# THE STROKE BOX

## (February 2022)

**PROTOCOL TITLE** 'The Stroke Box: a patient-centered eHealth approach for improving post-stroke care.'

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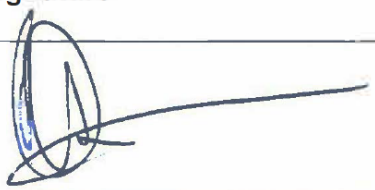
| Head of Department:<br>*Prof. dr. Jan J. G. M. Verschuuren* |  | 12 okt 202 |
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## LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

| | |
|---|---|
| **ABR** | **General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)** |
| **AE** | **Adverse Event** |
| **AF** | **Atrial Fibrillation** |
| **AR** | **Adverse Reaction** |
| **CA** | **Competent Authority** |
| **CCMO** | **Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek** |
| **CV** | **Curriculum Vitae** |
| **CVRM** | **Cardio Vascular Risk Management** |
| **DSMB** | **Data Safety Monitoring Board** |
| **EMR** | **Electronic Medical Record** |
| **EU** | **European Union** |
| **EudraCT** | **European drug regulatory affairs Clinical Trials** |
| **GCP** | **Good Clinical Practice** |
| **GDPR** | **General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)** |
| **GP** | **General Practitioner** |
| **IB** | **Investigator's Brochure** |
| **IC** | **Informed Consent** |
| **IMP** | **Investigational Medicinal Product** |
| **IMPD** | **Investigational Medicinal Product Dossier** |
| **IMD** | **Investigation with Medical Device** |
| **IMDD** | **Investigational Medical Device Dossier** |
| **LUMC** | **Leiden University Medical Centre** |
| **METC** | **Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)** |
| **mRS** | **Modified Rankin Scale** |
| **PIF** | **Patient Information Form** |
| **(S)AE** | **(Serious) Adverse Event** |

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|---|---|
| **SPC** | **Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst** |
| **Sponsor** | **The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.** |
| **SUSAR** | **Suspected Unexpected Serious Adverse Reaction** |
| **UAVG** | **Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG** |
| **WMO** | **Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen** |

## SUMMARY

**Rationale:** Although there have been major advances in (personalized) stroke treatment in the last decade, the need for prevention of stroke remains critical. Prevention of recurrent stroke is currently primarily organized through management of cardiovascular risk factors including lifestyle, hypertension and atrial fibrillation (AF). To improve the cardiovascular risk management of stroke patients, more frequent measurements of blood pressure and heart rhythm are essential. In addition, actively engaging the patient with their own recovery could lead to an improved lifestyle. Recent studies have shown telemonitoring of patients can improve care, help with prevention of disease, and reduce healthcare costs, whilst keeping the patient more engaged with their disease.

The LUMC “Box” has shown to effectively monitor blood pressure of patients after myocardial infarction with equal results and patient satisfaction rates compared to standard care with less physical contact moments. We plan to use this framework for improving post-stroke care by introducing more frequent blood pressure and heart rhythm measurements. Additionally, we will provide more information around lifestyle improvement and have the patient actively engage with their weight and physical activity.

In this study we will be evaluating the technical feasibility and clinical implementation of the home-based self-measurements using the Box in a post-stroke pilot setting: the Stroke Box. The results will be used as a basis for the power calculation for a future randomized clinical trial on the effect of the Box on hypertension treatment and AF detection.

**Objective**: The overall aim of this pilot is to evaluate the technical feasibility and clinical implementation of the Stroke Box by evaluating user experience and hypertension management. The primary objective is gathering data on blood pressure management for power calculation for a future randomized clinical trial where the effect of the Stroke Box on hypertension management and AF detection will be studied. The secondary objectives will be gathering and evaluating data on heart rhythm, weight and activity of patients using the Stroke Box, evaluating the technical- and workflow implementation for healthcare professionals, evaluating the self-management and user-experience of patients, assessing the patient adherence to the self-measurements and pharmacotherapeutic prophylactic therapy, and evaluating the correct functioning of the IT infrastructure, hardware and LUMC Care app, and to assess the correct use of all stakeholders involved in the eHealth support and telemonitoring with the Stroke Box.

**Study design:** This study is a prospective cohort study to evaluate the implementation of the Stroke Box and gather data. For the first 5 patients we will mainly evaluate the technical procedures of the study in addition to the other objectives. For the remainder, we will be gathering data on blood pressure management, patient engagement and have a user-based

evaluation of the eHealth infrastructure during a six-month follow-up period. We will do evaluations of the collected data based on a before-after comparison of blood pressure and questionnaire results.

**Study population:** Patients admitted for a TIA, ischemic or haemorrhagic stroke in the LUMC. We will include 55 patients in total of which in the first 5 patients we specifically focus on testing and evaluating the technical feasibility.

