DIALECT

"DIAbetes and LifEstyle Cohort Twente"

PROTOCOL TITLE DIAbetes and LifEstyle Cohort Twente

Protocol ID	**Not applicable**
Short title	**DIALECT**
Version	**2.4.3**
Date	**19-08-2019**
Coordinating investigator/project leader	**Dr. G.D. Laverman** **ZGT hospital Almelo** **Zilvermeeuw 1** **7609PP Almelo** **G.Laverman@zgt.nl** **088-7083079**
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	**Dr. G.D. Laverman** **ZGT hospital Almelo** **Zilvermeeuw 1** **7609PP Almelo** **G.Laverman@zgt.nl** **088-7083079**
Sponsor (in Dutch: verrichter/opdrachtgever)	**Dr. G.D. Laverman** **ZGT hospital Almelo** **Zilvermeeuw 1** **7609PP Almelo** **G.Laverman@zgt.nl** **088-7083079**
Subsidising party	***None***
Independent expert (s)	***Drs. D. Boumans*** ***Department of rheumatology*** ***ZGT hospital Almelo*** ***Zilvermeeuw 1*** ***7609PP Almelo*** ***D. Boumans@zgt.nl 088-7083403***
Laboratory sites	***Medlon ZGT Almelo***

	Poli Bloedafname routenummer 0.1 ***Zilvermeeuw 1*** ***7609 PP Almelo*** ***J.Sanderman@medlon.nl*** ***088 - 463 34 99***
Pharmacy	***Not applicable***

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or legal representative: **Head of Department:**		
[Coordinating Investigator/Project leader/Principal Investigator]:		

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

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)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**(Serious) Adverse Event**
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**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale:

Type 2 diabetes mellitus (T2DM) is a highly prevalent disease, causing significant morbidity and mortality worldwide. Poor regulation of serum glucose can lead to debilitating micro- and macrovascular complications such as nephropathy, cardiovascular disease and amputations. Therefore preventing complications is an important treatment goal in T2DM. While numerous research is done on the effect of drug interventions, little is known about the effect of lifestyle and dietary habits. In this research we will focus on the effects of lifestyle and dietary habits on outcomes in T2DM.

Objective:

The primary objective of this study is to investigate the effect of lifestyle and dietary habits on outcomes in patients with type 2 diabetes mellitus.

Study design:

The study is designed as an observational epidemiological study. Cross-sectional and prospective analyses will be performed in a cohort with patients with diabetes.

Study population: The study population will consist of adult male and female patients with type 2 diabetes.

Intervention (if applicable):

Not applicable

Main study parameters/endpoints:

Different research questions will be formulated regarding our main objective.

Endpoints are:

- All-cause mortality
- Macrovascular disease:
    - coronary disease: myocardial infarction, silent myocardial infarction, hospital admission for unstable angina pectoris or heart failure, coronary artery bypass graft, percutaneous coronary intervention
    - other: transient ischemic attack, cerebrovascular accident, diagnosis of peripheral vascular disease, peripheral bypass, percutaneous transluminal angioplasty, foot ulcers, amputation
- Microvascular disease: diagnosis of diabetic retinopathy, diabetic neuropathy, nephropathy

- Renal complications: nephropathy*, doubling of serum creatinine, start of renal replacement therapy

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

There are no direct benefits for the patients to be included. Participation in the study is on a free-will base. Patients will not receive any financial support or priority for treatment of other diseases in the clinic during this study.
Patients will be asked to fill in questionnaires concerning their dietary intake and lifestyles. 24-hour urine have to be collected by the patients, as well as a single portion of morning void urine. During their visit, blood pressure, weight, height, waist and hip circumference, body impedance and peripheral polyneuropathy will be assessed. Blood samples will be drawn using venipuncture. Samples of the 24h urine, morning void urine and blood will be stored in -80°C according to the UMCG biobank regulations. No further invasive measurements will be executed and therefore risks of participation in this study are minimal, if present at all.

