Medtronic
Further, Together

# FRailty WAlking Patterns (FRAP) Study

## Clinical Investigation Plan

Version 1
17 Feb 2016

| Sponsor |
| --- |
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## Change History record

| CIP Change History | | |
|---|---|---|
| **Version** | **Summary of Changes** | **Author** |
| 1 | Initial release | Ilaria Marcotullio |

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# A SYNOPSIS

## Title

FRailty WAlking Patterns (FRAP) Study

## Purpose

The aim of this study is to evaluate sit-stand phases and gait speed detection using an externally worn LINQ compared to an external reference (3D accelerometer, and/or the CAREN system) in one center in the Netherlands.

## Design

Prospective, non-randomized, single-center, post-market interventional study.

## Devices used in the study

The following products will be worn externally by the patients to capture movement signal:

- 3-D accelerometer – ActiGraph™ wGT3X-BT
- Accelerometer - Reveal LINQ™ with software RAMware REEF Research System, Rev 1.0 onboard
- DR220 Holter

All medical devices used in this study are CE marked. The intended use of the Reveal LINQ in this study will not be for medical purposes, but exclusively for technical reasons, therefore the Reveal LINQ will be considered a non-medical device in this study. The Reveal LINQ device will be used externally, will have the investigational software RAMware REEF Research System, Rev 1.0 onboard. The software will be downloaded through the 2090 programmer. Since RAMware REEF Research System is an accessory to the Reveal LINQ it will also be classified as a non-medical device. Subjects will perform part (i.e. Six Minute Walk Test, 4 Meter Gait Speed Test) of the walking exercises inside the Computer Assisted Rehabilitation Environment (CAREN) system, to record additional subject position information.

## Objectives and endpoints

Primary Objective

The primary objective of this study is to compare Gait parameters (i.e. gait speed, walking patterns) derived from the Reveal LINQ accelerometer signals during Six Minute Walk (6MW) Test, 4 Meter Gait Speed (4MGS) Test, Five Times Sit to Stand (FTSTS) Test, Expanded Timed Get-Up-and-Go (ETGUG) Test with those obtained from a validation accelerometer and the CAREN system.

Endpoints of the Study are the following:

- ETGUG phase data
- FTSTS timing
- Gait speed (4MGS test)
- Number of steps in 6 minutes (6MW test)
- Distance covered in 6 minutes (6MW test)
- Gait parameters from vertical acceleration axis

- Stand up phase slope
- HRV response to postural change

## Subject population

Approximately 20 Heart failure subjects will be enrolled in the study. This population was chosen to test the sensitivity of the accelerometer embedded in the LINQ device in a small cohort of subjects with reduced mobility and for which frailty is more prevalent than the general population, as well as recognized as an important prognostic indicator. Participants will be invited to attend one study visit. The study visit is expected to take approximately 2 hours. It is expected that the subjects will be enrolled over a period of 3 months and no follow up beyond the single visit is envisaged. The study will take place at a single center in the Netherlands (Maastricht University, Maastricht).

## Treatment

On arrival to the rehabilitation center subjects will have the Reveal LINQ, the 3D-accelerometers (one on the chest by medical-grade adhesives and a second at the level of the waist over the top of a medical grade adhesive) and the Holter attached externally. Then, they will be asked to perform the following exercises:

- Six Minute Walk (6MW) Test
- 4 Meter Gait Speed (4MGS) Test
- Five Times Sit to Stand (FTSTS)Test
- Expanded Timed Get-Up-and-Go (ETGUG) Test

Upon completion of the walking exercises, the Reveal LINQ device as well as the Holter and the Accelerometers will be removed from the subject and the subject's participation in the study will be complete. A Study Exit form will be completed.

## Inclusion criteria

- Chronic Heart Failure in NHYA class II and class III
- Willing to sign the informed consent form.
- At least 18 years of age.

## Exclusion criteria

- Not able to walk continuously for a period of 6 minutes and perform the walking exercises as necessary for the study protocol.
- Any known allergy to Titanium
- Any concomitant conditions which in the opinion of the investigator would not allow accurate measurement of gait and frailty parameters with an externally worn device.
- Any concomitant condition which in the opinion of the investigator would not allow a safe participation in the study.
- Enrolled in another study that could confound the results of this study, without documented pre-approval from a Medtronic study manager.

## Clinical Procedures

The point of enrollment is the time when a subject signs the Informed Consent Form. At that point, the subject is considered included in the study. All study data will be collected for each subject during Baseline visit and – should it be a standalone visit – during walking exercises performing visit. Information documented will include:

| Study Procedure | Enrollment/Baseline | Walking Exercises Visit |
|---|---|---|
| Patient informed consent | x | |
| Inclusion/exclusion assessment | x | |
| Relevant Medical History | x | |
| Demographics | x | |
| Physical examination | x | |
| Medications | x | |
| REEF software upload/download | | x |
| LINQ placement | | x |
| Holter placement and Recording | | x |
| Accelerometer placement and recording | | x |
| ETGUG test | | x |
| FTSTS test | | x |
| 6MW test | | x |
| 4MGS test | | x |
| Exit subject | As they occur | |
| Study deviations | As they occur | |

# B GENERAL INFORMATION

## B.1 Introduction

Frailty is a geriatric syndrome characterized by reduced homeostatic reserves, exposing the organism to extreme vulnerability to endogenous and exogenous stressors[1].

