The impact of self-quarantining on glycemic control, diabetes self-management and distress during the coronavirus outbreak

PROTOCOL TITLE 'The impact of self-quarantining on glycemic control, diabetes self-management and distress during the coronavirus outbreak'

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PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
Sponsor or legal representative: **Head of Department:**	*Department of Internal Medicine: Endocrinology,* *Leiden University Medical Center*	
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
AR	**Adverse Reaction**
BMI	**Body Mass Index**
CA	**Competent Authority**
CGM	**Continuous Glucose Monitoring**
COVID-19	**Coronavirus**
CV	**Curriculum Vitae**
DM	**Diabetes Mellitus**
DSMB	**Data Safety Monitoring Board**
DSMQ-R	**Diabetes Self-Management Questionnaire**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
FGM	**Flash Glucose Monitoring**
FSL	**FreeStyleLibre**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
HbA1c	**Glycated Hemoglobin**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
LUMC	**Leiden University Medical Center**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
NA	**Not Applicable**
PAID	**Problem Areas In Diabetes**
PI	**Principal investigator**
PSS	**Perceived Stress Scale**
QoL	**Quality of Life**
(S)AE	**(Serious) Adverse Event**
SDSCA	**Summary of Diabetes Self-Management Activities**
SMBG	**Self-monitoring of Blood Glucose**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie**

	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**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WHO-5	**Well-being questionnaire**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Diabetes mellitus is a chronic disease characterized by the inability of the body to maintain normoglycemia. Treatment of diabetes relies mostly on diabetes self-management, requiring a large investment of time and energy on a daily basis. Psychological wellbeing, behavioral patterns and social context have shown to play a major role in diabetes-self-management and glycemic control. Self-quarantining may impact glycemic control by influencing daily routines, self-measurement behavior, therapy adherence, physical activity and eating behaviors. A period of nationwide self-quarantine, such as during the outbreak of COVID-19 in the Netherlands, therefore may have a large effect on glycemic control in patients with diabetes.

Objective: We aim to assess the impact of long-term self-quarantine on glycemic control, diabetes self-management and distress in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).

Study design: This is an observational cross sectional study in Dutch patients with diabetes mellitus in tertiary care after self-quarantine for at least 6 weeks as result of the COVID-19 pandemic. Patients treated at the diabetes outpatient clinic of the Leiden University Medical Center (LUMC) will be approached for potential study participation. Measurements will be performed during the quarantine period or as soon as possible after. Patients will be asked to perform a fingerprick for HbA1c measurement once, which they can send back to the LUMC by mail. In addition, data from continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) devices will be collected according to standard clinical practice. Furthermore, patients will be asked to fill out an online questionnaire once on diabetes self-management behaviour, well-being and distress, along with questions about health status, level of education, medication use, employment, social situation and the impact of self-quarantine on daily routines.

Data on demographics, type of diabetes, weight, BMI and HbA1c prior to the COVID-19 outbreak will be derived from the electronic health dossier of the patient. The most recent HbA1c will be used for data analysis.

Study population: Patients with T1DM and T2DM that are currently in care at the outpatient diabetes clinic of the LUMC are eligible for participation.

Intervention (if applicable): NA

Main study parameters/endpoints: The main study parameter is glycemic control in patients with T1DM and T2DM assessed by HbA1c. We will also determine the change in HbA1c per patient group, as well as glucose variability, assessed by the standard deviation of glucose values in patients wearing continuous and flash glucose sensors, and the change in glucose variability before and after the nation-wide self-quarantine phase for COVID-19. In

addition, self-management, well-being and distress will be measured, using the DSMQ-R, SDSCA, WHO-5, PSS and PAID questionnaire.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

The risks associated with participation in this study are limited. The primary potential foreseeable risk associated with participation in this study is negative feelings resulting from the increased attention to the patient's illness and distress by filling out the questionnaires. Additionally, there is a limited burden of time for the patient for performing the fingerprick and filling out the questionnaires, however, this time is limited and the measurement is being performed only once. Performing the fingerprick may be another foreseeable risk, however, for most patients performing a fingerprick for measurement of blood glucose values is already part of their regular daily routine.