**Intervention (if applicable)**: The Stroke Box will contain a blood pressure monitor, weighting scale, single-lead ECG wristwatch with activity tracking and associated apps. Patients are asked to measure the associated factors on a weekly basis. In addition, all patients will be asked to fill in a questionnaire at the start and the end of the study. Patients will participate for 6 months in the pilot.

**Main study parameters/endpoints:** The primary objective of this study is the gathering of data on blood pressure management as a basis for power analysis in future trials. The secondary objectives will be gathering and evaluating data on heart rhythm, weight and activity of patients, evaluating the technical- and workflow implementation for healthcare professionals, evaluating the self-management and user-experience of patients, assessing the patient adherence to the self-measurements and pharmacotherapeutic prophylactic therapy, and finally evaluating the technical feasibility for all stakeholders.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** Patients are asked to measure weight, blood pressure and heart rhythm on a weekly basis, which takes approximately 5-10 minutes. All devices used by patients for personal management in this study are non-invasive, easy-to-use, CE marked and electrically safe within their intended use. Using the devices comes with very limited risks. This study has several potential benefits for patients. First, patients can measure their own blood pressure, heart rhythm and weight, which can give them more insight in their own health and may spark a healthier lifestyle (the so-called ‘patient empowerment’). Furthermore, these data give the GP or GP nurse more insight in the health status of patients, potentially leading to better cardiovascular risk management and hypertension control. Finally, the regular ECG measurements might help in detecting occult AF in patients at risk for AF.

## 1. INTRODUCTION AND RATIONALE

Although there have been major advances in (personalized) stroke treatment in the last decade, the need for prevention of stroke remains critical.[1] Currently in the Netherlands, prevention of stroke is primarily performed by the general practitioner (GP) in their cardiovascular risk management (CVRM). Lifestyle management, blood pressure regulation and cholesterol lowering interventions are the cornerstones in prevention of neuro- and cardiovascular disease. Resources - primarily time – are, however, limited in healthcare which leaves room for improvements to the CVRM. Post-stroke CVRM consists of regular visits to the GP or GP nurse where blood pressure, lifestyle and medication adherence is monitored. Although these visits are regular, a recurring problem is that these measurements are not always accurate. A patient may have taken his or her medication just before the measurement, is in a different and potentially stressful environment or might be fatigued from travel all of which can affect blood pressure. In addition to hypertension, atrial fibrillation (AF) is also an important risk factor.[2] However, studies show AF is missed during a hospital admission in a substantial number of stroke patients.[3]

Recent studies have shown telemonitoring of patients can improve healthcare. A study in patients with hypertension showed that increased monitoring and subsequent treatment led to a better controlled blood pressure in patients who were treated for hypertension.[4] Moreover, the application of telehealth reduces healthcare costs by a combination of preventing unnecessary hospitalisation, clinic visits and use of medical resources and by offering a solution for the demand of an effective chronic disease management with focus on patient-centered care.[5-9]

Over the past five years, smartphone compatible detectors of neuro- and cardiovascular disease parameters have been released on the consumer market. Examples of these wearable eHealth tools include ECG monitors, blood pressure monitors, activity trackers and fat percentages monitors. These monitors have often been validated and are CE-marked for use in the European Union within their intended use. Therefore, wearable eHealth technology is a promising tool to improve patient monitoring and patient safety.

Studies also show that home monitoring of blood pressure leads to more accurate measurements, reflecting actual blood pressure better than GP practice measurements.[10] Even for patients with poorly controlled blood pressure in primary care, home monitoring can significantly reduce the blood pressure.[11] Using a wearable ECG monitor, blood pressure sensor, activity tracker and weight scale at-home monitoring of stroke-risk is made well accessible. The thereby improved CVRM could hence improve chances for prevention of a recurrent stroke and also reduce the costs of unnecessary GP visits.

At the Leiden University Medical Center (LUMC) “The Box” initiative is getting widely adopted, providing a solid foundation for expanding to other areas of the clinic.[12] It is one of the three pillars of the LUMC2.0 digital strategy as it can effectively support patients by

giving them more insight into their own health status. Moreover, results from earlier “Box” studies, such as the “Cardio Box” for care after myocardial infarction, showed that patients were very satisfied with the care they received and that the blood pressure regulation in patients with the Box was as good as in regular care. This “Box” has many similarities to the project described here giving us confidence that the implementation of the Stroke Box can improve care. Additionally, "The Box" was cost effective with increased efficiency of care.[13] We therefore selected this well tested workflow as a basis for our patient-centered eHealth approach for improving post-stroke care.