Frailty is prevalent in older people and involves a progressive physiological decline of multiple body systems, typical signs and symptoms include weight loss, fatigue, muscle weakness, slow or unsteady gait declines in activity[2].

Frailty is increasingly recognized as an important prognostic indicator in heart failure (HF) and is more prevalent in HF than the general population[3,4].

The identification of frailty in its early stage is important because interventions may potentially prevent, or delay the clinical consequences of frailty[5].

Of particular focus in this study will be walking speed as prior research has demonstrated that slow gait speed has the strongest prognostic ability of the traditional components used to assess frailty[6,7], and has been reported as one of the strongest to predict adverse outcomes, such as mobility disability, falls, or hospitalization[8].

Also of interest is the detection of posture changes as this may have implications for detecting changes in sleeping habits and could also provide context for other biomarker signals collected by the LINQ device.

The literature has been reviewed and the scientific soundness of the proposed analytical techniques evaluated. The rationale for this study design is to evaluate the feasibility of using the Reveal LINQ™ to monitoring walking patterns.

HF patients (the target population for the study in discussion) would make it possible to test the sensitivity of the accelerometer embedded in the LINQ device in a small cohort of subjects with reduced mobility and for which frailty is more prevalent than the general population, as well as recognized as an important prognostic indicator.

No risk to the subjects is expected with this study.

## B.2 Device information

No devices are implanted in this study. During the study visit subjects will be asked to wear the study device Reveal LINQ, with the REEF Investigational software installed, attached on the left hemitorax by medical-grade adhesives (i.e. Tegaderm, steri-strips).

Part of the walking exercises requested by the protocol will be performed within the Motek Medical CAREN (Computer Assisted Rehabilitation Environment) system. It is a hardware and software system for registration, evaluation and training of functional human behavior consisting of a motion base (with a dual belt instrumented treadmill), a camera real-time motion capture system, a projection screen and the D-flow software (http://www.motekmedical.com/products/caren).

Study Device:

- Reveal LINQ: A Medtronic, CE marked miniaturized insertable cardiac monitor (ICM) that is usually inserted subcutaneously through a minimally invasive procedure in patients with suspected arrhythmias for continuous monitoring of a patient's ECG and other physiological parameters.
  In this study, the device will not be used according to its current indications. The Reveal LINQ will not be inserted subcutaneously, but will be worn externally on the chest and used as an accelerometer to register walking patterns. The same Reveal LINQ device will be worn externally by more than one subject and should be sanitized after each deployment as per common clinical practice.

  Although the Reveal LINQ devices used in this study have engraved "Not for Human Use" as measure to prevent any accidental implantation, they are to be used in humans but not to be implanted. The parylene coating is removed due to the engraving. The Reveal LINQ package study specific labeling will be in English identifying the device as "Exclusively for Clinical Investigation - External use only". Furthermore, a medical-grade adhesive will be placed below the Reveal LINQ as an additional safety measure aiming to avoid direct contact with the titanium case of the Reveal LINQ and patient's skin. Since the purpose of this study is to investigate whether it is technically possible to obtain information about movement with the Reveal LINQ, the device will be considered a non-medical device.

- REEF Research System, Rev 1.0, Medtronic investigational RAMware uploaded on Reveal LINQ to activate the patient position sensor circuitry (the accelerometer). The RAMware REEF Research System is an accessory to the Reveal LINQ and will therefore also be classified as a non-medical device.

- 2090 Carelink Programmer: Medtronic. The Medtronic CareLink 2090 Programmer is a portable, line-powered (AC) microprocessor-based system. It contains investigational software (REEF User Interface Updates) to upload/download the REEF RAMware in the LINQ device. The investigational software is considered an accessory to the Reveal LINQ and will therefore also be classified as a non-medical device. The 2090 programmer containing the investigational software will be designated and labelled as "Exclusively for Clinical Investigation".

Monitoring equipment :

- Holter Monitor: CE marked. The North-East Monitoring DR220 Digital Recorder is a Holter monitor designed to facilitate ambulatory cardiac monitoring. The device is capable of storing real-time data to a SD memory card. For this study, this device is used to store the surface ECG and accelerometer signals from the Reveal LINQ™ during the walking exercises and will be used within the labeled Indications for Use.

- ActiGraph™ wGT3X-BT: ActiGraph Corporation, CE marked. This activity monitor contains a 3-D accelerometer and will be worn externally by the subjects during the walking assessment and will be used within the labeled Indications for Use.

The labeling of the CE marked devices will be according local language requirements.

#### *B.2.1 Hospital equipment*

CAREN (Computer Assisted Rehabilitation Environment) System: Motek Medical. The CAREN System is a hardware and software system for registration, evaluation and training of functional human behavior. The CAREN system consists of a motion base (with a dual belt instrumented treadmill), a camera real-time motion capture system, a projection screen and the D-flow software.

### B.3 Comparator information

Not applicable.

## C STUDY PLAN

### C.1 Study objectives

The aim of this prospective, non-randomized, single-center, post-market interventional study is to evaluate sit-stand phases and gait speed detection in patients with chronic heart failure using an externally worn Reveal LINQ compared to an external reference (3D accelerometer, and/or the CAREN system).

#### *C.1.1 Primary objectives*

The primary objective of this study is to compare Gait parameters (i.e. gait speed, walking patterns) derived from the Reveal LINQ accelerometer signals during the Six Minute Walk (6MW) Test, 4 Meter Gait Speed (4MGS) Test, Five Times Sit to Stand (FTSTS) Test, Expanded Timed Get-Up-and-Go (ETGUG) Test with those obtained from a validation accelerometer and the CAREN system.