1. INTRODUCTION AND RATIONALE

Type 2 Diabetes Mellitus (T2DM) is a highly prevalent disease, and cause of great morbidity and mortality worldwide (1,2). T2DM is characterized by increased insulin resistance and therefore reduced glucose uptake throughout the body, causing chronic hyperglycaemia. These increased blood sugar levels can lead to an extensive array of comorbidity, including microvascular complications (i.e. nephropathy, polyneuropathy and retinopathy), and cardiovascular disease (i.e. coronary disease, peripheral arterial disease and cerebrovascular accidents) (3,4). Treatment of T2DM is focused on the one hand on stabilizing blood sugar levels with antidiabetics and insulin, and on the other hand on preventing cardiovascular complications by treating risk factors such as obesity, smoking, hypertension and hypercholesterolemia (5). Lifestyle interventions are a key part of T2DM treatment, while diet and physical activity not only can increase insulin receptor sensitivity and therefore improve blood sugar levels, but can also greatly reduce the risk of cardiovascular complications (4,6). However, many questions remain unanswered in regard to the effect of lifestyle on the management and outcomes of T2DM. In this study we will investigate multiple research questions regarding the dietary habits and lifestyle in patients with T2DM in a secondary health care centre in The Netherlands.

This study is a continued effort to build a registry of T2DM patients. To this purpose 800 patients will be included in the registry. Patients from a previously METc approved study will be invited to participate in this registry as well, so that data obtained from both studies can be pooled For the study protocol of the previous study please refer to section K1 of the application. The data from subjects in the previous study has already been collected, therefore no additional study visits or procedures are required for these patients.

2. OBJECTIVES

Primary Objective:
This study focuses on the dietary habits and lifestyle in patients with type 2 diabetes. Multiple research questions will be investigated to further elucidate important mechanisms of lifestyle characteristics on clinical parameters in type 2 diabetes. Therefore this study does not have a single primary objective. Currently multiple research questions have been formulated, as stated below. In the future more research question will be formulated in the scope of the study.
Data from a previous study which included patients with type 2 diabetes mellitus will be pooled with data collected in the present study in order to answer these research questions. Subjects participating in the previous study will be formally invited to participate in the present study as well, before their data will be used.

Research questions:
At this moment we have formulated the following research questions. We aim to formulate and answer more research questions in the future.
1. What is the incidence of microvascular complications in patients with type 2 diabetes, in a secondary care centre in The Netherlands, and what are their risk factors?
2. Is there an association between the use of proton pump inhibitors and hypomagnesemia?
3. Are increased serum levels of the heavy metals lead, cadmium, barium and strontium, associated with a greater incidence of albuminuria and nephropathy?
4. What is the association between dietary intake, physical activity and statin use on LDL-cholesterol?
5. Is the ratio of daily sodium intake and daily potassium intake (Na/K ratio) associated with systolic blood pressure and/or increased use of antihypertensive drugs?

3. STUDY DESIGN

The current study is designed as an observational epidemiological study. Cross-sectional and prospective analyses will be performed in a cohort of patients with diabetes. The study will be performed in the outpatient clinic of internal medicine, in the ZGT hospital Almelo and ZGT hospital Hengelo. Data collected from this study will be pooled with data collected in a previous study in ZGT Almelo (DIALECT-1, the first 450 patients included in DIALECT).

In the previous study, as of January 2016, 463 patients were included. As the first patient was included 31-8-2009, this coincides with an average inclusion rate of about 7 patients per month. The new study will start 1-7-2016. We aim to include 850 patients in both studies in total, therefore the inclusion period of the new study will end 31-12-2021. Follow up data will be collected until 31-12-2031. Minimum follow-up period for each patient will be 10 years, and maximum follow-up will be 19 years and 5 months.

4. STUDY POPULATION

4.1 Population (base)

The study population will consist of adult male and female patients with or type 2 diabetes

4.2 Inclusion criteria

- Male and female patients with type 2 diabetes
- Patients aged 18 years or older
- Follow-up taking place in the outpatient clinic internal medicine in the ZGT Hospital
- Written informed consent

4.3 Exclusion criteria

- Dependence on renal dialysis
- Severe general diseases or mental disorders making the participation in the study impossible
- Drug abuse (which will be assessed through anamnesis)

4.4 Sample size calculation

While our study has no primary objective, but is designed to answer multiple research questions, no sample size calculation is possible. We aim to include 850 patients in our study. This will provide us with sufficient power to answer a diverse number of research questions. When 850 patients is an insufficient number for a particular research question, we aim to cooperate with other diabetes cohorts guarantee enough power.