Before performing a randomized controlled clinical trial investigating the effects of the self-measurements on blood pressure and heart rhythm with the Stroke Box, we will run a pilot on a small group of patients.

For the first 5 patients in this pilot we mainly test the technical feasibility of the eHealth infrastructure and evaluate the stakeholder experience. This is essential because this study differs from previous Box projects in several ways. First, our patient population is expected to be generally older compared to previous studies and will likely have substantial physical or cognitive disabilities as a result of the stroke which may lead to a reduced adaptation to the self-monitoring and use of eHealth devices. Second, this is the first Box-related project in which the Box is used to facilitate the transfer between hospital and home care. Therefore the transfer to and communication with GPs, i.e. feasibility of setting up a collaboration with multiple practices, will have to be evaluated.

In the remaining 50 patients, we evaluate the clinical implementation where we will collect data as a basis for the power calculation in the future trial. In this protocol we will describe the setup of this pilot study.

## 2. OBJECTIVES

Primary Objective:

- Gathering data on self-measured blood pressure and AF detection of patients using the Stroke Box as a basis for power analysis of a future randomized controlled clinical trial and performing a quality assessment of the collected data.

Secondary Objectives:

- Gathering data on self-measured heart rhythm, weight and activity of patients using the Stroke Box, and performing a quality assessment of the collected data.
- Evaluation of the potential change in self-management, patient engagement and user experience of the patients using the Stroke Box, using questionnaires.
- Assessment of patient adherence to the self-measurements and pharmacotherapeutic prophylactic therapy, using questionnaires.
- To evaluate our implementation of the IT infrastructure, hardware and LUMC Care app, and to assess the correct use of all stakeholders involved in the eHealth support and telemonitoring with the Stroke Box. The devices themselves and their functioning are not a subject of research.
- User based evaluation of the technical – and workflow implementation for healthcare professionals using the Stroke Box, using questionnaires.

## 3. STUDY DESIGN

In this pilot study we will evaluate the technical feasibility and clinical implementation of the Stroke Box in a small prospective cohort. After providing the Stroke Box to the patients, detailed information will be provided on the use of the Stroke Box and the patient will be helped with their first use.

The patient will use the Stroke Box to take at-home measurements for six months. Here we will be gathering data on blood pressure management, cardiac rhythm, patient engagement and have a user-based evaluation of the eHealth infrastructure. Patients will perform regular home measurements which the GP can use at the regular visits, and a nurse specialist in the LUMC will assess ECG measurements. We will keep close contact with both patient and GP to help in case of any questions. The patients will have access to the LUMC Box Support helpdesk who are an established customer service desk to help with any Box-related issues. We will ask the patients and GPs to contact us in case of any questions they might have. At the end of the pilot the user evaluation will be done through a questionnaire.

During the regular GP visits after the stroke related hospital admission, the GP and the nurse specialist will have insight in the collected data. We will evaluate the GP’s experience of the data insight and technical usability using a questionnaire.

The study is estimated to take 12 months where we will have 6 months of inclusions and 6 months of follow-up.

# 4. STUDY POPULATION

## 4.1 Population (base)

We will recruit patients visiting for a TIA or admitted for an ischemic or haemorrhagic stroke in the LUMC.

## 4.2 Inclusion criteria

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

- The patient is admitted with a clinical diagnosis of a TIA, ischemic or haemorrhagic stroke in the LUMC
- The patient is able to communicate in Dutch (patients with severe aphasia - defined as not being able to respond to the questionnaires or perform the self-measurements – are excluded)
- The patient is at least 18 years of age
- The patient will be discharged from the hospital directly to home
- The patient has hypertension during hospital admission as defined by systolic blood pressure >140mmHg during two separate blood pressure measurements
- The patient has a suitable smartphone and is able to use it in a reasonable sense
- The GP of the patient is willing to collaborate in the study

## 4.3 Exclusion criteria

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

- The patient does not have internet access at home
- Patient is unwilling to sign the informed consent form
- Patient is considered an incapacitated adult
- The patient is a pregnant or breastfeeding woman
- The GP of the patient is not willing to partake in the study

## 4.4 Sample size calculation

In the LUMC there are 450 stroke patients per year, 50-60% of which are immediately discharged home. Of these patients we expect 85% willing to sign the informed consent form and have the GP willing to cooperate in the pilot. We will be including patients for a maximum of 6 months, in this time there will be about 105 potential patients for our study according to our calculations. We will be including 55 patients. We will use this patient population to estimate incidence of blood pressure out of the therapeutic window (>140mmHg) for the power analysis of a future clinical trial.