### C.2 Clinical endpoints

The endpoints to be measured during the study are the following:

- ETGUG phase data
- FTSTS timing
- Gait speed (4MGS test)
- Number of steps in 6 minutes (6MW test)
- Distance covered in 6 minutes (6MW test)
- Gait parameters from vertical acceleration axis
- Stand up phase slope
- HRV response to postural change

### C.3 Study hypothesis

As this is a feasibility study, no formal statistical hypotheses are being tested. The Study regards the feasibility of extracting walking patterns from the accelerometer embedded in the Reveal LINQ.

### C.4 Study population

Approximately 20 subjects with Chronic Heart Failure will be enrolled in the study. No control group will be used for this study.

### C.5 Study design

This is a prospective, non-randomized, single-center post-market interventional study. The Study will take place in the Netherlands at one investigation site.

### C.6 Randomization and blinding

No randomization and no blinding will be used in this Study.

## C.7 Sample size

The FRAP study is primarily designed to evaluate the possibility of extracting walking patterns from the accelerometer embedded in the Reveal LINQ.

A sample size of approximately 20 subjects will be enrolled to see if reproducible results indicating feasibility of extracting walking patterns could be obtained. No formal statistical hypotheses are being tested.

### C.8 Number of investigation sites and study duration

The single participating center is the NUTRIM School of Nutrition and Translational Research in Metabolism of the Faculty Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands. Approximately 20 subjects will be enrolled in the study and it is expected that the subjects will be enrolled over a period of 3 months and no follow up beyond the single visit is envisaged.

# D SUBJECT SELECTION

## D.1 Inclusion criteria

- Chronic Heart Failure in NHYA class II and class III.
- Willing to sign the informed consent form.
- At least 18 years of age.

## D.2 Exclusion criteria

- Not able to walk continuously for a period of 6 minutes and perform the walking exercises as necessary for the study protocol.
- Any known allergy to Titanium
- Any concomitant conditions which in the opinion of the investigator would not allow accurate measurement of gait and frailty parameters with an externally worn device.
- Any concomitant condition which in the opinion of the investigator would not allow a safe participation in the study.
- Enrolled in another study that could confound the results of this study, without documented pre-approval from a Medtronic study manager.

# E STUDY PREPARATION PROCEDURES

## E.1 Investigator/Investigation site selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study.

The NUTRIM School of Nutrition and Translational Research in Metabolism of the Faculty Health, Medicine and Life Sciences, Maastricht University and the Investigator, Dr. Kenneth Meijer, have been included in the study since they both comply with the following requirements:

- investigator's qualification: Investigator is qualified by training, education, and relevant experience appropriate to the use of the products and associated procedures; Investigator expects to have adequate time and resources to conduct the study throughout the duration of the study; Investigator has access to an adequate number of eligible subjects; Ability to comply with applicable EC and regulatory requirements; Investigator is not debarred, disqualified, or working under sanctions in applicable region
- sufficient patient population/referral base
- sufficient resources to conduct the study
- facilities and administrative support
- experience in the field of walking patterns
- past experience in conducting research in this area

Furthermore, the site is one of the few centers in Europe with the CAREN (computer Assisted Rehabilitation Environment) system.

### *E.1.1 Clinical Investigation Agreement*

A Clinical Investigation Agreement shall be in place, signed by the participating investigation site and/or principal investigator of the investigation site, as per the local legal requirements, and returned to Medtronic prior to the commencement of any clinical study activities. The investigator is indicating approval of the Clinical Investigation Plan and subsequent amendments, by a fully executed agreement. Amendments to this Clinical Investigation Plan shall be agreed upon between Medtronic and investigator(s) and be recorded with a justification for the amendments.

### *E. 1.2 Curriculum Vitae*

An up to date signed and dated curriculum vitae from each investigator and site staff participating in this clinical study, evidencing the required qualifications, including the year and where obtained, shall be collected and shall include their current position at the investigation site. The signature on the CV must be dated within 3 years prior to the date of activation of the site.

### *E.1.3 Delegated task list*

A Delegated Task List (DTL), signed by the Principal Investigator, documenting the attribution of responsibilities for investigation site staff, including their initials, signature, title and responsibilities in the clinical study will be in place prior to study start.

## E.2 Ethics

### *E.2.1 EC approval*

Prior to enrolling subjects in this clinical study, the investigation site's EC will be required to approve the current Clinical Investigation Plan, the Patient Information and Informed Consent

form, including any other written information to be provided to the subjects. EC approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the clinical study at an investigation site. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. In addition, the approval letter needs to be accompanied by an EC roster or letter of compliance, to allow verification that the investigator, other investigation site personnel, and/or Medtronic personnel are not members of the EC. If they are members of the EC, written documentation is required stating that he/she did not participate in the approval process. If the EC imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the investigator for reporting to the EC. Investigator must inform immediately Medtronic of any change in status of EC approval once the investigation site has started enrolment. If any action is taken by an EC with respect to the study, that information will be forwarded to Medtronic by the investigator immediately. If any Amendment to this Clinical Investigation Plan will be developed it must be approved by EC prior its implementation.

### *E.2.2. Informed consent process*

The investigator or authorized designee must obtain written informed consent before any clinical study related activity takes place.

