Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Frailty Walking Patterns (FRAP) Study
Clinical Investigation Plan Version	Version 1, 17 FEB 2016
Sponsor/Local Sponsor	Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands
Document Version	V. 1.0 20 APR 2017

Table of Contents

1. Version History 3

2. List of Abbreviations and Definitions of Terms 3

3. Introduction 3

4. Study Objectives 3

5. Investigation Plan 4

6. Determination of Sample Size 4

7. Statistical Methods 5

7.1. Study Subjects 5

7.2. General Methodology 6

7.3. Center Pooling 6

7.4. Handling of Missing, Unused, and Spurious Data and Dropouts 7

7.5. Adjustments for Multiple Comparisons 7

7.6. Demographic and Other Baseline Characteristics 7

7.7. Treatment Characteristics 7

7.8. Interim Analyses 7

7.9. Evaluation of Objectives 7

7.10. Safety Evaluation 8

7.11. Health Outcomes Analyses 8

7.12. Changes to Planned Analysis 8

8. Validation Requirements 8

9. References 8

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	Marco Di Bacco, Therapy SME/Biostatistician

2. List of Abbreviations and Definitions of Terms

Abbreviations should be indicated in parentheses at first appearance in the text. Abbreviations should appear in alphabetical order.

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

3. Introduction

The FRAP Study is a prospective, non-randomized, single-center, post-market interventional study.

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.

The intended use of the Reveal LINQ in this study is not for medical purposes, but exclusively for technical reasons, therefore the Reveal LINQ is considered a non-medical device in this study. The Reveal LINQ device is used externally with the investigational software RAMware REEF Research System, Rev 1.0 onboard. The software is downloaded through the 2090 programmer. Since RAMware REEF Research System is an accessory to the Reveal LINQ it is also classified as a non-medical device.

Subjects 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.

The Clinical Investigation Plan V. 1 17 FEB 2017 has been used to develop this Statistical Analysis Plan with the purpose to describe the Final Analysis foreseen for FRAP Study.

4. Study 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 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.

5. Investigation Plan

This is a prospective, non-randomized, single-center post-market interventional study. The Study will take place in the Netherlands at one investigation site. No randomization and no blinding will be used in this Study.

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

6. Determination of 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.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Disposition of patient will be reported following the STROBE Statement Checklist (2). Number of individuals at each stage of study (number of total assessed for eligibility, number enrolled, number analyzed) will be reported (see the flowchart example). Reason for not participation at each stage will be reported where known.

Table. Number of Subject Enrollments by Site

Site	Date of First Enrollment	Eligible patient	Subjects Enrolled (N = X)	Subjects Analyzed (N = X)
Xxxxx	XXDDDYYYY	N	X (Y%)	X (Y%)

7.1.2. Clinical Investigation Plan (CIP) Deviations

Reasons for deviation are:

- Patient informed consent procedure
- Patient eligibility criteria
- Study data collection and reporting

The following tables will describe study deviations:

Table. Types of Study Deviations by reason

Study Deviation Type	Number of Deviations (Number,% of Subjects)		
	Subjects in …. (N = N1)	Subjects in …. (N = N2)	Total Subjects (N = N)
Reason#1 Reason#1 ….	NE (NS, Y%) NE (NS, Y%) ….	NE (NS, Y%) NE (NS, Y%) ….	NE (NS, Y%) NE (NS, Y%) ….
Total	NE (NS, Y%)	NE (NS, Y%)	NE (NS, Y%)

Listing. Reason for exclusion

Reason for exclusion	Reason for excluding from analysis
Patid#1	Text
Patid#2	
….	
Patid#N	

.

7.1.3. Analysis Sets

All subjects who signed the informed consent document will be defined as the Full Analysis Set (FAS). 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 Population is defined as subjects that are enrolled in the study, who signed Informed Consent Form (ICF), fulfilled the inclusion and exclusion criteria and with a good quality of Holter, LINQ, Actigraph and CAREN data recordings and who completed at least one of the walking exercises. 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.

Population set	Baseline assessment	Primary and Secondary Endpoints
FAS		
Analysis Population	√	√

7.2. General Methodology

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.

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.

7.3. Center Pooling

Since this is a single center study this section is not applicable.

7.4. Handling of Missing, Unused, and Spurious Data and Dropouts

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.

7.5. Adjustments for Multiple Comparisons

No adjustments for multiple comparisons or multiple look at data will be performed.

7.6. Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristic variables for Analysis Population. This will include mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables.

Demographic and Baseline variables will be collected through a password protected excel file database and described with Tables, Listings and Figures as appropriate.

7.7. Treatment Characteristics

Since the study procedures consist in performing the above mentioned exercises during a single session, this section is not applicable.

7.8. Interim Analyses

Interim analyses are not planned for this study.

7.9. Evaluation of Objectives

No formal statistical hypothesis will be tested.

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.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

7.10. Safety Evaluation

Since the Reveal LINQ will not be used for medical purposes but exclusively for technical reasons and therefore it is considered a non-medical device in this study, no Safety outcomes analyses will be performed.

7.11. Health Outcomes Analyses

No health outcomes analyses were planned in the protocol.

7.12. Changes to Planned Analysis

No major modifications are required from the analyses planned in the protocol.

8. Validation Requirements

To ensure the quality of the results provided for the study in the form of tables, listings and figures the following processes are used:

- Statistical analysis will be done by qualified MDT personnel following best practices.
- Statistical results will be reviewed and confirmed by a second MDT statistician or designee.

According to Medtronic SOPs the validation will be implemented for statistical outputs

9. References

1. http://www.strobe-statement.org/index.php?id=available-checklist