5. TREATMENT OF SUBJECTS

Not applicable since no intervention study will be performed.

6. INVESTIGATIONAL PRODUCT

Not applicable since no intervention study will be performed.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable since no intervention study will be performed.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study endpoints

- All-cause mortality
- Macrovascular disease:
    - coronary disease: myocardial infarction, silent myocardial infarction, hospital admission for unstable angina pectoris or heart failure, coronary artery bypass graft, percutaneous coronary intervention
    - other: transient ischemic attack, cerebrovascular accident, diagnosis of peripheral vascular disease, peripheral bypass, percutaneous transluminal angioplasty, foot ulcers, amputation
- Microvascular disease: diagnosis of diabetic retinopathy, diabetic neuropathy, nephropathy
- Renal complications: nephropathy*, doubling of serum creatinine, start of renal replacement therapy

8.1.2 Secondary study parameters/endpoints

- Not applicable

8.1.3 Other study parameters

- NOTE: all parameter are collected in precisely the same fashion as in the previous study.
- From anamnesis at the study visit: drug use, medical history.
- From questionnaires: estimation of dietary intake of i.e. kilocalories, fats, proteins, aminoacids. Lifeystyle habits concerning smoking, heritage, and physical activity. Quality of life. Beliefs about medicines.
- From physical examination at the study visit: body impedance, Body Mass Index (BMI), hip and waist circumference, blood pressure, presence of diabetic polyneuropathy. 5 meter-walking test.
- From a single venapunction: serum creatinine, urea, sodium, potassium, haemoglobin, haematocrit, BSE, CRP, leukocyte count, thrombocyte count, bilirubin, alkaline phosphatase, gamma-GT, ASAT, ALAT, LD, NT-proBNP, phosphate, chloride, magnesium, calcium, albumin, uric acid, 25(OH) vitamin D, parathyroid hormone, thyroid stimulating hormone, fT4, glucose, HbA1c, lactate, venous blood gas, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides.
- From a single collection of 24h urine: urea excretion (as measure of dietary protein intake); sulphate excretion (as measure of dietary intake of sulphur-containing amino acids); aldosterone and cortisol excretion (as mediators of changes in blood pressure), Net renal acid excretion (NAE) (by assessment of ammonia, bicarbonate, potassium (assessment of dietary potassium intake), calcium, magnesium, chloride, phosphate and sulphate concentrations), excretion of tubulointerstitial damage markers (e.g. KIM-1; GST; NAG; NGAL; AAP), sodium excretion (assessment of dietary sodium intake); Urine-pH, urine-pCO_2, oxalate

- From electronic patient file and general practitioner: follow up data on macro- and microvascular complications of diabetes.
- From a FitBit wearable: Patients wear a FitBit wearable to measure their physical activity during one week. A FitBit wearable is a non-invasive wristband with 3-axis accelerometer that measures daily activity. It measures steps, burned calories and active minutes. Patients will wear it day and night.
- From a Freestyle Libre Sensor: continuous glucose measurements during 2 weeks (day and night). This will only be measured in patients included after approval of study protocol 2.2 (dd 7-3-2017).
- Food diary: Time, type and quantity of food intake.
- In 20 patients we will measure disease awareness and self-efficacy. Using an interview and a questionnaire.

8.2 Randomisation, blinding and treatment allocation

Not applicable

8.3 Study procedures

Patients will be recruited from the outpatient clinic of internal medicine. All eligible patients will receive written information about the study from their diabetic nurse during an outpatient visit. After one to two weeks these patients will be contacted by phone and invited to participate in this study. If they want to participate, three appointments are scheduled.

The following procedures will be applied:

- Outpatient visit appointment 1. During this appointment the study is explained and the study material (questionnaires, Freestyle Libre and Fitbit) are given to the patient.
    - Physical activity will be assessed using the Short QUestionnaire to ASses Health enhancing physical activity (SQUASH) questionnaire, which was previously validated. The same version of this questionnaire was applied equally in the previous study.
    - Diet will be assessed using a semi-quantitative food-frequency questionnaire (FFQ) inquiring about intake of 177 items during the last month, taking seasonal variations into account. The FFQ was developed at the Wageningen University (7) and has been updated several times. For the present study, the FFQ was slightly modified for accurate assessment of protein intake, including types and sources of protein. For each item, the frequency was recorded in times per day, week, or month. The number of servings was expressed in natural units (e.g., slice of bread or apple) or household measures (e.g., cup or spoon). Both questionnaires will be self-administered and filled out at home. The filled in questionnaires will be checked for completeness by a trained researcher, and inconsistent answers will be verified with the patients. Dietary data were converted into daily nutrient intake using the Dutch Food Composition Table of 2013 (8). The same version of the FFQ was applied equally in the previous study.