Well in advance of the consent discussion, the subject should receive the Medtronic and EC approved Patient Information and Informed Consent Form. During the consent discussion, the investigator or his/her authorized designee must fully inform the patient of all aspects of the clinical study that are relevant to the patient's decision to participate in the clinical study. If a patient is illiterate, an impartial witness must be present during the entire informed consent discussion. All items addressed in the Patient Information and the Informed Consent Form must be explained. The language used shall be native and as non-technical as possible and must be understandable to the patient and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the Patient Information and the Informed Consent Form, to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the subject.

Neither the investigator, nor the investigation site staff shall coerce, unduly influence or induce a patient to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the subject's rights.

When the subject decides to participate in the clinical study, the Informed Consent Form must be signed and personally dated by the subject and investigator or authorized designee. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the Patient Information and Informed Consent Form was accurately explained and clearly understood by the subject, and that informed consent was freely given.

After all persons have signed and dated the Informed Consent Form, the investigator must provide the subject with a copy of the Patient Information and the signed and dated Informed Consent Form.

### *E.2.3 Revisions in Patient Information and Informed Consent Form*

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The investigator or his/her authorized designee should inform the subject in a timely manner.

Medtronic will revise the written Patient Information and Informed Consent Form whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The revised information will be sent to the investigator for approval by the EC. After approval by the EC, the Patient Information and Informed Consent Form must be provided to the to the participating subjects who have not completed the study, and the informed consent process as described above needs to be repeated.

### *E.2.4 Regulatory notification / approval*

Since the Reveal LINQ will not be used for medical purposes during the study, but exclusively for technical reasons, the Reveal LINQ and REEF software are not considered a medical device as laid down in WMH Article 1, first paragraph. The medical devices used in the study are CE marked and used within their approved intended use; therefore no submission to Dutch Competent Authority is required.

## E.3 Regulatory compliance

This clinical study will be conducted in compliance with Declaration of Helsinki 2013, laws and regulations of the country in which the clinical study is conducted, including data protection laws, the Clinical Investigation Agreement and the Clinical Investigation Plan.

All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the patient informed consent process, EC approval, clinical study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

## E.4 Training requirements

Prior to investigation site activation or subsequent involvement in clinical study activities, Medtronic will provide clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities and investigator responsibilities.

As a minimum the CIP, PIC, use of data collection tools, applicable local regulations, as well as device training are required. Study-specific training will be documented prior to investigation site activation.

## E.5 Study materials and study-specific equipment

The sponsor will supply all required study materials for appropriate data collection before study start as the Paper CRFs and the Investigator Site File to maintain required study documentation.

The Sponsor will also provide the following clinical study-specific equipment, after the Clinical Study Manager has declared the investigation site ready to start the clinical study:

- 3-D accelerometer – ActiGraph wGT3X-BT
- Accelerometer - Reveal LINQ (including the 2090 programmer to upload/download the REEF software)
- DR220 Holter

These devices are the property of Medtronic, and will be collected by Medtronic personnel at the completion of the study.

It is the investigator's responsibility to ensure the CAREN (computer Assisted Rehabilitation Environment) system will be available at the Site for the Study procedures.

All reusable devices need to be cleaned/sanitized after each deployment as per clinical practice.

## E.6 Study device and equipment traceability

### *E.6.1 Supply of devices and equipment*

The Reveal LINQ (Study device) and the monitoring equipment will be provided free of charge by the sponsor for the duration of the study. The Reveal LINQ should be used only in this clinical study according to the CIP. Medtronic will only allow shipment of study device and equipment to the investigation site or investigator, after the Clinical Study Manager has declared the investigation site ready to start the clinical study. Medtronic will register the shipment and receipt of the devices at the sites.

### *E.6.2 Storage & handling of study devices and equipment*

The study device and the equipment must be stored in a secured area. The method of storage shall prevent the use of study device for other applications than mentioned in this Clinical Investigation Plan.

### *E.6.3 Device and equipment return procedures*

At the end of the study, the device and the equipment provided by Medtronic will be returned to Medtronic. The Sponsor will ensure collection of all the device and equipment at the end of the study.

### *E.6. 4 Device and equipment disposition requirements*

Each study device and monitoring equipment component provided to the site will be traced during the clinical study recording on a specific device tracking log, with the relative serial numbers, with date of receipt and final return date to Medtronic. The investigator is responsible for maintenance of each Device Tracking Log in the Investigator Site File. On this log, the receipt, return and disposal of the study devices shall be documented. At the end of the clinical study the principal investigator must sign and date the original Device Tracking Logs. In addition, all information on the use, storage and handling of the product and download of the investigational software will be provided under a separate cover

# F STUDY METHODS

## F.1 Point of enrollment

The point of enrollment is the time when a subject signs and personally dates the Informed Consent Form. At that point, the subject is considered enrolled in the investigation.

The investigator will maintain a log of all subjects enrolled in the study, assigning an identification code linked to their names, alternative subject identification or contact information.

## F.2 Baseline

The Baseline visit can be a standalone visit or can be performed on the same day of the walking exercises prior to perform the tests. In the case the walking exercise visit is a standalone visit, it needs to be done within 1 month of the baseline.

The following baseline information will be collected:

- Patient informed consent,
- Inclusion/exclusion assessment,
- Relevant Medical History,
- Subject Demographics
- Physical Examination, (i.e. height, weight, blood pressure, heart rate)
- Ongoing Relevant Medications.