1. INTRODUCTION AND RATIONALE

In the early Spring of 2020 the worldwide pandemic viral outbreak of COVID-19 caused a rapid increase in morbidity and mortality especially in patients. In an attempt to control the outbreak, many countries implemented forms of mass quarantine. Quarantine strategies diverged from total lock-down of cities or countries, voluntary home curfews, travel restrictions and prohibition of public and social events (1). In all affected countries these strategies required major adaptations of behavioral patterns, social activities and employment of the population.

Such sudden and major disruptions from every-day-life are known to influence both mental and physical health. Recent studies describing the psychological impact of quarantine, showed that experiencing quarantine is related to a wide range of stress and mood related symptoms, such as depression, anxiety, irritability, poor concentration, insomnia and post-traumatic stress disorder (PTSD)(1, 2). Longer periods of quarantine have been associated with increased chances of developing PTSD. In addition, several studies suggest that such symptoms might even last long after ending quarantine (1, 2).

Recent studies and global media suggest that individuals with diabetes mellitus (DM) are at higher risk for complications and death from COVID-19 (3). Especially patients with T2DM, who are frequently overweight and have other comorbidities such as hypertension and cardiovascular disease are at a high risk for a complicated course of COVID-19 (4). People with diabetes and their relatives may therefore experience increased feelings of stress, fear and anxiety regarding the risk of being infected with the coronavirus. And additionally, they may put even greater emphasis on the importance of self-quarantine.

Emotional distress as well as changes in daily structures and behaviors are known to influence diabetes self-management and glycemic control (5-8). Maintaining glycemic control during self-quarantine can therefore be challenging. Alterations in physical activity, diet and daily patterns may result in an imbalance between blood glucose values and the amount of insulin injected or other drugs prescribed, resulting in glycemic dysregulation (9-11). Furthermore, feelings of anxiety or distress towards the situation may further increase blood glucose values and add to the psychological burden of disease (5-8, 12).

The current study aims to assess the impact of self-quarantine on glycemic control in patients with type 1 and type 2 diabetes. In addition, this study describes diabetes self-management, well-being and distress in Dutch patients with type 1 and type 2 diabetes, during a nationwide period of self-quarantine.

It is hypothesized that experiencing this period of nationwide quarantine influences glycemic control and that patients reporting severe distress or low well-being experience more

problems in regard to diabetes self-management and maintaining glycemic control than those without psychological distress or low well-being (13).

Research hypotheses:

H1: Experiencing self-quarantine impacts glycemic control and glucose variability

H2: a) Experiencing high levels of distress is related to (poorer) glycemic control

H2: b) Experiencing low levels of well-being is related to (poorer) glycemic control

H3: a) Experiencing high levels of distress is related to suboptimal diabetes self-management

H3: b) Experiencing low levels of well-being is related to suboptimal diabetes self-management

H4: Experiencing self-quarantine impacts HbA1c, glucose variability, well-being, distress and self-management more in patients with type 1 than in patients with type 2 diabetes

2. OBJECTIVES

Primary Objective:

- To determine the effect of a period of nationwide self-quarantine on glycemic control, assessed by HbA1c, in patients with type 1 and type 2 diabetes

Secondary Objective(s):

- To determine the effect of a period of nationwide self-quarantine on glucose variability assessed by the standard deviation (SD) of glucose values (glucose variability) in patients with type 1 and type 2 diabetes
- To assess the association between well-being and glycemic control during a period of nationwide self-quarantine. Well-being will be measured by the WHO-5.
- To assess the association between (diabetes) distress and glycemic control during a period of nationwide self-quarantine. (Diabetes) distress will be measured by 'Perceived Stress Scale'(PSS) and 'Problem Areas in Diabetes' (PAID).
- To assess the association between diabetes self-management and glycemic during a period of nationwide self-quarantine. Self-management behaviour will be measured by the 'Summary of Diabetes Self-Care Activities' (SDSCA) and 'Diabetes Self-Management Questionnaire-rev.' (DSMQ-R)
- To determine differences HbA1c, glucose variability, well-being, distress and self-management between patients with type 1 and type 2 diabetes