In 37.5% of patients, we expect to see a change in blood pressure in 6 months,[14] this would amount to 20 patients in our population of 55 patients. This would be sufficient to power a future trial focusing on blood pressure measurements using the Stroke Box infrastructure. Earlier studies focussing on long term recording of heart rhythm in patients with cryptogenic stroke found occult atrial fibrillation in 9% to 16% of patients.[3,15] As 87% of stroke patients have ischemic strokes[16] and about a third of those have cryptogenic strokes, we expect to find cryptogenic strokes in about 29% of the LUMC stroke population.[17] Therefore, we expect around two to three patients in which we would detect atrial fibrillation after hospital discharge. This would be the minimum to power a future trial focussing on atrial fibrillation detection using the ECG smartwatch. In conclusion, 55 patients amounts to the minimum size we would need to obtain sufficient results.

# 5. TREATMENT OF SUBJECTS

## 5.1 Investigational product/treatment

Patients receive the Stroke Box containing several monitoring devices. The Stroke Box uses a dedicated app, the LUMCcare app. A list of devices is presented below and described in more detail in section 6 of this protocol. All devices and products are CE-marked and used within the scope of their intended use in this certification.

The devices within The LUMC Box are connected to the LUMCcare app. All measurements performed by the patient with the connected devices will be automatically uploaded into the LUMCcare app, and safely transferred to the hospital for evaluation. Furthermore, illness specific questionnaires are presented within the app at the appropriate time points.

The Stroke Box contains the following devices and products:

- Withings BPM connect
- Withings Body Weight Scale
- Withings Move ECG Watch
- LUMCcare app
- Withings Health Mate app
- IkOefenZelf access (for 10 patients only)
- StopAdvisor app access

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

Not applicable.

## 5.3 Escape medication (if applicable)

Not applicable.

# 6. INVESTIGATIONAL PRODUCT

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

Withings Body Weight Scale

The Withings body weight scale is a CE-marked Bluetooth enabled weight scale which measures weight, body fat mass, heart rate and the $CO_2$ ppm in the air. It sends the results to the LUMCcare app. The Withings Weight Scale is battery powered, CE-marked and electrically safe. In order to measure weight, patients have to stand on the weight scale. Data are automatically sent to the smartphone via Bluetooth.

Withings BPM Connect

The Withings BPM Connect Blood Pressure Monitor is a CE-marked, Bluetooth enabled blood pressure cuff which can be placed around the upper arm of the patients. The inflation and deflation of the cuff will lead to a systolic and diastolic blood pressure, as well as a heart rate, which are shown on the device itself and in the LUMCcare app on the smartphone. The Withings BPM Connect Blood Pressure Monitor is battery powered and electrically safe. It is CE-marked for blood pressure measurement. A previously published study that showed that median values are within the 5 mmHg range.[18]

Withings Move ECG Watch

The Withings Move ECG Watch is a wearable, CE-marked, Bluetooth enabled smart watch. The wristwatch combines single lead ECG measurements with activity tracking such as walking, running, swimming and many other activities and workouts. It measures steps, distance and calories consumed and sends all its results to the LUMCcare app via Bluetooth. The Withings Move ECG Watch is battery powered and electrically safe.

LUMCcare app

Data are presented on the LUMCcare app. The data resides within the Withings Health Mate connection app on the smartphone in encrypted form. The Withings Health Mate connection app initial logon will require several privacy-related patient data: full name and date of birth. This procedure complies with the LUMC requirements and has been approved by the LUMC security officer. For the Withings connection app, an integration (API) in the Electronic Medical Record (EMR, EPD-Vision) has been built. This API has been functional for 6 years already. Physicians and specialized nurses can thus evaluate the e-Health measurements of the patients in the EMR.

The LUMCcare app presents the data to the patient in an intuitive interface. The app is co-created with Pharos, the advocate group for people with low literacy, in order to ascertain the measurements are understandable for a large group of patients. The app reminds

patients to take measurements based on the protocol prescribed by the health care provider. It allows patients to fill in questionnaires at appropriate time points. The app communicates with the LUMC infrastructure according to LUMC guidelines and is approved by the LUMC security officer. As for how to use the app, patients will receive oral and written instructions. If they run into problems, a helpdesk is available, which is run by an LUMC employed technician.

Withings Health Mate app

The Withings3 Health Mate connection app requires a user specific account, that is accessed using a hospital-provided, coded username and a password. The account cannot be linked to an individual patient. This procedure complies with the LUMC requirements and has been approved by the LUMC security officer. For retrieving the data from the Withings Health Mate app, the LUMC uses an API connection, which unlocks the patient measurement data. This API has been functional for 6 years already. Authorized users can thus evaluate the e-Health measurements of the patients in the electronic patient file.