## F.3 Walking exercises

No devices are implanted in this study. Before the Walking protocol is initiated the RAMware will be downloaded onto the device via the 2090 programmer.

At the beginning of the walking exercises:

- The Reveal LINQ memory will be cleared
- The Reveal LINQ, the accelerometers and the DR220 Holter monitor will be placed on the subject. A medical-grade adhesive will be placed underneath the Reveal LINQ as an additional safety measure aiming to avoid direct contact with the patient's skin
- Time will be recorded;

- The Reveal LINQ and the Actigraph will be manually tapped simultaneously to provide a marker for the further data analysis;

The following exercises will be performed:

• Six Minute Walk (6MW) Test

The 6MW test measures the distance an individual is able to walk over a total of six minutes on a flat surface. The goal is for the individual to walk as far as possible in six minutes. The 6MW test will be performed within the CAREN system environment

• 4 Meter Gait Speed (4MGS) Test

The 4MGS test measures the gait speed an individual is able to walk over 4 meters on a flat surface. The goal is for the individual to walk as fast as possible over 4 meters.

It will be repeated 3 times within the aforementioned 6MW test (after approximately 1, 3 and 5 minutes) to get variability due to subject tiredness. The test will be performed within the CAREN system environment.

• Five Times Sit to Stand (FTSTS) Test

The STS test measures the time a subject takes to stand up from an armchair 5 times in a row, without stopping in between. It is a short test which measures dynamic balance and functional mobility.

• Expanded Timed Get-Up-and-Go (ETGUG) Test

The ETGUG test measures the time it takes a subject to stand up from an armchair, walk a distance of 10 m, turn, walk back to the chair, and sit down. It is a short test of basic mobility skills for frail community-dwelling elderly.

To minimize potential bias due to subject tiredness and fatigue during the execution of the physical tests:

- The order of the tests will be randomly defined at discretion of the investigator;
- A resting time between tests may be granted, at discretion of the investigator.

The tests may or may not be conducted by the same investigator.

Upon completion of the walking exercises the Reveal LINQ device as well as the Holter and the Accelerometers will be removed from the subject and the subject's participation in the study will be complete. A Study Exit form will be completed.

Upon completion of the study the RAMware will be removed from the LINQ device.

## F.4 Data collection requirements

The following data will be collected as summarized in the table below:

- Demographic data for patients, Relevant medical history, Medications, Subject demographics, Physical Examination, Inclusion/exclusion assessment.
- Device Data: LINQ/Holter, Actigraph and CAREN system data, during the Tests

| Table 1 – Data collection requirements | | |
|---|---|---|
| **Study Procedure** | **Enrollment/Baseline** | **Walking Exercises Visit** |
| Patient informed consent | x | |
| Inclusion/exclusion assessment | x | |
| Relevant Medical History | x | |
| Demographics | x | |
| Physical examination | x | |
| Medications | x | |
| REEF software upload/download | | x |
| LINQ placement | | x |
| Holter placement and recording | | x |
| Accelerometer placement and recording | | x |
| ETGUG test | | x |
| FTSTS test | | x |
| 6MW test | | x |
| 4MGS test | | x |
| Exit subject | As they occur | |
| Study deviations | As they occur | |

## F.5 Role of the sponsor's representatives

Sponsor representatives may provide support as required for the study under supervision of the Principal Investigator, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at all visits under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at sites.
- Provide clarification in case of need on correct completion and/or correction of CRFs
- Monitoring and auditing activities

The sponsor's representatives providing technical support may be listed on the sponsor's technical support list

## F.6 Source documents

Regular hospital charts are considered source documentation. Also files collected on SD cards from the LINQ/ the Holter, the 3-D Accelerometer and on an external Hard Drive from the CAREN System are considered source data. The study paper CRFs, signed and dated by the investigator or an authorized designee can be used as source document for the data collection points specified in table 4; See table below for each data specific source document. See table below for each data specific source document.

| Table 2 – Source Documents | |
|---|---|
| **Data** | **Source Document** |
| Inclusion/exclusion assessment | Patient Hospital chart/worksheets |
| Relevant Medical History | Patient Hospital chart/worksheets |
| Demographics | Patient Hospital chart/worksheets |
| Physical examination | Patient Hospital Chart/worksheets |
| Medications | Patient Hospital Chart/worksheets |
| LINQ data/Holter data | SD Card |
| 3-D Accelerometer Data | SD Card |
| CAREN System data | External Hard Drive |

The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical study.

The access to source documents must be guaranteed as reported in section G 2.2.

## F.7 Adverse events and Device Deficiency

No MDT CE market release device involved in the study considered as medical device; it will be responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic of any other manufacturer.

## F.8 Subject accountability

Subjects may withdraw from the study at any time and for any reason, no subject replacement will be considered. Since no device is implanted nor used for diagnostic or therapeutic purposes, but will be used just to collect data, request for permission to follow-up subjects outside the clinical study in case of withdrawal due to problems related to investigational device safety or performance is not applicable in this study.

If a subject decides to withdraw from the study, the investigator will document in the Study Exit Case Report Form the reason for withdrawal and indicate any relationship of the withdrawal to the study. Subject's subsequent health care will be unaffected by withdrawal. The investigator may elect to withdraw the subject from the study at any point if deemed to be in the subject's best interest (e.g. the subject becomes too fatigued when performing walking exercises).