  - Quality of life will be measured using the Dutch translation of the RAND-36 (9).
  - Attitude towards medicines will be tested using the Dutch translation of the beliefs about medicines questionnaire (10).
  - Every patient will wear the non-invasive FitBit wristband for two weeks. During this week they will be asked to adhere to their daily activities as normal. After two weeks, the patients will return the FitBit and the data of their daily activities will be analyzed.
  - Patients included after approval of amendment number 2, study protocol 2.2 (dd 7-3-2016) will wear the freestyle libre sensor for two weeks. This sensor continuously measures glucose values and can be worn for two weeks. The sensor will be placed on the upper right arm during the first visit in the outpatient clinic. The patients will receive a reader with which he has to 'read' the sensor every 8 hours. After two weeks the patient will deliver us the reader and the data will be uploaded to the ZGT server. Thereafter the reader will be reset. On this day we will also investigate insulin resistance by determining plasma insulin and glucose levels (venapunction).
  - Patients will be asked to keep a food diary during the two weeks of glucose measurements. They will be asked to note the time, type and quantity of food intake during these days.
- Patient are called 2 or 3 days after the first visit. During this call patients are asked if the Freestyle Libre works, if they scan their glucose as instructed, if the Fitbit is working, if they have questions about the questionnaires and if they have general questions about the research.
- Outpatient visit appointment 2. During this appointment it is checked if the patient performs the study as asked, the Fitbit is synchronized to prevent data loss, measurements are performed and the patient visit the laboratory to hand in the urine and for the venapunction
  - Weight, height, waist and hip circumference, and peripheral polyneuropathy will be assessed. Body impedance will be determined by two non-invase devices: Bodyscan® Quadstad 4000 and TANITA® BC418MA.
  - Physical condition will be tested using the 5-meter walking test. For this test we will install 2 lines on the floor, with 5 meters distance in between. The patient will be asked to walk a distance starting somewhat before the first line, and cross the second line. The time from the crossing of the first line until the crossing of the second line will be measured using a stopwatch, and will be used to calculate walking speed.
  - Blood pressure will be measured automatically every minute for 15 minutes in a supine position through the Dinamap®.
  - Every patient will gather one sample of 24 hour urine, which will be sent to the laboratory for analysis and storage. Since patients with diabetes do not routinely gather 24h urine collections, they will be instructed how to collect it.
  - Patients will collect a single morning void urine, which will be sent to the laboratory for analysis and storage.
  - Through a single venapunction blood samples (2 vials of 10 mL and 3 vials of 3 mL, 2 vials of 10 mL and 1 vial of 4mL heparin plasma, 2 vials of 6 mL citrate plasma, 2 vials of 10 mL and 1 vial of 4 mL blood for serum) will be drawn and sent to the laboratory for analysis and storage.

- Part of the 24h urine, morning void urine and blood samples will be stored at -80°C in the UMCG for later analysis. The stored urine samples will allow for later assessment of non-regular analyses (e.g. tubulointerstitial damage markers). The stored plasma and serum will allow for later assessment of laborious and/or expensive laboratory markers in selected subgroups of patients. This will allow us to investigate novel markers for increased risk of diabetic complications. Analysis will all be performed within the scope of proposed research project.
  - For the handling of the stored samples we refer to the UMCG biobank regulations. The processing of the samples for storage will be performed in the local laboratory at the ZGT Almelo hospital site. From there, they will be transferred to the UMCG for long-term storage. This storage facility is only accessible by authorized personnel. Samples will be stored labeled only with subject code.
  - Samples will be destroyed 15 years after the end of the study (31-12-2046)
- Serum levels of heavy metals lead, cadmium, barium and strontium will be determined in the stored samples. At the same time these analyses will also be performed on the stored samples of the previous study. Data of both studies will be pooled.
- In the future we hope to perform DNA profiling to study genes associated with outcomes of T2DM. In the previous study DNA profiling was not described. Therefore, when we invite subjects of the previous study to participate in the new study, we will inform them accordingly and they have the opportunity to give or withhold consent for DNA profiling. DNA profiling will be performed with state of the art techniques, conform to the national standard.
- In 20 patients we will measure disease awareness and self-efficacy. Using an interview and a questionnaire. This will be performed during a study visit.