Data is securely shared with the GP office via Medical Dashboard, an dedicated information portal that allows GPs to assess specific data from the LUMC. The Medical Dashboard is operational at the LUMC for already 8 years and complies with the LUMC requirements and has been approved by the LUMC security officer. Over the course of the next years, the underlying technology will be updated to new technology, in line with the established roadmap of the It&DI department of the LUMC. This effort is currently underway and may result in selection of a novel target architecture for regional connectivity in the coming period. All efforts will be taken to ensure this study protocol can continue also during implementation of novel architectures.

In addition to this, the Health Mate app also gives the patient insight into his/her measurements. Moreover, when the Move ECG detects signs of AF during a measurement the patient is notified via the watch and the app. The patient is instructed to then take up contact with our specialist nurse.

IkOefenZelf

Rehabilitation centre Basalt developed the portal “ikoefenzelf.nl” for online stroke rehabilitation. The goal of “ikoefenzelf.nl” is to implement the use of eRehabilitation and to give stroke patients the opportunity to practice where, when, and how often they want. More practice contributes to more participation and a better quality of life. The portal is

already used by at least 50% of all stroke patients in Basalt and offers stroke patients blended care applications for both physical and cognitive/mental training. After logging in to the portal using a hospital-provided, coded username and a password, patients can start their personal training, prepared for them by the rehabilitation professionals. The platform consists of education about stroke and the applications “Physitrack” (physiotherapy and occupational therapy), “MindDistrict” (psychology and social work), “Topwoordvinding” (speech therapy) and a time writing module (occupational therapy).[19]

StopAdvisor

The StopAdvisor app for support of smoking cessation has been developed by the Trimbos Institute, Pharos and NeLL, and is based on a scientifically proven intervention developed by the University College London. The StopAdvisor app is currently being used in collaboration with SineFuma, and will be made available to those patients participating in the pilot who smoke and are interested.

Coding the data

In general, the Withings connection-app requires an e-mail address, first name, last name, birth date and password for the patient in order to register himself. Without those details, the app cannot be used. Therefore, for privacy reasons, all patients receive a personal account. The key between the anonymous e-mail address of this account and the patient identity resides in the Electronic Medical Record (EPD-Vision). This procedure complies with LUMC requirements and has been approved by the LUMC security officer.

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

Not applicable, as this research cannot have been carried out in non-clinical settings.

### 6.3 Summary of findings from clinical studies

Not applicable.

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

Patients will have to measure their weight, temperature, blood pressure and heart rhythm on a regular basis. Regularly, they also will be asked questions about their general health. These activities may take some of their time.

A potential risk is that patients may be incorrectly assured that their data is monitored all the time by a trained physician. This might give them a false sense of security and hold them back from seeking medical assistance when this is required. To prevent this, we will

very clearly state in the patient information form (PIF) that this is not the case, and will make this integral part of the explanation when a patient starts with The Box.
A second potential risk is that patients may become alarmed by an incorrect detection of atrial fibrillation by the Withings Move ECG. Since it is not CE marked for AF detection, and given the results from a current validation study, we cannot exclude the occurrence of false positives or negatives. The smart watch and associated app give a warning when the measurement shows irregularities. It then either results in an “inconclusive” measurement or detects “atrial fibrillation”. It has been shown that this occurs when there are small irregularities in the hearth rhythm, such as atrial or ventricular extrasystoles or short pauses . The device then usually results in “inconclusive” but can also show “atrial fibrillation”. This can hence (incorrectly) distress the patient and cause him/her to seek unnecessary medical help. We will remedy this by clearly instructing the patient with what to do and who to contact in case of suspected AF.
After a measurement the Withings Move ECG performs a standard analysis resulting in either “normal”, “inconclusive” or “atrial fibrillation”. If their ECG smartwatch shows “atrial fibrillation” they are instructed to contact a dedicated nurse specialist who will check the measurements and refer them to the cardiology outpatient clinic if necessary. If the result is “inconclusive”, the patient is asked to repeat the measurement the next day. When the repeated measurement shows “inconclusive” again or when the measurement shows a warning for potential AF, they are instructed to also contact the dedicated nurse specialist who will contact the patient for further follow-up if necessary.
All devices used by patients for personal management in this study are CE marked, non-invasive, easy-to-use and electrically safe within their intended use. Using the devices is with very limited risks.
This study has multiple potential benefits for the patients: First, patients can measure their own blood pressure, weight, activity, and heart rhythm, which can reassure patients and give them more insight in their own health (the so-called ‘patient empowerment’). Furthermore, this data gives the doctor more insight in the health status of patients, potentially leading to better hypertension management and earlier detection of atrial fibrillation.

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

Not applicable.

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

Not applicable.

### 6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable.

### 6.8 Drug accountability

Not applicable.

