The LiPAT protocol

Light-**i**ntensity **P**hysical **A**ctivity **T**rial

- December 2016 -

PROTOCOL TITLE:

Light intensity Physical Activity and Arterial Stiffness in Type 2 Diabetes (LiPA-Trial)

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Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	*Dr. ir. Annemarie Koster (Department of Social Medicine, CAPHRI)* *Dr. Ronald M.A. Henry (Department of Internal Medicine, CARIM)* *Prof. Dr. Coen D.A. Stehouwer (Department of Internal Medicine, CARIM)*
Sponsor (in Dutch: verrichter/opdrachtgever)	Maastricht UMC+ / Maastricht University c/o: prof. dr. CDA Stehouwer CARIM School for Cardiovascular Diseases Universiteitssingel 50 6229 ER Maastricht the Netherlands
Subsidising party	European Foundation for the study of Diabetes
Independent expert (s)	Dr. F. van Molkot, internist Maastricht UMC+ / dept of internal medicine

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or legal representative: **Head of Department:**	**prof. dr. CDA Stehouwer** **Chair Dept. of Medicine**	
[Coordinating Investigator/Project leader/Principal Investigator]:	**prof. dr. CDA Stehouwer** **principal investigator**	

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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:

In type 2 diabetes (T2D), physical activity is an important modifiable risk factor of cardiovascular disease (CVD) and increased physical activity has been shown to positively impact upon cardiovascular health. Unfortunately (long-term) compliance to exercise programs in patients with T2D is poor. Light-intensity physical activity ((LiPA); i.e., walking slowly, household activities or taking a flight of stairs) is also associated with a decreased CVD risk and can be more easily incorporated into daily life.

Objective:

To evaluate the effect of a LiPA intervention on arterial stiffness in individuals with T2D.

Study design:

This study is a single-blinded randomized controlled trial. The duration of the study is 12 months; a 6-month intervention with a 6 month follow-up period.

Study population:

160 men and women with T2D, aged 40-65 years old.

Intervention:

The intervention group will receive 4 workshops focussing on strategies to increase LiPA by reducing sedentary time. Participants in the intervention group will receive a feedback physical activity monitor worn on the wrist, data will be synchronized with a mobile phone app. The activity monitor will give real-time feedback on activity levels and will be used to set activity goals. Participants in the intervention group are encouraged to decrease their sedentary time with 10%. Participant in the control group will also receive 4 workshops focused on healthy lifestyle without an activity monitor.

Main study parameters/endpoints:

The primary outcome is pulse-wave velocity and carotid distensibility which will be determined with the use of applanation tonometry and arterial ultrasound. The effect of the intervention on the primary outcome PWV at month 6 will be analysed.

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

Study measurements of all participants will take place at baseline, month 3, month 6, and month 12 at the Maastricht UMC+. For the LiPA intervention only non-invasive low risk study procedures will be performed and the risk of any adverse events due to the different study procedures is low. A possible burden for the participant is the use of the activity monitors that participants are requested to wear continuously as a wristwatch.

1. INTRODUCTION AND RATIONALE

Cardiovascular Disease and Arterial Stiffness

Cardiovascular disease (CVD) is the major cause of morbidity and responsible for 75% of deaths in patients with type 2 diabetes (T2D). Besides atherothrombosis, also arteriosclerosis or increased arterial stiffness has been identified as an underlying cause of this increased CVD risk as increased arterial stiffness causes ischaemic heart disease, heart failure and stroke [1]. Importantly, compared to individuals without T2D, patients with T2D are characterized by greater arterial stiffness [2, 3]. Thereby, arterial stiffness is an important therapeutic target in T2D.

In this regard, we have shown previously that: 1) arterial stiffness is increased in patients with diabetes [4-6]; 2) that there are complementary and additional roles for aortic and carotid arterial stiffness in the prediction of incidence of CVD [7] and, 3) that increased carotid arterial stiffness is independent from increased aortic arterial stiffness associated with incident stroke [8].

Physical activity and Cardiovascular Health

In T2D, physical activity is an important modifiable risk factor of CVD and increased physical activity has been shown to positively impact cardiovascular health [9]. Unfortunately (long-term) compliance to exercise programs in patients with T2D is poor. These programs consist of a combination of aerobic and resistance training for several times a week and most participants quit exercising as soon as the (supervised) exercise intervention ends [10, 11]. Most individuals with T2D have led a sedentary lifestyle over decades and they will generally find it difficult swiftly and consistently incorporate participation in exercise programs in their routine. Therefore, for patients with T2D the need to test alternative lifestyle changes that will be actually adopted by these individuals is compelling. From this perspective, it is important to shift our focus from exercise programs to physical activity of daily life or light-intensity physical activity ((LiPA); i.e., standing, walking slowly, household activities or taking a flight of stairs) which may play a crucial role to lower CVD in patients with T2D. Importantly, LiPA has been recognized as also having beneficial effects on cardiovascular health [12] and we have recently shown that high levels of sedentary time are associated with poor health and premature death independent of exercise [13, 14]. Furthermore, we have also shown that replacement of sedentary time with LiPA lowers mortality risk [15]. Thereby these results point at the importance of LiPA to improve (cardiovascular) health. Finally, LiPA can more easily be incorporated into daily life of sedentary individuals as it is made mainly of activities that are already part of everybody's routine [16-18].

Physical Activity and Arterial Stiffness in Type 2 Diabetes

Data on the association between LiPA and arterial stiffness in T2D is currently scarce. The association between objectively measured LiPA and arterial stiffness [19-22] has been examined only in few observational studies and the conclusions of these studies are conflicting. In fact, one study showed that low LiPA was associated with increased arterial stiffness [19], but the same was not found in the others [20-22]. The results of these studies are difficult to interpret and compare especially due to differences in study populations and the different physical activity monitor devices employed. Nevertheless, compelling data from intervention studies show aerobic exercise significantly decreases arterial stiffness, as estimated by aortic pulse wave velocity (PWV) [23]. Interestingly, this review, where the results from a large number of studies were pooled, shows that the decrease in arterial stiffness was greater in individuals that had the stiffest arteries at the start of the interventions [23]. This observation suggests that patients with T2D, in whom arterial stiffness is increased as compared to those individuals without T2D, will benefit most from increased (light) physical activity, when considering arterial stiffness as endpoint. Nevertheless, solid interventional data on the association between LiPA and arterial stiffness (in T2D) is currently lacking and this is the gap that we aim to fill.