## F.9 Study deviations and CIP changes

A study deviation is an event where the investigator or site personnel did not conduct the clinical study according to the Clinical Investigation Plan or Clinical Investigation Agreement. The investigator is not allowed to deviate from the above mentioned documents except with prior approval and under emergency circumstances. All deviations shall be documented and explained, regardless the reason for the deviation.

Medtronic will assess the significance of all deviations and evaluate the need to amend the Clinical Investigation Plan or to early terminate the study, in accordance with Medtronic SOPs.

### *F.9.1 Request for approval of study deviations*

The investigator shall obtain documented approval from Medtronic and, if required, from EC, before implementation of any change in or deviation from the Clinical Investigation Plan. The

investigator shall timely contact the Clinical Study Manager for review of the proposed change/deviation.

Prior approval is not always realistic in situations where unforeseen circumstances are beyond the investigator's control. However, also in these cases, the event is considered a deviation and shall be reported.

In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. Such deviations from the Clinical Investigation Plan do not require the prior approval of Medtronic. The investigator shall report the deviation as soon as possible to Medtronic and the reviewing EC, if applicable. Medtronic will inform the regulatory authorities, if required.

#### *F.9.2 Reporting requirements for study deviations*

Study deviations will be collected throughout the study and reported to Medtronic on a Protocol Deviation Form, one for each Protocol Deviation and documenting an explanation of the deviation.

The investigator shall adhere to EC requirements and procedures for reporting study deviations.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan, and in some cases freeze enrolment or ultimately terminate the investigator's participation in the study.

#### *F.9.3 Amendments to the Clinical Investigation Plan*

The investigator will propose any appropriate modification(s) of the Clinical Investigation Plan or investigational device or investigational device use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate regulatory authorities and to the investigator to obtain approval from their EC, if applicable. Administrative amendments to the Clinical Investigation Plan will be submitted to the EC and appropriate regulatory authorities for notification, if applicable.

# G QUALITY CONTROL PROCEDURES

## G. 1 Procedures for data management

### *G.1.1 Data collection*

The investigator must ensure accuracy, completeness, legibility and timeliness of the data reported in the Paper CRFs and in all other required reports. Data reported on the CRFs which are derived from source documents (e.g. hospital records) must be consistent with the source documents or the discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, to be filed in the patient medical file.

Only authorized persons can complete CRFs. CRFs shall be signed by investigators as specified on the Delegated Tasks List included in the Investigator Site File.

In order to maintain an audit trail, changes or corrections in CRFs are made by making a single strike-through on the wrong data and an addition of the correct data. The change in the CRF must be signed, dated, and explained (if necessary) by the person that made the change. If a person only authorized to complete CRFs made changes to an already signed CRF, the investigator shall re-sign this CRF.

Beside the data on the Case Report Forms, LINQ files, Accelerometer files, Holter files will be collected by means of SD cards, while CAREN system files will be collected by means of an external Hard Drive

All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

Additional details regarding data management will be described in the Data Management Plan.

A copy of final Case Report Forms will be provided under a separate cover.

### *G.1.2 Source data to be directly recorded on the Case Report Forms*

The following data will be recorded directly on the CRF and is considered as source data:

ETGUG data, FTSTS timing, Gait speed (4MGS test), Distance covered in 6 minutes (6MW test). Refer to Table 3 for further details:

**Table 3 –Source data to be directly recorded on CRFs**

| Data | Source Document |
|---|---|
| LINQ placement | CRF |
| Holter placement and recording | CRF |
| Accelerometer placement and recording | CRF |
| ETGUG test | CRF |
| FTSTS test | CRF |
| 6MW test | CRF |
| 4MGS test | CRF |
| Exit subject | CRF |
| Study deviations | CRF |

### *G.1.3 Data review and processing*

Data management will be done according to Medtronic SOPs and the Data Management Plan for this clinical study. These documents will be made available on request.

All collected data will be reviewed for completeness, correctness and consistency. In case of issues, queries will be sent to the investigator to complete, correct or comment the data.

## G.2 Monitoring procedures

Monitoring visits will be conducted during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan.

It is the responsibility of Medtronic to ensure proper monitoring of the study. Appropriately trained Medtronic personnel or delegates appointed by Medtronic will perform study monitoring at the study center in order to ensure that the study is conducted in accordance with the Clinical Investigation Plan, the signed Clinical Trial Agreement (CTA), and applicable regulatory requirements. Medtronic must therefore be allowed access to the subjects' clinic and hospital records when requested as per the Patient Informed Consent and CTA.

### *G.2.1 Accessibility of investigation site staff and study materials*

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be available to Medtronic field personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the Case Report Form Direct access to patient medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

#### *G.2.2 Audits and investigation site inspections*

In addition to the foreseen monitoring visit, Medtronic may conduct audits at participating investigation sites. The purpose of an audit is to verify the adequate performance of the clinical study related activities. Independent of the employees involved in the clinical study. Regulatory authorities may also perform inspections at participating investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to the Medtronic study contact person.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, EC review and regulatory inspections.

### G.3 Study suspension or early termination

#### *G.3.1 Early study suspension or termination*

Medtronic or Regulatory Authority may decide to suspend or prematurely terminate the clinical study. If the clinical study is terminated prematurely or suspended, Medtronic shall promptly inform the Principal Investigator of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC, the study subject and their General Practitioner.

#### *G.3.2 Early investigation site suspension or termination*

Medtronic or EC may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing EC, non-compliance to the Clinical Investigation Plan or lack of enrollment). If an investigation site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC, the study subject and their General Practitioner. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the sponsor and EC if applicable.