## 7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

# 8. METHODS

## 8.1 Study parameters/endpoints

### 8.1.1 Main study parameter/endpoint

The primary objective of this study is the gathering of data on blood pressure management as a basis for power analysis in future trials. This will be evaluated by a before-after-comparison of systolic and diastolic blood pressure in mmHg as measured by the self-measurements with the Stroke Box.

### 8.1.2 Secondary study parameters/endpoints

The secondary objectives of this study are:

- Gathering data on self-measured heart rhythm from the Withings Move ECG as an indicator of atrial fibrillation, weight and activity of patients using the Stroke Box, and performing a quality assessment of the collected data as assessed by regularity of assessments and frequency of occurrence of measurement error.
- The potential change in self-management of the patients due to the Stroke Box as measured through changes in lifestyle. This will be measured using changes in results from questionnaires on physical activity and healthy lifestyle intentions taken at the start and at the end of the study and the development of weight of the patient.
  For the evaluation of physical activity we will adapt the Short Questionnaire to Assess Health enhancing physical activity questionnaire (SQUASH)[20], for the evaluation of healthy lifestyle intentions we will use the Healthy Lifestyle Intentions (HLI) questionnaire.
  The evaluation of the self-management of the patient will be assessed by the Reach Efficacy Adoption Implementation Maintenance (RE-AIM) model with a mixed model evaluation based on the normalization process theory.[21-23]
- Assessment of the patient adherence to the self-measurements and pharmacotherapeutic prophylactic therapy, using the Partners In Healthcare (PIH) questionnaire which measures how the patient manages his/her own disease. At the end of the study a comparison will be made between the group of patients who used the IkOefenZelf platform and those who did not.
- The technical implementation and patient adherence to the self-measurements by analysing how often they performed the measurements, if they experienced any problems as measured through the questions they asked during the study, and how they experienced the overall implementation as measured through the mHealth App Usability Questionnaire (MAUQ)[24] at the end of the study.
- User based evaluation of the technical – and workflow implementation for the GPs using the Stroke Box as evaluated with the Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM)[25] questionnaires for healthcare professionals.

### 8.1.3 Other study parameters

- Age
- Sex
- Body Mass Index
- Cardiovascular risk factors including medication (hypertension, diabetes mellitus, hypercholesterolemia, smoking, alcohol)
- Cardiovascular medical history (atrial fibrillation, stroke including all subtypes, heart failure, myocardial infarction)
- Stroke specific (stroke related disabilities as assessed by the National Institutes of Health Scale Score at discharge, modified Rankin Scale at discharge)
- The GP practice where the patient is registered and how the self-measurements are shared with the GP (i.e. via Medical Dashboard or manually)

## 8.2 Randomisation, blinding and treatment allocation

This is a non-randomized, non-blinded study.

## 8.3 Study procedures

For the small prospective cohort for the pilot, patients who are admitted for an ischemic or hemorrhagic stroke in the LUMC will be included in the day or days before dehospitalization and after post-stroke stabilization. After inclusion we will personally contact the GP of the patient to also ask their willingness to collaborate in the pilot. After agreement of their GP, the included patients will receive the Stroke Box with all devices listed under section 6 of this protocol. Patients will be instructed on usage of the devices by a neurology PhD student. Furthermore, for each device a detailed user guide is available on https://hartlongcentrum.nl/informatie-voor-patienten/the-box/handleidingen/.

If extra help is necessary, patients will have an e-consult in which a patient does not have to go to the hospital. Instead, he or she will talk with a specialist from the Box-helpdesk who will be able to guide the patient through the self-measurements and provide technical assistance where necessary.

Patients will be asked to measure their weight and blood pressure once a week where they are recommended to do this on the same day and time every week. Additionally, they will be asked to keep track of their activity data (i.e. steps) on a regular basis, which can be monitored continuously by wearing the smartwatch. All

data will be automatically transferred to the LUMC. In order to code the data, patients will receive an anonymous email address, as described earlier in this protocol. Data will be stored on LUMC-owned servers.

The patient's blood pressure measurements and lifestyle data (measured weight and activity) is accessible for the GP through Medical Dashboard. For GPs who do not yet work with Medical Dashboard, the patient will be asked to show his measurements to the GP in the following way during the regular visits. The patient can either show his measurements in the app or make a printout of the data to be shown to the GP or GP nurse.

When the patient records abnormal measurements indicating a high or rapid increase in blood pressure, they are instructed to not immediately contact a physician. This, in order to reduce the amount of (unnecessary) additional consults with the GP. Specifically, the patient is instructed to only contact their GP if they record a systolic blood pressure >140 mmHg for three days in a row or take up immediate contact if they record a systolic blood pressure >180 mmHg which is cause for immediate adjustment of the hypertension medication according to the NHG guidelines.