- Outpatient visit 3. During this last appointment the patient gives the study materials back and the patient receives a copy of an overview of the Freestyle Libre measurements.

Follow up data

In order to be able to perform prospective analysis concerning the relation between dietary protein intake and blood pressure, no extra study visits will be performed, but information will be collected from the electronic patient file and will be requested from the general practitioner. It is important to note that in The Netherlands diabetes care is standardized, both in the outpatient clinic and at the general practitioner. This consists of four follow up visits per year, which are performed according to a national protocol and include laboratory diagnostics.

The following data will be collected:

- Drug use
- Routinely performed laboratory measurements
- Macro- and microvascular complications
- Death

When data in the electronic patient file or from the general practitioner is incomplete or unreliable – for example when diabetes care was not performed according to the protocol – , subjects will be invited for a new study visit. In this visit the following procedures will be performed:

- Anamnesis: Drug use, medical history
- Physical examination: weight, height, waist and hip circumference, and peripheral polyneuropathy.

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)

Not applicable.

8.5 Replacement of individual subjects after withdrawal

Subjects who decide to withdraw from the study will not be replaced. As there is a large pool of type 2 diabetes patients in Almelo and Hengelo we expect to be able to include sufficient patients to assure the possibility of drawing reliable conclusions. If subjects decide to withdraw from the study, we will remove their data from our database, and destroy their Biobank samples.

8.6 Follow-up of subjects withdrawn from treatment

Not applicable, as no treatment is applied.

8.7 Premature termination of the study

Since the occurrence of adverse events or urgent medical problems is unexpected, a clause on premature termination of the study does not seem necessary.

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 investigational product / trial procedure/ the experimental intervention]. 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.

As this study follows the patients during 2 weeks in his normal daily life and up to 9 years after participation, without bringing the patients at any increased risk, SAEs are not reported.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable as there is no intervention.

9.3 Annual safety report

Not applicable.

10. STATISTICAL ANALYSIS

Study participants will be described with their demographical and medical data. Further, all outcome variables will be evaluated with descriptive statistical methods. For quantitative variables this includes maximum, mean and minimum as well as standard deviation, and median and IQ ranges for not-normally distributed parameters. For qualitative variables absolute and relative frequencies will be used. A two-sided *P*-value less than 0.05 will be considered statistical significant.

Each formulated research question will we analyzed with the appropriate statistical method. This statistical method will be determined before the start of data analysis.

To identify determinants of a nominal variable, we will perform multivariate logistic regression analysis. First all possible determinants will be tested univariately, using chi^2, Student T test or Mann whitney U test (when distributed nominal, normally or not-normally respectively). All variables with a P<0.200 will be considered a candidate for the multivariate model. We will use a backward technique to elimate variables step by step.

The following research questions will be analyzed using multivariate logistic regression analyses:

1. What is the incidence of microvascular complications in patients with type 2 diabetes, in a secondary care centre in The Netherlands, **and what are their risk factors?**

2. Is there an association between the use of proton pump inhibitors and hypomagnesemia?

3. Are increased serum levels of the heavy metals lead, cadmium, barium and strontium, associated with a greater incidence of albuminuria and nephropathy?

To identify determinants of a continuous (normally distributed) variable we will use multivariate linear regression analysis. First all possible determinants will be tested univariately using linear regression analysis. All variables with a P<0.200 will be considered a candidate for the multivariate model. We will use a backward technique to elimate variables step by step.

The following research question will be analyzed using multivariate linear regression analysis:

4. What is the association between dietary intake, physical activity and statin use on LDL-cholesterol?
5. Is the ratio of daily sodium intake and daily potassium intake (Na/K ratio) associated with systolic blood pressure and/or increased use of antihypertensive drugs?

Determinants of end points will be analyzed using either Kaplan-Meier (difference in 2 or more groups), or cox regression (effect of multiple risk factors).