### G.4 Study close out

Study close out occurs when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic, whichever occurs first. Medtronic will inform the Principal Investigator when this occurs. Study closure also includes, but is not limited to data query resolution. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last.

## H DATA ANALYSIS AND REPORTING

### H.1 Analysis of clinical data

Descriptive statistics will be used to summarize the patient demographic and clinical characteristics at baseline. Data for qualitative variables will be presented as prevalence rates (total number of subjects, number of events, and percent). Data for continuous variables will be summarized using measures of central tendency and dispersion.

All subjects who signed the informed consent document will be defined as the All Enrolled Population. The Analysis Population is defined as subjects who are enrolled and complete at least one of the walking exercises. Subjects who are enrolled but are found to have a protocol deviation such that the clinical interpretability of the results obtained from the patient is impacted, will not be included in the primary analysis, but will be reported in the patient disposition table. The analysis exclusion of subjects due to inclusion or exclusion criteria violation or a significant CIP deviation will be decided upon by the study team blinded without prior knowledge of statistical analysis results. Safety will be reported on the All Enrolled Population and the primary objective will be reported on the Analysis Population.

During the study all movement data is continuously collected. The primary endpoint for this study are the gait parameters obtained from the Reveal LINQ – REEF Research System, Rev 1.0 (accelerometer) and the external reference system (i.e. validation accelerometer and/or computer assisted rehabilitation system). All data processing will be performed offline.

The gait speed (and additional parameters) will be calculated from the Reveal LINQ accelerometer signals, from the validation accelerometer and/or from the computer assisted rehabilitation system. Correlation coefficients between the Reveal LINQ parameters and those from the reference system will be calculated for each maneuver (4MGS, FTSTS, ETGUG and 6MHW). The agreement between the Reveal LINQ derived parameters and the reference parameters will be reported and visualized using Bland and Altman plots.

The agreement between the parameters derived during the different maneuvers will also be evaluated using correlation coefficients and Bland-Altman plots.

Any change to the data analysis methods described in the Clinical Investigation Plan, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Missing data will not be imputed. The number included in each analysis will be reported so that the reader can assess the potential impact of missing data.

### H.2 Publication Policy

Publications and presentations referring to this clinical study will be coordinated by Medtronic to allow the use of all available data. The following publication policy will have to be adhered to by the participating investigation site:

Medtronic may intend to publish the results of the study in scientific journals and congresses.

Authorship on any publication(s) resulting from this clinical study will be assigned according to the latest ICMJE Recommendations (“Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals”, 2013).

The number of authors will be dependent on the regulations of the concerning journal.

There are no plans to form a publication committee. Publication activities will be assessed after the study is completed and any collaboration with the investigator will be determined at that time.

Based on the principle that Medtronic owns the data of this clinical study, the investigation site may access and use the data provided by itself for scientific publications following prior approval by Medtronic.

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use.

The study sponsor will collect data in such way that no subject can be identified, and monitor study records.

Participating subjects will not be identified by name in any published reports about the clinical study.

## I STUDY MANAGEMENT

## I.1 Study staff

**Sponsor**
Medtronic Bakken Research Center
Endepolsdomein 5
6229 GW Maastricht
The Netherlands

**Scientist**
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**Study Manager**
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**Monitor**
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## I.2 Advisory committees

This feasibility study will not involve any Data Monitoring Committee, Steering Committee, Safety Committee or Adverse Event Advisory Committee as no clinical/therapeutic intervention is being applied or evaluated, the participants will be invited to wear external monitoring equipment during the study visit. Additionally, the study will be conducted at one center only which has experience and operating procedures related to the use of this monitoring equipment.

### *I.2.1 DataMonitoring Committee*

No Data Monitoring Committee will be installed for this clinical study as no interventions intended to prolong life or reduce risk of a major adverse health outcome (e.g., cardiovascular events) are evaluated, for which favorable or unfavorable study results suggest study

termination. Nor there are safety concerns suggesting the need for a Data Monitoring Committee.

### *I.2.2 Publication Committee*

There are no plans to form a publication committee

## I.3 Records and reports

### *I.3.1 Investigator records*

At a minimum, the following records must be kept by the investigator:

- Clinical Investigation Plan and, any amendments
- EC notification, correspondence and approval
- EC voting list
- Medtronic and EC approved Patient Informed Consent
- Fully signed clinical investigation agreement and confidentiality agreement (if not included in the clinical investigation agreement)
- Insurance certificates
- Completed Delegated Task List and Curriculum Vitae of all investigation site personnel
- Training documentation of all investigation site personnel
- Relevant communications that pertains to the clinical study
- Subject identification log
- Signed, dated and fully executed informed consent forms
- Fully executed CRFs and corrections
- Device accountability records
- Final report

All study related information and records are subject to inspection and must be retained for a period of two years after study termination or closure or longer if required by local or hospital regulations

### *I.3.2 Investigator reporting responsibilities*

The investigator is responsible for the preparation (review and signature) and submission to Medtronic of all case report forms and deviations from the clinical investigation plan. If any action is taken by the EC with respect to the study, the information must be forwarded to Medtronic immediately. Reports are subject to inspection and to the retention requirements as described above for investigator records. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in Table 4.