In addition to the standard care where patients receive a 48-hour Holter, patients who are suspected to have atrial fibrillation because of e.g. a cryptogenic stroke will be asked to also perform home measurements of their heart rhythm on a daily basis. They are recommended to do this on the same day and time every day. They will be very clearly instructed that their ECG measurements are not monitored regularly and that they should contact 112 in case of emergency.

After a measurement the Withings Move ECG performs a standard analysis resulting in either "normal", "inconclusive" or "atrial fibrillation". If their ECG smartwatch shows "atrial fibrillation" they are instructed to contact a dedicated nurse specialist who will check the measurements and refer them to the cardiology outpatient clinic if necessary. If the result is "inconclusive", the patient is asked to repeat the measurement the next day. When the repeated measurement shows "inconclusive" again or when the measurement shows a warning for potential AF, they are instructed to also contact the dedicated nurse specialist who will contact the patient for further follow-up if necessary. It should be noted that a clinical diagnosis will never be based on the self-measurements. Instead they serve as an early screening tool leading to patients with potential AF to be invited to the cardiology outpatient clinic to receive a diagnosis via the standard Holter measurement.

All ECG data are collected after the study and re-inspected by a PhD researcher of the LUMC for AF and in case of doubt checked again by an experienced cardiologist. In case of suspected AF, the patient is invited to the cardiology outpatient clinic. As 87% of stroke patients have ischemic strokes[16] and about a

third of those have cryptogenic strokes, we expect to find cryptogenic strokes in about 29% of the LUMC stroke population.[17]

Finally, the first ten patients with a modified Rankin Scale (mRS) ≥ 2 will receive access to the IkOefenZelf platform and will be asked to perform the practice modules on a regular basis.

Patients who smoke will also be asked to install the StopAdvisor app. This app will help them to quit smoking. The app is freely available from the IOS App Store and the Google Play Store.

Questionnaires

At the start and end of the study the patient will receive several questionnaires to evaluate their experiences with self-management, physical activity, healthy lifestyle intentions, their user experience, and their experience with eHealth. To evaluate the change in physical activity and lifestyle of the patient, they will be asked to fill out the SQUASH and HLI questionnaires at the start and end of the study. These questionnaires investigate respectively the amount of physical activity (e.g. sports) a patient has and what their intentions to a healthy lifestyle are (which includes questions on e.g. diet, smoking and alcohol use). In order to evaluate the experience of the patient with the self-management, they will be asked to fill out the PIH questionnaire at the start and the end of the pilot which measures how the patient manages his/her own disease. Finally, to evaluate the patient experience with the overall implementation of the Stroke Box, we will ask them to fill out the MAUQ questionnaire at the end of the study which includes questions on the technical ease-of-use, the general appearance and usefulness of the Stroke Box.

Moreover, we will evaluate the GP experience with the Stroke Box via the AIM, IAM and FIM[25] questionnaires for healthcare professionals which are four-item measures of implementation outcomes that are often considered “leading indicators” of implementation success.[26] An overview of the questionnaires used is given in the Table below.

Implementation will be assessed by the Reach Efficacy Adoption Implementation Maintenance (RE-AIM) model with a mixed model evaluation based on the normalization process theory.[21-23] The implementation will be evaluated from the perspective of the neurologists, GPs, practice assistant GP and patients.

| **Subject** | **Questionnaire** | **Estimated time** |
|---|---|---|
| Physical activity | Short Questionnaire to Assess Health enhancing physical activity questionnaire (SQUASH)[20] | 5 min |
| Healthy lifestyle intentions | Healthy lifestyle intentions questionnaire | 4 min |

| | | |
|---|---|---|
| Self-management | Partners In Health (PIH) questionnaire[18] | 4 min |
| Patient experience | mHealth App Usability Questionnaire (MAUQ)[24] | 4 min |
| GP experience | Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM)[25] | 3 min |

### 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.

### 8.5 Replacement of individual subjects after withdrawal

If a subject decides to withdraw from the study, they will not be replaced.

### 8.6 Follow-up of subjects withdrawn from treatment

Subjects who withdraw from treatment will be followed according to regular medical care.

### 8.7 Premature termination of the study

Not applicable.

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

### 9.2.2 Serious adverse events (SAEs)

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

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

An elective hospital admission will not be considered as a serious adverse event.

The 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.

Because this study is without any risks for the patient, we will report all SAEs once per year.

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

Not applicable.

### 9.3 Annual safety report

Not applicable.

### 9.4 Follow-up of adverse events

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

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

Not applicable.

# 10. STATISTICAL ANALYSIS

## 10.1 Primary study parameter(s)

We will use descriptive statistics to assess blood pressure management, patient engagement and user-based evaluation of the eHealth infrastructure. We will analyze their self-measurement frequency of blood pressure, heart rhythm, weight, and activity using the mean measurements per week. The dropout rate will be described and the change in blood pressure in mmHg. This will be used as a basis for sample size calculation for future trials.
Moreover, we will use descriptive statistics to assess the clinical characteristics of our sample population.