3. STUDY DESIGN

This study is an observational, cross sectional study to assess the impact of self-quarantining on glycemic control, diabetes self-management, distress and well-being. Patients with type 1 and type 2 diabetes mellitus currently in care at the diabetes outpatient clinic of the LUMC will be eligible to participate and will receive information about this study and an informed consent form. A few days later they will be contacted by phone to resolve any questions they may have and ask if the patient wants to participate in the study. If patients want to participate, they will sign the informed consent form and send it to the LUMC by mail. Once informed consent is provided, patients will be sent an envelope including a fingerprick device and a small tube. They will be asked to fill the tube with several drops of blood up to a mark on the tube and send the envelope back to the LUMC postage free. At the LUMC the HbA1c will be measured by the clinical chemistry lab. If the patients wears a continuous or FSL sensor, sensor data will be collected according to standard clinical practice. Furthermore, patients will receive a link by e-mail to a set of online questionnaires, containing the DSMQ-R, SDSCA, PSS, PAID and WHO-5, along with questions about level of education, medication use, employment, social situation and the impact of self-quarantine on daily routines. The HbA1c measurement and questionnaire will be performed at least 6 weeks after starting the quarantine period but still within a period of quarantine measures. Questionnaires will assess the extent and impact of the quarantine measures for each individual patient and assess the effect on glycemic control, distress and well-being. Data on HbA1c measurements in the 12 months prior to the period of nationwide self-quarantine will be retrieved from the electronic health record of each patient, if available.

4. STUDY POPULATION

4.1. Population (base)

Patients with type 1 diabetes and type 2 diabetes will be recruited from the diabetes outpatient clinic of the LUMC.

4.2. Inclusion criteria

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

- Age ≥ 18 years
- Diagnosed with type 1 or type 2 diabetes
- Ability to perform fingerpricks
- Sufficient comprehension of the Dutch language
- Ability to fill out online questionnaires

4.3. Exclusion criteria

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

- Pregnancy
- Newly diagnosed malignancy, with the exclusion of non-melanoma skin cancer, in the previous 6 months
- Chemotherapy or immunotherapy for malignancy
- Admission to hospital or rehabilitation center

4.4. Sample size calculation

Patients with type 1 and type 2 diabetes mellitus are eligible for participation. HbA1c is the primary outcome parameter. Blood for HbA1c will be collected at home by a fingerprick and send to the LUMC. This is a method to obtain insight in glycemic control that many patients perform, and prefer, in clinical practice as it saves them a visit to the hospital. The clinical laboratory in the LUMC is set up to analyse these samples. But this method, which is appropriate in the context of social distancing and limiting hospital visits during this COVID-19 outbreak, also has some consequences regarding the number of patients that need to be approached. From clinical practice we know that not all patients carry out the blood sampling in an appropriate way, despite clear instructions. Also the duration in the postal service renders some samples not suitable for analysis. In this COVID-19 period the postal service

may take longer than normal. Based on our experience from clinical practice and the current COVID-19 situation we estimate that 20% of samples cannot be analysed for HbA1c.
The aim is to detect a difference in HbA1c of 4.0 mmol/mol (standard deviation 11 mmol/mol) in comparison to the HbA1c prior to the period of quarantine, which is considered to be clinically relevant in our population of patients with often well regulated diabetes. For an alpha error of 0.05 and a power of 90%, the minimum sample needed is 159 patients per patient group (type 1 and type 2 diabetes). Taking in consideration an estimated response rate of 35% and an estimated proportion of 20% of HbA1c missing measurements as a result of logistical, practical or technical problems, 568 patients per patient group (type 1 and type 2 diabetes) will be invited to participate. This is a total of 1136 patients.
The numbers of participants mentioned above are much higher than the number that is minimally needed (15 per variable) to calculate the hierarchical regression analyses (see statistical analyses) on secondary outcomes.

5. TREATMENT OF SUBJECTS

NA. Observational cross-sectional study.

5.1. Investigational product/treatment

NA

5.2. Use of co-intervention (if applicable)

NA

5.3. Escape medication (if applicable)

NA

6. INVESTIGATIONAL PRODUCT

NA. Observational cross-sectional study.

6.1. Name and description of investigational product(s)

NA

6.2. Summary of findings from non-clinical studies

NA

6.3. Summary of findings from clinical studies

NA

6.4. Summary of known and potential risks and benefits

NA

6.5. Description and justification of route of administration and dosage

NA

6.6. Dosages, dosage modifications and method of administration

NA

6.7. Preparation and labelling of Investigational Medicinal Product

NA

6.8. Drug accountability

NA

7. NON-INVESTIGATIONAL PRODUCT

NA. Observational cross-sectional study.