As far as the possibility to achieve a significant and long-term change of chronic sedentary behaviour is concerned, it has been shown that sedentary behaviour can be reduced [16-18, 24] and it is possible to increase LiPA by simply decreasing sedentary time [16-18]. For example, a randomized controlled trial that focused on reducing TV viewing time showed a significant increase in total daily energy expenditure in those who just reduced their TV viewing time [17], whereas an Australian study showed that a brief intervention program to reduce sedentary behaviour in older adults successfully reduced sedentary time and thus showed its feasibility even in older sedentary individuals [16]. Thereby, our randomized controlled trial to increase LiPA levels are expected to result in a long-term change in physical activity behaviour and, improve arterial stiffness in patients with T2D. In the end, this research will lead to a meaningful LiPA recommendation to decrease CVD risk in individuals with T2D.

2. OBJECTIVES

Primary Hypothesis:

A LiPA intervention program based upon increasing LiPA by replacing sedentary time (approx. 1 hour) is effective in lowering arterial stiffness as estimated by aortic PWV and carotid distensibility in individuals with T2D.

Primary objective:

To evaluate the effect of a LiPA intervention on arterial stiffness in individuals with T2D.

Secondary Objective(s):

Next to its associations with cardiovascular health, physical activity has been positively associated with numerous other outcomes including favourable metabolic health, body composition, quality of life, physical and mental health. Therefore, these health outcomes are included as secondary end points.

To investigate the feasibility of a LiPA intervention program in the reduction sedentary time and increase in standing and stepping time obtained by the activPAL.
To investigate the effect of a LiPA intervention program on metabolic health.
To investigate the effect of a LiPA intervention program on body composition.
To investigate the effect of a LiPA intervention program on quality of life.
To investigate the effect of a LiPA intervention program on depressive symptoms.

3. STUDY DESIGN

This study is a single-blinded randomized controlled trial (enrollment via block randomization (block size of 4). The duration of the study is 12 months; a 6-month intervention with a 6 month follow-up period to examine both the long-term health effects of the intervention as well as any long-term compliance to the intervention.

Study measurements of all participants will take place at baseline (month 1 (t = 0)), month 3 (t = 3), month 6 (t = 6), and month 12 (t = 12) at the Maastricht UMC+.

Participants in the intervention group will be instructed to increase their LiPA by decreasing sedentary time. Participants will follow 4 workshops in group sessions on strategies to change their behaviour and will receive a feedback physical activity monitor that will be worn continuously on the wrist and provide e-feedback on activity behaviour. The intervention procedures are described in more detail in section 5.

Participants in the control group will receive 4 workshops in group sessions on healthy lifestyle including information and strategies to increase LiPA and reduce sedentary time similar to the intervention group, but will not receive a feedback-activity monitor.

3.1 Duration

The total duration of the study is 3 years. The duration of the RCT is 12 months.

The intervention period is 6 months with a 6-month follow-up.

Expected starting date for the study: quarter 4, 2016

Expected starting date for enrolment participants: quarter 1, 2017

Expected date finished enrolment participants: quarter 1, 2018

Expected date end of follow-up: quarter 1, 2019

Statistical analyses and report of the results: quarter 3, 2019

3.2 Evaluations by visit

An overview of the procedures and examinations are shown in table 1. All participants (both the intervention and the control group) will be invited to the research centre at t=0 (baseline visit at month 1); at t=1 (first investigational visit at month 3), at t=2 (second investigational visit at month 6); and at t=3 (third investigational visit at month 12) at the Maastricht UMC+.

Screening

A preliminary screening will be carried out by telephone interview in order to decide whether the participant is eligible for the study (see section 4.2 and 4.3 for the in- and exclusion

criteria). The participant will then be invited for the baseline visit, which starts with the informed consent procedure (please see appendices for informed consent) and an explanation of this very first baseline visit. The baseline namely consists of two parts. Part A is strictly part of the inclusion procedure. During this part a standard physical examination will take place and an ultrasound scan will be performed to screen for large atherosclerotic plaques of the carotid arteries (see below). If then the participants is indeed eligible part B will take place in which the investigational baseline measurements are performed. After the above procedure randomization will take place. From then on participants will run through the protocol either being part of the intervention or control group.

Measurements at the four investigational visits (t = 0, 3, 6 and 12)

- sociodemographic data
- medical history & medication use: by means of an interview
- lifestyle factors (alcohol use and smoking behaviour), quality of life, depressive symptoms – by means of questionnaires
- Sedentary and physical activity monitoring: by means of the activPAL® activity monitor for 7 days
- venous sampling (approx. 25 ml per person per visit; 5 collecting tubes of 5 ml) for fasting glucose, fasting insulin, HbA1c, lipid profile, creatinine, albumin and biomarkers of endothelial dysfunction (vWF, s-VCAM-1, sE-selectin, sTM, SICAM-1) and low-grade inflammation(CRP, SAA, IL-6, TNF-alfa, IL-8). The remainder of the material will be stored in a biobank for future determination of any potentially interesting (bio)markers on the topic of physical activity. For any such future procedures further approval will be sought from the METC/MUMC+.
- Anthropometric data (height, weight, waist and hip circumference and bio-electrical impedance measurements)
- vascular measurement (arterial stiffness and blood pressure)
- physical function measurements (grip strength and timed chair test)

Table 1 Overview of the study procedures

	Screening	Baseline	Intervention						Follow-up
Time point (months)		0	1	2	3	4	5	6	12
Eligibility									
Informed consent									
Randomisation									
Examinations									
Intervention group									
Workshop, group session									
Continuous activity monitoring									
Biweekly feedback on activity by phone									
Monthly feedback on activity by phone									
Control group									
Workshop									

4. STUDY POPULATION

4.1 Population (base)

Basically all community-dwelling individuals with type 2 diabetes are eligible for participation in the current trial taking into account the in- and exclusion criteria described below. Participants will therefore be drawn from the community with the help of public advertising and targeted recruitment with the help of general practitioners and nurse practitioners. In addition, participants will be drawn from the out-patient diabetes clinic from the Maastricht UMC+.