**Table 4: Investigator Reports**

| Reports | Submit To | Description / Constraints |
|---|---|---|
| Withdrawal of EC approval | Medtronic | Notification immediately after the investigator first learns of withdrawal of EC approval. |

| Table 4: Investigator Reports | | |
|---|---|---|
| **Reports** | **Submit To** | **Description / Constraints** |
| Study Deviations | Medtronic, EC, as applicable | Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance.<br><br>Note: When relevant, Ethics Boards, competent authorities or the appropriate regulatory bodies should be informed. |
| Failure to obtain informed consent | Medtronic, EC | Notification within five working days. |
| Progress Reports and final report (if required) | Medtronic, EC | Provide if required by local law or Ethics Board |

### *I.3.3 Sponsor records*

At a minimum, the sponsor will keep the following records:

- All essential study documents and correspondence that pertains to the clinical study
- CIP and any amendments
- Curriculum vitae of investigators and site staff
- Delegated Task Lists and training records of investigators and site staff
- EC approvals/notifications/voting list
- Signed Clinical Investigation Agreements
- Insurance certificates
- A copy of Device accountability records
- Shipping records for study devices/equipment
- Medtronic and EC approved Patient Informed Consents
- monitoring visit reports
- Study training records for site personnel and Medtronic personnel involved in the study.
- Final report of the study.
- Fully executed CRFs and corrections

Medtronic records and reports will be stored in locked file cabinets at Medtronic during the course of the study. After closure of the study, all records and reports will be archived indefinitely.

### *I.3.4 Sponsor reporting responsibilities*

Medtronic shall prepare and submit the complete, accurate, and timely reports listed in Table 5. In addition, Medtronic shall, upon request of reviewing EC or regulatory agency, provide accurate, complete and current information about any aspect of the study.

**Table 5: Sponsor Reports**

| Report | Submit to | Description |
|---|---|---|
| Early termination or suspension of the clinical study | Investigator | Provide prompt notification of termination or suspension and reason(s) |
| | EC | Inform the EC promptly, if required per local law |
| Withdrawal of EC approval | Investigator | Notify all applicable investigators, if required by local laws or EC |
| Progress Reports | EC | Submit to EC, if required per local law |
| Final Report | EC | Submit to EC, if required per local law |
| Study Deviation | Investigator | Site specific study deviations will be submitted to the investigator quarterly. |

### *I.3.5 Record retention*

The investigator must retain the Investigator Site File, patient medical files and CRFs in accordance with local law and regulations.

The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

## I.4 Miscellaneous

### *I.4.1 Insurance*

The Bakken Research Center B.V is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the EC.

### *I.4.2 Subject compensation and indemnification*

The subjects enrolled will not receive any compensation for the participation in the study. They will only receive compensation for reasonable, necessary and properly documented (e.g., copy of train ticket) travel expenses (for example, kilometer compensation, public transportation or parking costs) in connection with participation in the study.

### *I.4.3 Subject confidentiality*

The study sponsor will collect data in such way that no subject can be identified, and monitor study records. All records and other information about subjects participating in this study will be treated as confidential.

Participating subjects will not be identified by name in any published reports about the study.

# J RISKS AND BENEFITS

## J.1 Anticipated Clinical Benefits

The objective of this study is to collect data from the subjects with no direct clinical benefit to them. However, this study design will be the first to evaluate the feasibility of using the Reveal LINQ™ to monitoring walking patterns, which could be useful for the identification of frailty in its early stage, which is important because interventions may potentially prevent, or delay the clinical consequences of frailty, therefore the benefit may be for future patients.

## J.2 Risks

Since the study devices will not be used for therapeutic purposes, but just to collect accelerometer data and considering the nature and duration of the study, no major risks to the subjects are expected with this study. It may be possible to anticipate local events at the level of the study tool/product placement (i.e. Allergenic reaction, Skin irritation) - which the medical grade adhesive placed below the device should prevent - and/or events related to the physical execution (i.e. accidental fall) of the walking exercises.

Any further detail coming from risk assessment on potential risks and risks minimization will be provided under a separate cover.

# K REFERENCES

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# L. APPENDICES

## L.1 Names and addresses

### *L.1.1 List of participating investigation site and investigator*

| Investigator | Site |
|---|---|
| Dr. Kenneth Meijer, Maastricht University | Maastricht University, NUTRIM School of Nutrition and Translational Research in Metabolism of the Faculty Health, Medicine and Life Sciences, Minderbroedersberg 4-6, 6211 LK Maastricht, The Netherlands |

## L.2 Case Report Forms

Case Report Form will be provided it under a separate cover.

## L.3 Abbreviations

| | |
|---|---|
| ADE | Adverse Device Effect |
| AE | Adverse event |
| AEAC | Adverse Event Advisory Committee |
| CA | Competent Authority |
| CAREN | Computer Assisted Rehabilitation Environment |
| CV | Curriculum Vitae |
| DTL | Delegated Task List |
| CIP | Clinical Investigation Plan |
| CRF | Case Report Form |
| DMC | Data Monitoring Committee |
| EC | Ethics Committee |
| CRF | Case Report Form |
| ETGUG | Expanded Timed Get-Up-and-Go |
| FTSTS | Five Times Sit to Stand |
| 6MW | Six Minute Walk |
| 4MGS | Four Meter Gait Speed |

| | |
|---|---|
| FU | Follow up |
| HD | Hard Drive |
| HF | Heart Failure |
| HRV | Heart rate variability |
| NHYA | New York Heart Association |
| PIC | Patient Informed Consent |
| SD | Secure Digital |
| SOP | Standard operating procedure |