7.1. Name and description of non-investigational product(s)

NA

7.2. Summary of findings from non-clinical studies

NA

7.3. Summary of findings from clinical studies

NA

7.4. Summary of known and potential risks and benefits

NA

7.5. Description and justification of route of administration and dosage

NA

7.6. Dosages, dosage modifications and method of administration

NA

7.7. Preparation and labelling of Non Investigational Medicinal Product

NA

7.8. Drug accountability

NA

8. METHODS

8.1. Study parameters/endpoints

8.1.1. Main study parameter/endpoint

Glycemic control assessed by HbA1c (mmol/mol)

8.1.2. Secondary study parameters/endpoints (if applicable)

- Glucose variability assessed by the standard deviation (SD) of glucose values during continuous or flash glucose monitoring
- Extent of well-being as assessed by the WHO-5
- Extent of psychological distress as assessed by the 'Perceived Stress Scale'(PSS) and 'Problem Areas in Diabetes'(PAID)
- Evaluation of self-management behaviour measured by 'Summary of Diabetes Self-Care Activities'(SDSCA) and 'Diabetes Self-Management Questionnaire' (DSMQ-R)

8.1.3. Other study parameters (if applicable)

Baseline characteristics: age, gender, length, weight, type of diabetes, level of education, medication use, social situation, employment, impact of self-quarantine on daily routines, and health status.

8.2. Randomisation, blinding and treatment allocation

NA

8.3. Study procedures

Eligible patients from the diabetes outpatient clinic will be sent a letter with study information and informed consent forms. Within several days after receiving the letter, patients will be contacted by phone and will be invited to participate in the study as well as given the opportunity to ask questions. If patients are willing to participate they will be asked to sign the informed consent form and send it back to the LUMC by mail. Once informed consent is provided, patients will be sent a HbA1c fingerprick measurement envelope. They will be asked to fill the tube with several drops of blood up to a mark on the tube and send the envelope back to the LUMC postage free. At the LUMC the HbA1c will be measured by the clinical chemistry lab.

If patients are using a continuous or flash glucose monitoring device data of the most recent 3 months will be collected according to standard clinical practice.

Additionally, patients will receive a link in their e-mail to a set of online questionnaires, containing the DSMQ-R, SDSCA, PSS, PAID and WHO-5, along with questions about level of education, medication use, social situation, employment, impact of self-

quarantine on daily routines, and health status.

The HbA1c measurement and questionnaire will be performed once two months after the start of the nationwide quarantine phase as a result of the COVID-19 outbreak. Data on HbA1c measurements in the 6 months prior to the period of nationwide self-quarantine will be retrieved from the electronic health record of each patient.

8.4. 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.

8.4.1. Specific criteria for withdrawal (if applicable)

- Patient tested COVID-19 positive within 2 weeks after the HbA1c measurement
- Patient diagnosed with a malignancy, potentially resulting in unreliable HbA1c values
- Patient pregnant during HbA1c measurement in retrospect

8.5. Replacement of individual subjects after withdrawal

No replacement of individual subjects will take place after withdrawal.

8.6. Follow-up of subjects withdrawn from treatment

This is an observational cross-sectional study without any follow-up period.

8.7. Premature termination of the study

The study will be terminated prematurely if the nationwide quarantine is unexpectedly lifted within a week. In that case, the inclusion of participants will be stopped. Also, the study will be terminated if it is temporarily suspended for reasons of subjects' safety and the accredited METC gives a negative decision after assessing the reasons that led to the temporary suspension (see below).

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

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 the study procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

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
- 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 investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a

period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3. Suspected unexpected serious adverse reactions (SUSARs)

NA.

9.3. Annual safety report

NA.

9.4. 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.

9.5. [Data Safety Monitoring Board (DSMB) / Safety Committee]

NA. This is an observational cross-sectional study without any follow-up period.