For both the intervention and control group an equal sex- and age distribution is aimed for. It is estimated that recruitment is achievable within the proposed timeframe because of the potential large number of eligible participants (total number of estimated of number of patients with type 2 diabetes within the Maastricht UMC+ region approx. 12.000 of whom approx. 2/3 will be eligible).

4.2 Inclusion criteria

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

- 40-65 years old
- having type 2 diabetes
- BMI 23-33 kg/m^2
- having a sedentary lifestyle (i.e., self-reported moderate-to-vigorous physical activity < 150 minutes per week)
- willingness to undergo randomization
- being in the possession of personally owned smart phone

4.3 Exclusion criteria

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

- not being able to walk for 15 minutes for any (medical) reason
- currently engaged in an (medical) exercise program
- plan to move out of the study area in the next 12 months
- (*digital)* illiteracy or being unable to read Dutch
- a history of any cardiovascular event (including stroke) three months prior to possible inclusion

- a history of signs or symptoms of ischemic heart disease and(or) heart failure three months prior to possible inclusion
- a history or signs or symptoms of peripheral arterial disease three months prior to possible inclusion
- a history or signs or symptoms of severe diabetic neuropathy or diabetic foot ulcers three months prior to possible inclusion
- a history of sign or symptoms of severe diabetic retinopathy three months prior to possible inclusion
- a history or sign or symptoms of severe osteoarthritis or severe joint complaints three months prior to possible inclusion
- a history or signs or symptoms of COPD (eligible are those participants with a COPD Gold classification ≤ I)
- uncontrolled diabetes (i.e., uncontrolled hypo- or hyperglycaemia)
- uncontrolled hypertension (i.e., systolic / diastolic blood pressure ≥ 180 / 95 mmHg)

4.4 Sample size calculation

For the primary objectives of the study:

to be able to detect a 10% difference in PWV after the intervention between the intervention group and the control group set against a probability of a type 1 error at 0.05 (i.e., alfa) and the ability to detect a true difference between the intervention group and the control group set at 80% (i.e., beta) both groups should consist of a minimum of 73 participants each. These estimates are conservative taking into account only PWV values at entry and exit of the trial. The 10% difference is speculative and based upon a mean PWV estimates from The Maastricht Study data as there is currently no data available on LiPA and arterial stiffness. For reasons of efficiency in addition to potential drop (roughly estimated at 10%) out we will include in each group 80 participants

to be able to detect a 10% difference in carotid distensibility after the intervention between the intervention group and the control group set against a probability of a type 1 error at 0.05 (i.e., alfa) and the ability to detect a true difference between the intervention group and the control group set at 80% (i.e., beta) both groups should consist of a minimum of 73 participants each. These estimates are conservative taking into account only carotid distensibility values at entry (t = 0) and exit of the investigational period of the trial (t = 6) .

The 10% difference is speculative and based upon mean estimate from The Maastricht Study data as there is currently no data available on LiPA and arterial stiffness. For reasons of efficiency in addition to potential drop (roughly estimated at 10%) out we will include in each group 80 participants.

According to:

$K = n_2 / n_1$

$n_1 = (((\sigma)n_1)^2 + ((\sigma)n_2)^2) / k) / (z_{1-a/2} + z_{1-b})^2 / \delta^2$

$n_1 = x$; $n_2 = K n_1$

$\delta = |\mu 2 - \mu 1|$ = absolute difference between two means

$\sigma 1$, $\sigma 2$ = variance of mean 1 and 2

n1 = sample size for group 1

n2 = sample size for group 2

α = probability of type I error

β = probability of type II error

z = critical Z value for a given α or β

k = ratio of sample size for group 2 to group 1

Rosner B. *Fundamentals of Biostatistics*. 7th ed. Boston, MA: Brooks/Cole; 2011

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Intervention group

The goal of the LiPA intervention program is to increase LiPA by reducing sedentary time by making use of a feedback activity monitor that is described in more detail below. The aim is to reduce sedentary time roughly by 10% as compared to baseline. Given that participants are sedentary for on average 9.3 hours (560 minutes) per day, participants are encouraged to decrease their sitting time by replacing approximately one hour per day of sitting time with LiPA activities. Sedentary behaviour, standing, and stepping time will be objectively measured making use of the activPAL ® activity monitor that will be worn for 7 days continuously at baseline, month 3, month 6, and month 12. This device is blinded to the participant. The activPal ® is a commercially available research tool (www.paltech.plus.com). Data from the activPAL provide detailed and accurate information on the participants' sedentary, standing, and stepping time for each day.

Participants in the intervention group will be invited for a workshop, as a group session with approximately 20 participants. During this first workshop, extensive attention will be paid to what LiPA itself is, what the potential health benefits of LiPA are and how it can be incorporated into daily life and thus increased. Generic strategies to increase LiPA over the whole day will be discussed with participants. In month 2 and 3 of the trial, two additional group sessions will be organized during which progress will be discussed and if necessary further advise on how to increase LiPA. In the last month of the trial a final group session is planned which is followed by an unsupervised follow-up of 6 months. During the workshops topics related to a healthy lifestyle are being introduced. This information is based upon general healthy lifestyle guidelines, exercise guidelines and diabetes guidelines (please see below) In addition this will be an opportunity for participants to share their experiences.

