldoende tijd gehad om te beslissen of ik mee zou doen.

Ik weet dat deelname aan het onderzoek vrijwillig is. Ik weet dat ik op ieder moment kan beslissen om toch niet mee te doen. Daarvoor hoef ik geen reden op te geven.

Ik weet dat sommige mensen mijn gegevens kunnen inzien. Die mensen staan vermeld in de algemene brochure.

Ik ga akkoord met deelname aan dit onderzoek.

☐ Akkoord

Ik ga akkoord dat ik in de toekomst benaderd kan worden over deelname aan vervolgstudies in het POWER2DM-project.

☐ Akkoord ☐ Niet akkoord

Naam deelnemer aan onderzoek: Datum: __ / __ / __

Handtekening