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (Tokyo, 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

Patients will be recruited from the outpatient clinic of internal medicine. All eligible patients will receive written information about the study from their diabetic nurse during an outpatient visit. The information describes a full explanation of the study, advantages and disadvantages of participating, and contact information of the research team members working on this study. Moreover, the letter contains contact information of an independent physician, to whom subjects can address questions about the research before, during and after a study. After one to two weeks these patients will be contacted by phone by one of the researchers and invited to participate in this study. If they want to participate, three appointments are scheduled. During the first appointment they will then be asked to sign their written informed consent before they take part in the study.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

11.4 Benefits and risks assessment, group relatedness

There are no direct benefits for the patients to be included. Participation in the study is on a free-will base. Patients will not receive any financial support or priority for treatment of other diseases in the clinic during this study.
Participation in the proposed study is accompanied with only minor risks, if any at all. The blood samples will be drawn through venipuncture. All further performed measurements are non-invasive and therefore no risks are associated with participation.

11.5 Compensation for injury

No burden and risks are associated with participation in this study. Research participants will not be injured nor damaged physically due to the proposed study. Therefore, dispensation of insurance will be requested for this research project.

11.6 Incentives (if applicable)

Participation of patients in the study is a free-will decision. Patients will not receive any financial support or priority for treatment of other diseases in the clinic during this clinical trial. Costs for transportation to attend in the clinic for the study purpose are not refunded. However we will provide parking validation.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

A subject identification code list will be made to link the data to the subject in order to be able to trace data to an individual subject. This code will not be based on the patient initials or birth-date. The key to the code will be safeguarded only by the principal investigator. The handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp).

All documents and questionnaires will be stored in ZGT Almelo until fifteen years after the end of the study (until 31-12-2046). Here they will be stored in a locked room.

Stored samples of blood and urine will be labeled only with the subject code which is not traceable to the individual subject. The principal investigator safeguards the key to identify the subject from the code list. The storage space is only accessible by authorized personnel of the UMCG. Stored samples will be destroyed fifteen years after the end of the study (31-12-2046).

12.2 Monitoring and Quality Assurance

Not applicable

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.

All substantial amendments will be notified to the METC and to the competent authority.

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

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

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

12.5 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 10 years after the last patient's baseline visit (expected end of study date: 31-12-2031).

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

Publication policy is in agreement with the CCMO publication statement. Nor the sponsors, nor the principal investigator has a right of veto regarding the way of publishing the results. Partners/ sponsors have the right to take cognizance of the results in order to patent some of the outcomes (if applicable).

13. STRUCTURED RISK ANALYSIS

Not applicable.

14. REFERENCES

(1) Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006 Nov;3(11):e442.

(2) Volksgezondheidenzorg.info. Diabetes Mellitus. Available at: https://www.volksgezondheidenzorg.info/onderwerp/diabetes-mellitus/cijfers-context/prevalentie-en-incidentie.

(3) Atkins RC, Zimmet P, 2010 International Society of Nephrology/International Federation of Kidney Foundations World Kidney Day Steering Committee (RA), International Diabetes Federation (PZ). Diabetic kidney disease: act now or pay later. J Bras Nefrol 2010 Mar;32(1):7-10.

(4) Fox CS, Golden SH, Anderson C, Bray GA, Burke LE, de Boer IH, et al. Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association. Diabetes Care 2015 Sep;38(9):1777-1803.

(5) Chamberlain JJ, Rhinehart AS, Shaefer CF,Jr, Neuman A. Diagnosis and Management of Diabetes: Synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes. Ann Intern Med 2016 Mar 1.

(6) Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013 Jul 11;369(2):145-154.

(7) Feunekes GI, Van Staveren WA, De Vries JH, Burema J, Hautvast JG. Relative and biomarker-based validity of a food-frequency questionnaire estimating intake of fats and cholesterol. Am J Clin Nutr 1993 Oct;58(4):489-496.

(8) Rijksinstituut voor Volksgezondheid en Milieu. NEVO-tabel (dutch food composition table): Nederlands voedingsstoffenbestand. 2013;4.0.

(9) McHorney CA, Ware JE,Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993 Mar;31(3):247-263.

(10) Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology and Health 1999;14(1):1-24.