Participants in the intervention group will receive a feedback physical activity monitor (iHealth ®; commercially available consumer product (www.ihealthlabs.com). Participants will receive extensive instructions on its use, the internet interface and how it will provide feedback during the first group workshop. The iHealth® is worn on the wrist like a wristwatch. It has a watch interface and it tracks movement tri-axially. The data is synchronized with the mobile phone app, with a protected cloud-based platform that collects and analyses data from the device. The app is designed to help the participant to self-monitor their physical activity levels and includes information on total activity, number of steps, kcals burned, and sleep parameters. Based on the collected data the investigators will be able to provide personalised recommendations to the participants with the use of proprietary algorithms on

activity levels and activity goals can be set. After the first week of data collection, information about participants' average activity is available which will be used to set an activity goal. This goal will be adjusted accordingly during the trial. For example if a participant has on average 4 hours of activity a day, a goal of 4,5 hour of activity a day could be set as an activity goal. Furthermore, participants will be alerted automatically during the day (from 0800 to 2100 hrs) when he/she has been inactive for prolonged periods of time (based on an activity goal of 250 steps per hour). This should remind the participant to engage in LiPA.
Participants will be instructed to wear the activity monitor continuously, also during the night, to be able to monitor sleeping behaviour. Participants are advised only to take the device off when the battery has to be recharged. Data will be automatically transferred by Bluetooth to the mobile application and the protected cloud-based platform and internet interface so that the participant can monitor progress and, if so required additional e-feedback can be dispersed. If LiPA goals are met, participants will be automatically rewarded by means of positive (e-)reinforcement (e.g., by encouragement messages in the app ("Well done! You have met your LiPA goal!) and encouragement symbols (e.g., a smiley). There will be no negative messages dispersed to the participant if LiPA goals are not met. During the intervention, small (digital) prizes for encouragement (e.g. fruit basket or a digital "thumbs up") will be raffled among participants who reach their activity goals.
During the first month of the intervention, participants will get acquainted with the use of the iHealth® and bi-weekly phone calls with participants are planned to monitor use of the feedback activity monitor and set LPA goals based on their habitual activity. After this run-in period, monthly phone calls with participants are planned during the second and third month to provide feedback on the iHealth® use and to help participants to reach their LiPA goals with the use of the watch and web-based interface. As from month 4 onwards, no structural phone calls with participants are planned anymore and feedback rests entirely upon the digital platform as by choice of the participant. During the complete period of the intervention a manned help-desk is available for any questions by the LiPAT participants.

Control group

Participants in the control group are, like the intervention group, invited for 4 workshops. These workshops are similar to the workshops of the intervention group, yet without the iHealth® device. During the workshops topics related to a healthy lifestyle are being introduced. This information is based upon general healthy lifestyle guidelines, exercise guidelines and diabetes guidelines. Participants in the control group will not receive the e-feedback monitoring device. During the complete period of the study a manned help-desk is available for any questions by the participants about LiPA.

For safety reasons, for both the intervention and control group, a medical doctor (internist) is available (24/7) to discuss / advise on any alterations in the use of glucose lowering medication for both participant and general practitioners (or diabetes nurse practitioners). It can be expected that the most enthusiastic participants will experience alterations in their glucose levels which may require adjustment of their medication. Daily clinical care however remains the responsibility of the participant's own diabetes care provider either being the general practitioner or the diabetes nurse practitioner.

To note: the activPal ® (www.Paltech.plus.com) and iHealth (www.iHealthlabs.com) are both commercially available research and consumer products and are incorporated into the trial as measurement tools but are themselves not part of the research aims of the current project. Both the ActivPal ® and the iHealth ® will be purchased by the investigational team from the respective companies.

Overview of workshop contents:

Intervention group

Workshop 1 – month 1 (duration 2 hours)

Topics to be covered:

- the health risks of sedentary behaviour
- what is LiPA and what are the health benefits
- what are generic strategies to increase LiPA by reducing sedentary time
- introduction of the iHealth ® and the mobile application
- individual goal setting

Workshop 2 – month 2 (duration 1 hour)

- physical activity and a healthy lifestyle in type 2 diabetes; therapeutic benefits
- reflection of participants on their LiPA levels
- experience with the iHealth ® and the what is LiPA and how can it be increased
- activity levels and change in the workshop group (comparing participants' progress (anonymized)
- individual goal setting

Workshop 3 – month 3 (duration 1 hour)

- activity levels and change in the workshop group (comparing participants' progress (anonymized)
- group discussion on progress and discuss strategies to increase LiPA
- preparing for second part of the intervention without progress phone calls

- individual goal setting

Workshop 4 – month 6 (duration 1 hour)

- looking back at the study
- activity levels and change in the workshop group (comparing participants' progress (anonymized)
- sharing LiPA progress
- Long-term maintenance of LiPA

Control group

Workshop 1 – month 1 (duration 1 hour)

Topics to be covered:

- the health risks of sedentary behaviour
- what is LiPA and how can it be increased
- what are generic strategies to increase LiPA by reducing sedentary time
- how to goal set LiPA in general

Workshop 2 – month 2 (duration 1 hour)

- physical activity and a healthy lifestyle in type 2 diabetes; therapeutic benefits
- reflection of participants on their LiPA levels
- group anonymized group feedback without comparison

Workshop 3 – month 3 (duration 1 hour)

- group anonymized feedback without comparison
- group discussion on strategies to increase LiPA
- preparing for second part of the intervention without meetings or feedback at group level

Workshop 4 – month 6 (duration 1 hour)

- looking back at the study
- group anonymized feedback without comparison
- long-term maintenance of LiPA healthy lifestyle

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

Arterial Stiffness:

The primary outcome variables in the LiPA-Trial will be pulse wave velocity (PWV; i.e., aortic [carotid to femoral] PWV) and carotid distensibility which will be determined with the use of applanation tonometry and arterial ultrasound, respectively. More details are described in section 8.2. The outcome variables will be determined at t = 0 (month 0; baseline visit), t = 3 (month 3, first investigational visit), t = 6 (month 6; second investigational visit) and t = 12 (month 12; third investigational visit (end of the trial)).

6.1.2 Secondary study parameters/endpoints (if applicable)

Blood pressure:

Any changes in blood pressure and blood pressure lowering medication determined at t = 0 (month 0; baseline visit), t = 3 (month 3, first investigational visit), t = 6 (month 6; second investigational visit) and t = 12 (month 12; third investigational visit (end of the trial)) determined with the use of the705-IT (Omron Healthcare (oscillometric blood pressure device)).