10. STATISTICAL ANALYSIS

- Categorical data: gender, level of education, type of diabetes, medication use, type of blood glucose measurements (fingerprick or glucose sensor (FGM/CGM)) will be presented by percentage and standard deviation (SD).
- Continuous variables: age, BMI, weight, height, HbA1c will be presented using the mean and the standard deviation (SD). Derived parameters: BMI will be calculated from height (m) and weight (kg) using the formula (weight (kg)/(height (m))^2 and will be presented as continuous variable by mean and standard deviation (SD). Glucose variability will be calculated by the standard deviation of the glucose values from the continuous and flash glucose monitors obtained during the previous week in the quarantine period. This SD will be compared to the SD from the glucose values during the last non-quarantine week. Other glycemic measures include time spent in range 4.0-10.0 mmol/l, time spent in hypoglycaemia (<3.0, 3.0-3,5, and 3.5-3.9 mmol/l), time spent in hyperglycemia (≥ 10.0 mmol/l)
- Missing data will be excluded from analyses.

- Data will be statistically analysed using STATA intercooled 16.0. HbA1c measurements and SD measurements prior to and after the quarantine period will be compared using a paired-sample t-test in case of normal distribution or Wilcoxon Signed Rank Test in case of abnormal distribution. Furthermore, differences in HbA1c and glucose variability between patients with type 1 and type 2 diabetes will be measured using independent T-tests. Differences in well-being, distress and self-management between patients with type 1 and type 2 diabetes will be analysed using independent T-tests. The association between glucose variability and parameters for distress, well-being and self-management will be analysed using multivariate regression analysis.

10.1. Primary study parameter(s)

HbA1c

HbA1c will be assessed in whole blood obtained by a fingerprick. The HbA1c will be compared to the last HbA1c in the non-quarantine period.

10.2. Secondary study parameter(s)

Standard deviation (SD) of glucose values

In patients who wear a continuous or flash glucose sensor the SD of the glucose values will be determined in the previous week before uploading the glucose data during the quarantine period. The SD will be compared to the SD during the last non-quarantine week.

Well-being (WHO-5)

To measure the extent of well-being we will administer the WHO-5 Well-Being Index (WHO-5). The WHO-5 is one of the most widely used questionnaires assessing well-being and consists of five simple, non-invasive questions (14). 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. The WHO-5 has been found to correlate moderately to strongly with diabetes specific measures of distress and depression in both T1DM and T2DM (15, 16).

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 (17). Participants rate 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 Dutch version is available.

Diabetes Distress: PAID

The Problem Areas in Diabetes (PAID) questionnaire is a 20-item measure of psychosocial adjustment to diabetes (18). 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. The PAID was developed for routine clinical usage in both T1DM and T2DM. The PAID has been validated in Dutch (19).

Diabetes Self-Management: SDSCA and DSMQ-R

The Summary of Diabetes Self-Care Activities (SDSCA) .The SDCSA is a short questionnaire that covers basic aspects of diabetes self-care in regards to general diet, specific diet, exercise, blood-glucose testing, foot care, and smoking (20). The core questionnaire consists of 11 questions but it can be expanded and adapted to specific needs using the additional self-care items published with the original instrument. The core set of questions has been validated in Dutch.

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 days (21). These items can be grouped into four subscales (glucose management, dietary control, physical activity, and physician contact) from which an overall sum score for 'diabetes self-management' can be calculated. All subscales as well as the overall sum score have shown to be 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.

Relationship between well-being/distress and glycemic control

To assess the relationship between well-being/distress and glycemic control, a (stepwise) hierarchical regression analysis will be performed, with HbA1c during self-quarantine as dependent variable and demographics (age, gender, education), diabetes/treatment related variables (type of diabetes, medication, previous HbA1c), well-being (WHO-5)

stress (PSS) and distress (PAID) as independent variables.

Relationship between well-being/distress and diabetes self-management

To assess the relationship between well-being/distress and self-management, five separate (stepwise) hierarchical regression analyses will be performed, with the total DSMQ-R self-management score, and four (DSMQ-R) diabetes self-management subscale scores (glucose management, dietary control, physical activity, physician contact) as five separate dependent variables. Independent variables are: demographics (age, gender, education) and diabetes/treatment related variables (type of diabetes, medication), well-being, stress (PSS) and distress (PAID).

10.3. Other study parameters

NA

10.4. Interim analysis (if applicable)

NA. This is a observational cross-sectional study.