## 10.2 Secondary study parameter(s)

We will evaluate the change in lifestyle and user experience using qualitative questionnaires. Here we will make a quantitative comparison between questionnaires taken at the start and at the end of the study where we take into account the baseline characteristics of the patient, the type of stroke at hospital admission and whether the patient followed the IkOefenZelf modules as potential confounders.

## 10.3 Other study parameters

We will perform a qualitative comparison between GP practices that are used to box vs practices that are new with box based on the responses we get from the respective GPs.

## 10.4 Interim analysis (if applicable)

Not applicable.

# 11. ETHICAL CONSIDERATIONS

## 11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 10, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

## 11.2 Recruitment and consent

Recruitment of patients will be done by the resident physician on duty at that moment. He/She will check for potential interest in the study with patients and, in case of consent, introduce the researcher. Patients will be asked to participate by a dedicated PhD-Student during the day or days prior to dehospitalization, after the patient has been stabilized after stroke. In case of a TIA visit in the LUMC, patients are asked to participate in between clinical procedures during this day. Patients will be given written information about the study. Patients are allowed a reflection period of 24 hours if they wish to have so. If patients agree to participate, written informed consent will be obtained by a dedicated PhD-Student. Of course, patients can refuse participation at any time without a reason.

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

Not applicable.

## 11.4 Benefits and risks assessment, group relatedness

Additional to their usual care patients will be asked to fill in several questionnaires at the start and end of the study and will measure their blood pressure, activity, weight and potentially their heart rhythm regularly. The devices used in the pilots are non-invasive and easy to use.
Potential benefits of participating in this study are both short and long term. In the short term, patients may develop an increased awareness with regards to their health, leading to an improved lifestyle. This, on the long term may reduce the risk of cardiovascular disease by a possible positive change in lifestyle.

A major potential risk is the false sense of safety created by the self-measurements. Patients may, incorrectly, assume that a physician constantly monitors their wellbeing and therefore not directly seek treatment when this is required. We will therefore explicitly make sure this is avoided by indicating this at inclusion, in the patient information form. In

the Withings Healthmate app, a notification is also included by default indicating that the patient's data is not monitored by a physician.

### 11.5 Compensation for injury

The sponsor requested the accredited METC for dispensation from the statutory obligation to provide insurance, because participating in this study is without risks.

### 11.6 Incentives (if applicable)

All devices will be provided by the LUMC. Patients do not have to pay for the devices. Patients are allowed to keep their devices after the study is finished. This is the same for patients who withdraw from the study.

# 12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

## 12.1 Handling and storage of data and documents

Routine health care data will be accessible through the electronic patient system of the GP where the patient is registered. After approval, all necessary patient study data will be collected in a coded database. The key to which is available at the research coordinator H.J.A. van Os. Only investigators are authorized to look into the data. A key file will be made, to be able to trace back each individual patient. Both files will be password protected and the password for both files will be changed every three months. No mobile data carriers (i.e. USB-drive, DVD) will be used for that purpose.

Data Collection Forms, Case Report Forms, Informed Consent Forms and all other study documentation containing subject information will be stored under locked conditions when not in use. Computers and all storage devices containing study data will be password-protected. Data stored on the computer will use an alphanumeric code to identify the subject. Access to data is restricted to study personnel and when required the REC or other regulatory bodies as required by law. Essential trial documents and data, as well as a data back-up, will be retained for at least fifteen years. The data back-up will be stored on the network drive of the principal investigator, within the LUMC. To access this network drive, it is required to know the investigator's password, which is changed every three months. Also, it is required to know the passwords to the anonymized database as well as the key file, which are also changed every three months.

## 12.2 Monitoring and Quality Assurance

This study has been classified as of negligible risk (according to the LUMC risk score form V07-F01). We propose to let nurses from LUMC who are independent function as a monitor for this research project.

## 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.

## 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 at 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 for 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

We expect this project to give information of home monitoring in patients with a high risk of neuro- and cardiovascular disease. We will gain information on knowledge implementation of "The Box" in primary care. This is of importance to health managers, medical professionals and patients. It is our intention to publish the results in a peer reviewed medical journal.

# 13. STRUCTURED RISK ANALYSIS

## 13.1 Potential issues of concern

Not applicable

## 13.2 Synthesis

Participating in this study is without any risks. Therefore, chapter 13.1 has been skipped. "The Box" is an effective program for home monitoring patients. The extra burden due to the research aspect of this study is minimal and is outweighed by the benefits of participation.

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