Metabolic health:

Any changes in fasting blood glucose, HbA1c, total cholesterol, HDL- and LDL-cholesterol, triglycerides and glucose lowering medication use determined at t = 0 (month 0; baseline visit), t = 3 (month 3, first investigational visit), t = 6 (month 6; second investigational visit) and t = 12 (month 12; third investigational visit (end of the trial)).

Body composition:

Any changes in height, weight, waist- and hip-circumference and any changes in body composition with regard to muscle- / fat mass with the use of bio electrical impedance measurements, determined at t = 0 (month 0; baseline visit), t = 3 (month 3, first investigational visit), t = 6 (month 6; second investigational visit) and t = 12 (month 12; third investigational visit (end of the trial)).

Quality of life

Any changes in quality of life with use of the SF-36 questionnaire, determined at t = 0 (month 0; baseline visit), t = 3 (month 3, first investigational visit), t = 6 (month 6; second investigational visit) and t = 12 (month 12; third investigational visit (end of the trial)).

Depressive symptoms PHQ 9

Any changes in quality of life with use of the PHQ9 questionnaire, determined at t = 0 (month 0; baseline visit), t = 3 (month 3, first investigational visit), t = 6 (month 6; second investigational visit) and t = 12 (month 12; third investigational visit (end of the trial)).

Physical functioning

Any changes in handgrip strength and timed chair-stand test with use of the JAMAR Hydraulic Handdynamometer (SEHAN Corp. Korea- Biometrics Europe BV, Almere) determined at t = 0 (month 0; baseline visit), t = 3 (month 3, first investigational visit), t = 6 (month 6; second investigational visit) and t = 12 (month 12; third investigational visit (end of the trial)).

6.1.3 Other study parameters

Individual patient characteristics: age, sex, ethnicity, level of education, employment status, medical history and medication use.

A process evaluation of LiPAT will give insight into the reach, implementation, and satisfaction of the intervention program. Research questions for the process evaluation are:

- Who participated in the intervention and who dropped out?
- Was the intervention executed as planned?
- How did participants experience the intervention and specifically the workshops and the use of iHealth and the mobile application?

A partially structured interview at the end of the intervention (month 6) with all participants and the research nurse will be carried out to capture their experiences with LiPAT. The following aspects will be covered during the interviews; some items are only relevant for the intervention group (e.g. the use of the iHealth). This process evaluation is based upon Moore, GF et al. BMJ 2015.

Dose delivered (for the intervention and control group)

1. Extent to which the research nurse:
    a. informed the participant about the risks of a sedentary lifestyle and the benefit of LiPA
    b. collaboratively set goals and set up an action plan with the participant
    c. gave feedback based on the general physical activity goals
    d. discussed with the participant barriers and facilitators for being active

Fidelity

1. Extent to which LiPAT was implemented as planned by the participant?
2. Have the participant and research nurse perceived any technical problems with the iHealth device? (for intervention group only)
3. Have the participant and research nurse experienced any technical problems with the mobile application? (for intervention group only)

Dose received (exposure)

1. Overall opinion of the participant regarding engagement in the intervention program
2. Instruction of the iHealth and the mobile application (use of the manual and the instruction)(for intervention group only)

Dose received (satisfaction)

1. Experience with LiPAT
    a. Activity monitoring
    b. Workshops
    c. Feedback messages
2. Experience with the mobile application (for intervention group only)
    a. Goal setting
    b. Activity monitoring
    c. Feedback messages
3. How satisfied were the participants and the research nurse with the intervention program – workshops and LiPAT?
4. How did the participants perceive the outcomes and relevance of the interventions?

- Furthermore, the remainders of the blood samples after quantification of the primary laboratory values will be stored in a biobank for future determination of (bio)markers that might be associated with physical activity. For any such future procedures further approval will be sought from the METC/MUMC+. In addition we will ask the participants for their specific approval to share / use their data with third parties for scientific valorization purposes only.

6.2 Randomisation, blinding and treatment allocation

Randomisation by the research staff will take place during the baseline visit (please see above) with / via block randomization in a block size of 4 (Suresh, KP. J Hum Reprod Sci. 2011).

Participants will be randomly assigned using a web-based system (www.randomizer.org) to the LPA intervention group or the control group.

Randomisation will be stratified according to sex to ensure an equal distribution of men and women in both groups.

This is a single-blind design. To ensure blinding, participants will be instructed to not discuss their assigned intervention during any of the trial visits with the research nurse or vascular technician performing any of the trial measurements.

The participants in the intervention group will be asked not to wear their iHealth ® device on trial visit days and will be reminded not to do so via the web interface.

6.3 Study procedures

Investigational visits will be carried out at t = 0 (month 0; baseline visit), t = 3 (month 3, first investigational visit), t = 6 (month 6; second investigational visit) and t = 12 (month 12; third investigational visit (end of the trial)).

The investigational visits will consist of:

Arterial Stiffness measurements

Aortic pulse wave velocity (aPWV); i.e., carotid to femoral pulse wave velocity) will be determined with the use of applanation tonometry according to recent guidelines [25].
In brief, pressure waveforms will be determined at the right common carotid and right common femoral arteries. The difference in the time of pulse arrival from the R-wave of the electrocardiogram between the two sites will be calculated with an intersecting tangents algorithm. The pulse wave travel distance will be calculated as 80% of the direct straight distance (measured with an infantometer) between the two arterial sites. aPWV will then be calculated as the median of three consecutive aPWV recordings (defined as travelled distance/transit time).

Carotid arterial stiffness will be determined at the left common carotid, with the use of an ultrasound scanner equipped with a 7.5-MHz linear probe (MyLab 70, Esaote Europe B.V., Maastricht, the Netherlands) together with a dedicated PC-based acquisition system (ART.LAB, Esaote Europe B.V. Maastricht, the Netherlands).
This setup enables the measurement of diameter, distension and intima-media thickness as described previously [6].
From these data carotid distensibility will be determined. All arterial ultrasound measurements will be analysed off-line in a blinded fashion.