11. ETHICAL CONSIDERATIONS

11.1. Regulation statement

The study will be conducted according to the principles of the ‘declaration of Helsinki' (as amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2. Recruitment and consent

Patients with type 1 and type 2 diabetes that are currently in care at the diabetes outpatient clinic will be sent a letter with study information and informed consent forms. Within several days after receiving the letter, patients will be contacted by phone by a member of the study team and invited to participate in the study as well as given the opportunity to ask questions. If patients are willing to participate they will be asked to sign the informed consent form and send it back to the LUMC by post. Once informed consent is provided, patients will be sent an envelope with a lancet, small tube and instructions to collect blood with a fingerprick. They will be asked to fill the tube that is in the envelope with several drops of blood until the mark on the tube is reached and send the envelope (special envelope for medical samples) back to the LUMC. At the LUMC the HbA1c will be measured by the clinical chemistry lab.

If patients are using a continuous or flash glucose monitor, data will be collected according to standard clinical practice and will be covering the last non-quarantine week and the quarantine period.

Additionally, patients will receive a link in their e-mail to a set of online questionnaires, containing the DSMQ-R, SDSCA, PSS, PAID and WHO-5, along with questions about level of education, medication use, social situation, employment, impact of self-quarantine on daily routines.

The HbA1c measurement and questionnaire will be performed once at the predicted end of the nationwide quarantine phase as a result of the COVID-19 outbreak.

11.3. Objection by minors or incapacitated subjects (if applicable)

NA. Minors and incapacitated subjects are not eligible to participate.

11.4. Benefits and risks assessment, group relatedness

The risks associated with participation in this study are limited. The primary potential foreseeable risk associated with participation in this study is negative feelings resulting from

the increased attention to the patient's illness and distress by filling out the questionnaires. Additionally, there is a burden of time for the patient for performing the fingerprick and filling out the questionnaires, however, this time is limited and the measurement is being performed only once. Performing the fingerprick may be another forseeable risk, however, for most patients performing the fingerprick for measurement of blood glucose values is already part of their regular daily routine.

11.5. Compensation for injury

The sponsor/investigator has 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.

11.6. Incentives (if applicable)

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1. Handling and storage of data and documents

- All data will be handled confidentially and will be coded, according to the EU General Data Protection Regulation and Dutch Act on Implementation of the General Data Protection Regulation (AVG/UAVG). All data will be preserved for 15 years. A secure datasafe folder is used for all output and storage of all data. Only the researchers have access to this folder.
- Consent forms will be stored securely in a locked cabinet at the at the Leiden University Medical Center by the researchers. After giving consent, each patient will be provided with an unique study code. This unique study code contains no traceable data, such as birth date or names. This will be generated by a secured online database (CASTOR). CASTOR will be used to gather questionnaire data. No traceable data is stored in CASTOR. Access to CASTOR is restricted to only the researchers conducting the study. Two factor authorization is used to enter the database. After filling out the questionnaires, the export of the coded data is stored by the researcher in the datasafe. A secured list with restricted access (HIX eigen lijsten) will be used to enable coupling of the patient ID to the CASTOR study code, to ensure that HbA1c measurements can be matched to the questionnaire outcomes. Only the researchers of this study will have access to this list. The management of the key HIX and study ID is the responsibility of the PI. In the analysis phase of the study, the researchers do not have access to this key file.
- Patients' continuous or flash glucose measurements (FSL) will be collected according to standard clinical practice. They will be stored by study ID in the datasafe with access restricted to the researchers.
- HbA1c measurements will be done by the clinical laboratory of the LUMC and data will be stored in the electronic health dossier (HIX) using the patient ID. The blood sample is destroyed by the clinical laboratory immediately after use.

12.2. Monitoring and Quality Assurance

Monitoring will be executed by (internal) monitors of the LUMC according to the monitoring plan.

12.3. 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. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4. Annual progress report

N.A.

12.5. 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 'completion of the report on primary and secondary outcomes'.

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.

12.6. Public disclosure and publication policy

Results will be presented at national and international (diabetes) conferences, and published in peer reviewed (inter)national journals.

13. STRUCTURED RISK ANALYSIS

NA. This study is a cross-sectional study, based on self-report data.

13.1. Potential issues of concern

NA.

13.2. Synthesis

NA

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