For the above procedures theoretically a risk of stroke exists in case of the presence of carotid plaques. Manipulation of these plaques may theoretically cause stroke. Yet, the risk of plaque rupture during ultrasonography can be considered small as in accordance with standard practice no pressure should be applied to the skin in order to execute these measurements reliably. With regard to tonometry, this risk can be considered somewhat higher as this procedure requires the application of a certain amount of pressure to a relatively small area of the carotid artery wall via the tonometer. Despite the fact that none of the international guidelines on arterial ultrasonography and tonometry have noted warnings in their guidelines with regard to this issue LiPAT will withdraw participants with severe carotid atherosclerotic plaques from the study. A severe carotid plaque is identified by an IMT thickness >= 5 mm in addition to both in longitudinal and tranversal images into the lumen protruding wall structures. The vascular technician will bring such a participant to the attention of the principal investigator whom will present such a participant to the department of neurology for further examination.

Sedentary behaviour and physical activity

Daily activity levels are measured using the activPAL3™ physical activity monitor (PAL Technologies, Glasgow, UK). The activPAL3 is a small (53 × 35 × 7 mm), lightweight (15 g) triaxial accelerometer that records movement in the vertical, anteroposterior and mediolateral axes, and also determines posture (sitting or lying, standing and stepping) based on acceleration information.
The device will be attached directly to the skin on the front of the right thigh with transparent, waterproof, 3M Tegaderm™ tape and the use of a nitrile sleeve.
Participants will be asked to wear the accelerometer for 8 consecutive days, without removing it at any time. Data will be uploaded using the activPAL software and processed using customised software written in MATLAB R2013b (MathWorks, Natick, MA, USA).
The total amount of sedentary time is based on the sedentary posture (sitting or lying), and calculated as the mean time spent in a sedentary position during waking time per day. The method used to determine waking time has been described elsewhere [26].
The total amount of standing time was based on the standing posture, and calculated as the mean time spent standing during waking time per day. The total amount of stepping is based on the stepping posture, and calculated as the mean time stepping during waking time per day. Stepping time (physical activity) is further classified into higher intensity physical activity (HPA; minutes with a step frequency >110 steps/min during waking time) and lower intensity physical activity (LPA; minutes with a step frequency ≤110 steps/min during waking time) [27].

Metabolic outcomes

Venous blood sampling:

Blood withdrawal will take place, according to standard hospital operating procedures, via the insertion of a cannula into a proximal vein of the non-dominant arm. In total 4 collecting tubes will be collected (total blood volume of 25 mL) for (standard) laboratory assessments (please see above). Any remainders of the blood samples after quantification of the primary laboratory values will be stored in a biobank for future determination of (bio)markers that might be associated with physical activity.
There are no specific risks associated with blood withdrawal except for bruising or vasovagal collapse as a reaction to the sharp sting whist penetrating the skin. In case of collapse the study physician on call will be alerted and appropriate action will be undertaken.
As a safety measure the fasting circulating level of glucose is assessed on site with the use of Lifescan One Touch Verio glucose meter to identify those with low (< 3.8 mmol/L) or high fasting glucose levels (> 15 mmol/L). Low or high fasting glucose levels will be brought to the attention of the internist on call who will take any necessary step according to good clinical

practice guidelines (if necessary bring the participant either into immediate care or notify the very same day the participant's General Practitioner).

Body composition:

Weight and height will measured without shoes and wearing light clothing only using a scale and stadiometer to the nearest 0.5 kg or 0.1 cm (Seca, Hamburg, Germany). Waist circumference will be measured with a flexible plastic tape measure (Seca, Hamburg, Germany), in duplicate midway between the lower rib margin and the iliac crest at the end of expiration, to the nearest 0.5 cm. In addition, body composition will be assessed non-invasively using bio-electric impedance spectroscopy (BIS: model 4200; Xitron Technologies, San Diego, California). This procedure will be executed with the use two handgrips through which a low-voltage current will run and the computed electrical resistance determines fat free mass. There are no known risks to this procedure.

Quality of life:

Health related quality of life will be measured with the SF-36 and EQ-5D, the most widely used generic preference-based health status measures. The EQ-5D is a short questionnaire that covers five dimensions of health: Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. The SF-36 is a generic and easily self-administered quality of life instrument.

Depressive symptoms:

Depressive symptoms will be assessed by a validated Dutch version of the 9-item Patient Health Questionnaire (PHQ-9) [28]. The PHQ-9 is a self-administered questionnaire based on the DMS-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria for a major depressive disorder. It comprises nine items rated on a 4-point scale, ranging from 0 = "not at all" to 3 = "nearly every day". Response options can generate a continuous score ranging from 0 (no symptoms) to 27 (all symptoms present nearly every day); scores 10–14 represent moderate and 15–27 moderately severe to severe depression symptoms. The PHQ-9 scale will also be used as a dichotomous variable with a pre-defined cut-off level of 10, which represents the presence of clinically relevant depressive symptoms.

Physical function:

Timed-chair stand test will be carried out as a measure of physical performance. The time taken to rise from a sitting to a standing position with straight back and legs, and then sit

down again 10 times as fast as possible was measured using a stopwatch. The times recorded were used to calculate chair rise speed.
Handgrip strength (kg) will be measured with hand-held dynamometer, three maximum force trials with each hand.

Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences with regard to their medical treatment in general or any treatment at all at the Maastricht UMC+. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Reasons for withdrawal of drop-out will be logged.

6.3.1 Specific criteria for withdrawal (if applicable)

If during the inclusion visit a severe carotid atherosclerotic plaque is discovered in the region of interest the participant will be withdrawn from the trial.
If during the duration of the trial any cardiovascular events occurs participants will be withdrawn from the trial.
If participation in the trial leads to uncontrollable hypo- or hyperglycaemia participants will be withdrawn from the trial.
If any other serious medical condition arises during the trial which requires medical specialty treatment or hospitalisation, participants will be withdrawn from the trial.

6.4 Replacement of individual subjects after withdrawal

Participants will not be replaced.

6.5 Follow-up of subjects withdrawn from treatment

Any participants withdrawn from the trial will be followed up by questionnaire to be able to determine, also in retrospect, whether their withdrawal might have been due to any medical condition which occurred as a consequence of participation in the trial. If such is suspected the participant will be asked to consent to contact his or her general practitioner for further information. This questionnaire specifically bears the option: “I do not wish to be contacted any further by the LiPAT and do not grant permission to contact my general practitioner”.

6.6 Premature termination of the study

It is not to be expected that LiPAT will be terminated prematurely. In principle because the level of exercise intensity does not exceed the participants individual level of exercise intensity (e.g., we do not suggest that the participants start running / jogging etc.). We do suggest that the participant actively diminishes his or her sedentary behaviour in a fashion he or she thinks appropriate (e.g., by going for a short walk or having a sedentary break by simply standing up from sitting after 45 mins). We do encourage them to undertake such light-intensity physical activity more often. In fact, light- physical activity behaviour is already part of normal daily life.

7. SAFETY REPORTING

7.1 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 the participant's 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.

7.2 AEs and SAEs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to trial procedure and the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

For the above purpose LiPAT will keep a digital AE-log which is accessible to the LiPAT investigational staff at all times. This AE-log will be checked daily and discussed at the weekly LiPAT clinical monitoring meeting. In addition, an internist is available for the investigational staff 24 hours a day to discuss any such AE.

7.2.2 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 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.

For the above purpose LiPAT will keep a digital sAE-log which is accessible to the LiPAT investigational staff at all times. This sAE-log will be checked daily and discussed at the weekly LiPAT clinical monitoring meeting. In case of a sAE the principal investigator will be notified. In addition an internist is available for the investigational staff 24 hours a day to discuss any such sAE.

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.

7.3 Follow-up of adverse events

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

8. STATISTICAL ANALYSIS

The significance levels used in the statistical analyses will be 0.05. The validity of the normality assumption will be check for all outcomes. Baseline characteristics will be compared between the intervention and the control group. For continuous variables (e.g. age, BMI) mean and standard deviations will be presented; numbers and percentages will be shown for categorical variables (e.g. smoking, medication use). T-tests will be used to compare differences in continuous baseline characteristics between the intervention and control group and chi-square test will be used for categorical variables. Assuming that the randomization was successful no differences are expected. Missing data will be imputed using multiple imputations techniques.

8.1 Primary study parameter(s)

The effect of the intervention on the primary outcome PWV at month 6 will be analysed using intention-to-treat (ITT) approach according to randomization assignment. The ITT analyses will be used as primary method for our statistical analyses and any outcomes in our reports will be primarily based upon these ITT analyses. In addition, a per protocol analysis will be performed for those who attended the workshops. These analyses will be used to gain some insights into any potential non-response / drop out. These per protocol analyses will not be the primary source for reporting outcomes. General linear models will be used to analyse the effect of the intervention on PWV at month 6. In addition, repeated measures will be taken into account, baseline, month 3, and month 6 using mixed models in SPSS. In these models, subject is entered as a random effect and intervention (categorical variable with 2 levels: 1: intervention; 2: control group) as a fixed effect .The baseline value of PVW and sex will be used as covariates in analyses.

8.2 Secondary study parameter(s)

Sedentary time, as measured by the activPAL will be analysed as total sedentary minutes on an average day as well as the percentage of sedentary during wake time. Similarly, time standing and stepping, also derived from the activPAL data will be analysed. All metabolic health parameters will also be analysed as continuous variables. Quality of life and mental functioning are also analysed as continuous variables. Finally, measures of body composition measures are also all continuous outcomes variables

Similar to the primary outcome analyses, general linear mixed models will be used the analyses the change the secondary outcome measures from baseline to month 6. Using mixed models, the repeated measures will be taken into account similar the analyses with the primary outcome.

All analyses, for the both primary and secondary outcomes will also be conducted for the follow-up (month 12 data) to examine the long-term effect of the intervention, taking into account all repeated measures (baseline, month 3, month 6) in a mixed model.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

LiPAT will be conducted according to the principles of the Declaration of Helsinki (version 2013 (www.wma.net)) and in accordance with the Medical Research Involving Human Subjects Act (WMO); www.wetten.overheid.nl/BWBR0009408/2015-12-17)).

9.2 Recruitment and consent

The initial information about LiPAT will be passed on to the potential participant via advertisements (see attachment) and a general invitational letter (see appendix) distributed freely via the outpatient-clinic (information display) and the GP's waiting room (information display). There is no active role for the potential participants own consultant or GP in LiPAT recruitment and they will not receive any recruitment fees. If any potential participant then contacts us, either by telephone or email, the initial LiPAT telephone interview will be held to determine preliminary eligibility. Each potential participant will be informed about the consequences of participating in the study for his or her personal life.
From then onwards the participant will follow the logistics as described in section 3.2. Briefly, after the telephone interview the potential participant will be send an envelope containing the invitation letter (see appendix) including the informed consent form and an appointment will be made for the baseline visit. We aim for a time window between the telephone interview and the baseline visit of minimally 1 week which will give the participant the opportunity to think over his/her participation and if necessary discuss any topics with family, friends, general practitioner of the independent doctor attached to this trial (please see appendix)
The baseline namely consists of two parts. Part A is strictly part of the inclusion procedure. During this part a standard physical examination will take place and an ultrasound scan will be performed to screen for large atherosclerotic plaques of the carotid arteries (see below). The participant will be informed that the outcome of this first part of the visit may still to exclusion. If then the participants is indeed eligible part B will take place in which the investigational baseline measurements are performed. After the above procedure randomization will take place. From then on participants will run through the protocol either being part of the intervention or control group. The informed consent procedure and physical examination of the base line visit will be performed by both the principal investigator (RMA Henry) and the MD /PhD-student

9.3 Benefits and risks assessment, group relatedness

LiPAT will not recruit minors and(or) incapacitated adults. The age range of the study population will be 40 to 65 years.

Health check-up

To a certain extent, LiPAT will offer its participants an extra outpatient clinic check-up at 4 moments in time. LiPAT has decided that results of these standard tests should be communicated with the participant, as they may lead to any adjustments in their care (e.g., any weight loss might results in adjustment of an insulin regimen). Communicated to the participant will therefore be: glucose, HbA1c, lipid profile, urine (albuminuria)), next to standard findings from the physical examination (e.g., weight). The above tests would also be part of standard or routine care procedure for those with diabetes at e.g., their general practitioner.

Risks of specific measurements

For LiPAT only non-invasive low risk study procedures will be performed. The investigational research team hold the opinion that the current protocol subscribes to the above and considers the risk for any adverse events due to the different study procedures low. Nevertheless it cannot wholly be excluded, that behavioural changes with regard to any changes in movement patterns may lead to unforeseen adverse events. LiPAT considers the risks in light of the recruited study population nevertheless acceptable.

Time and inconvenience

A possible burden for the participant is that LiPAT (and especially the intervention arm) may be intrusive, as the iHealth ® allows for continuous feedback (also by giving timed reminders). It will be possible however to turn such reminders off and from month 4 to 6 feedback is entirely voluntarily and digital.

9.4 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.

9.5 Incentives (if applicable)

Each participant will receive a sum of € 80 compensation for their invested time or any (travel) expenses made during his or her participation. If a participant drops out before completion of all three study visits he will be reimbursed € 10 per visit fulfilled.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

All data that is collected within LiPAT will be stored in the secured AZM ICT environment, applying to similar security levels as data that is collected in general patient care of the AZM. A central database will be established that corresponds with the needs and requirements of this study. The central database consists of two separate components:
Section 1 contains personal information on the participants and is physically separate from the research results. This section records and stores a participant's ID and personal information, such as name, address and contact information. This section is also responsible for monitoring consent forms. The file does not contain research information and capable of meeting the logistical requirements.
Section 2 contains the research results with the corresponding participant-specific ID code and is only accessible to the investigational team. This file contains all registered research results such as questionnaire data, physical examination information and imaging research. It also records which researcher conducted the measurements and whether any adjustments were made. The key to the ID code will be under the charge of the principal investigators of LiPAT. Data will be stored in this fashion for 15 years after the end of the study. We state explicitly that the following parties will have access to the data next to all primary investigators of LiPAT themselves, governmental parties from the ministry of Health (e.g., Inspectie voor de Gezondheidszorg (or others if obliged to do so by law)), trial monitors (e.g, CTCM) and METC-members.
With regard to the remainders of the blood samples after determination of the primary laboratory variables, these will be stored, under their ID-code, in a MUMC+ owned biobank for a period of 15 years after the end of the study.
We state explicitly that the following parties will have access to the biodata next to all primary investigators of LiPAT themselves, governmental parties from the ministry of Health (e.g., Inspectie voor de Gezondheidszorg (or others if obliged to do so by law)), trial monitors (e.g, CTCM) and METC-members.
In order to be able to determine any potential (future) (bio-)markers that might be associated with any changes in physical activity. If any such question would arise additional approval will be sought from the METC/MUMC+. Participants have to specifically approve the uptake of their samples in this biobank. The participants will however not be asked extra permission for any future analyses upon this material.
Data may also be shared with industrial partners. Participants of LiPAT will have to specifically approve their permission to do so via the informed consent form. Criteria for such

a partnership include that the data are used for scientific research, which may include development or validation of algorithms (e.g., to further develop any sedentary behaviour identification algorithms). An agreement with business partners will be made about sharing of data in which at least the rights of the donor are warranted. Data that are shared, if any, will always be coded, according to the above, in order to protect the privacy of participants. No personal details of any of the participants will be handed over to any industrial partner.

10.2 Monitoring and Quality Assurance

Monitoring will take place by CTCM.

10.3 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.

10.4 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.

10.5 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 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.

10.6 Public disclosure and publication policy

LiPAT aims to obtain breakthrough results with important impact on prevention of chronic diseases. The results of this study (also in the case of negative findings) will be published in scientific articles in national and international journals.

Authorship

- Authorship should be decided by the scientist/s most involved in designing and executing the research, and the author/s should be able to take public responsibility for the content of the publication and defend its criticism; (http://www.icarda.org/Publication_Policy.pdf)
- Co-authorship of papers will be determined according to international guidelines;
- Authors have three main ethical responsibilities in presenting their work for publication: (a) honest and full reporting, which implies accurate and complete description of the observations made and data collected, (b) honest relation of their work to that of others allowing the reader to objectively evaluate their report, and (c) follow institutional procedures for the approval of their manuscripts to protect the institution's scientific reputation. (http://www.icarda.org/Publication_Policy.pdf)
- Unpublished data drawn from other sources should be identified as such and be appropriately credited, with indication that such acknowledgement is with the consent of the person being credited (http://www.icarda.org/Publication_Policy.pdf)

Acceptance of articles prior to publication

- Ensure high standards of writing, editing, and production consistent with the international status; (http://www.icarda.org/Publication_Policy.pdf)
- Disputes on the interpretation of the results may not lead to an unnecessary delay in publication. Disputes can be dealt with by continuing the debate in the form of letters sent to the scientific journal; (www.ccmo.nl)
- Before submission for publication, all manuscripts will be reviewed internally to ensure consistency according to the following procedure: (a) On receipt of the manuscript from the

author, the management team will evaluate its suitability for publication (b) The author will revise the manuscript, incorporating the reviewer's comments where necessary, and submit a copy of the revised manuscript to the members of the management team. (http://www.icarda.org/Publication_Policy.pdf)

- The editors and reviewers must treat manuscripts as confidential communications and not divulge their contents without the consent of the author/s. Reviewers are responsible not only for unbiased, objective critical analysis of manuscripts but also for completing their task within the time allowed. (http://www.icarda.org/Publication_Policy.pdf)
- None of the parties concerned has a right of veto. The parties concerned must attempt to resolve disputes by negotiation. Should one of the parties feel that it has been disadvantaged, or should any other problem relating to publication arise, the parties can contact the CCMO or the METC for mediation; (www.ccmo.nl)

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