STATISTICAL ANALYSIS PLAN

Post-Embolic Rhythm Detection with Implantable versus External Monitoring (PER DIEM) Study

Feb 2019

Version 1.0

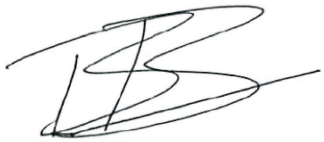
Trial Registration ClinicalTrials.gov Identifier: NCT02428140

Statistical Analysis Plan v1.0

Clarification Note:

The statistical analysis plan v1.0 (SAP) defines the primary outcome using the endpoint from the protocol version 4.0 (dated February 22, 2016). There was an additional amendment to the protocol on April 26, 2016, where the AF adjudication process was specified, and the primary endpoint was defined as **definite AF lasting 2 minutes or more, including atrial flutter**. Version 1.0 of the SAP incorrectly carried forward the primary endpoint based on the Feb 22, 2016 version 4.0 protocol rather than the updated definition of the primary endpoint as approved by the steering committee and amended to the protocol on April 26, 2016.

SIGNATURES OF APPROVAL



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LIST OF ABBREVIATIONS

AE	Adverse Event
AIS	Acute Ischemic Stroke
ANCOVA	Analysis of Covariance
CI	Confidence Interval
ECG	Electrocardiogram
EMS	Emergency Medical Services
e-CRF	Electronic Case Report Form
ICH	Intracerebral Hemorrhage
IQR	interquartile range
mRS	Modified Rankin Scale
NCCT	Non-contrast Computed Tomography Scan
NIHSS	National Institutes of Health Stroke Scale
PERDIEM	Post-Embolic Rhythm Detection with Implantable versus External Monitoring (PER DIEM) Study
PP	Per Protocol
SAE	Serious Adverse Event
SD	Standard Deviation

1.0 INTRODUCTION

This document provides the details of statistical analyses planned for the PERDIEM study. In addition, it discusses the statistical issues relevant to these analyses (e.g., sample data to be used and missing data).

1.1 Background

The PERDIEM study is a randomized trial comparing 30-day external loop recording cardiac rhythm monitoring to implantable loop recorder for 1-year, for stroke patients. The study included stroke patients with various mechanisms of stroke. The study is conducted in Calgary (1 tertiary site) and Edmonton (1 tertiary, 1 community site). The planned sample size is 300 patients.

1.2 Primary Objectives

The implantable loop recorder (ILR) plus remote monitoring will diagnose more paroxysmal AF / atrial flutter and provide better assessment of the total burden of AF resulting in a greater proportion of patients started on an OAC versus the external loop recorder (ELR) strategy.

1.3 Study Design

Randomized, open label trial comparing two different extended ECG monitoring strategies for the detection of paroxysmal AF / atrial flutter after ischemic stroke or transient ischemic attack (TIA).

Inclusion Criteria:

1. Informed consent from the patient
2. Age ≥ 18 years
3. Diagnosis of the index event* made by a stroke specialist of an acute ischemic stroke or TIA occurring within the last 6 months. The event must be either:
   i) arterial ischemic stroke confirmed by neuroimaging; or ii) transient ischemic attack with DWI positive lesion on MRI
4. The patient is expected to survive at least 6 months
5. At least one 12-lead ECG has already been obtained as part of the routine clinical post-stroke/TIA work-up, and no ECGs have shown any episodes of atrial fibrillation or atrial flutter

6. The patient is being actively investigated for the etiology of the stroke/TIA event and additional cardiac monitoring is desired to screen further for the possibility of occult paroxysmal atrial fibrillation/flutter

Exclusion Criteria:

1. Previously documented atrial fibrillation/flutter.
2. Planned carotid endarterectomy or carotid artery stenting within 90 days.
3. Any condition for which there is already an indication for long term OAC.
4. Pacemaker or ICD device that would allow for detection of AF / atrial flutter.
5. Work-up for stroke that has already included extended (>7 days) external ECG.
6. Stroke and/or comorbid illness will prevent completion of planned follow-up assessments.

1.4 Sample Size Determination

A total of 300 patients will be randomized. This sample size reflects 8% inflation for cross over (2% with either strategy) and loss to follow-up (5% in each group).
This sample size provides 85% power to assess a clear difference in rates of atrial arrhythmia (AF / atrial flutter) that results in initiation of additional anti-platelet or OAC therapy between the two strategies (two- sided alpha of 5%). This estimate is based on the following assumptions:

1. Equal allocation (1:1) to ELR for 30 days vs. ILR plus remote monitoring for 12 months.
2. 10% rate of AF / atrial flutter that results in initiation of additional anti-platelet or OAC therapy in the ELR and 20% rate of this endpoint in the ILR plus remote monitoring group.

This estimate was derived using the Two Independent Proportions (Null Case) Power Analysis estimation method (PASS 2012).

Table 1. Schedule of Assessments

	Pre-study (routine clinical studies)	Baseline (Day 0)	Day 30 (±1 week)	6 months (± 2 weeks)	12 months +/- 4 weeks (telephone)	24 month +/-4 weeks (telephone)
Holter (optional)	X	*Reports collected*				
Echo (optional)	X	*Reports collected*				
Neuroimaging (CT or MRI)	X	*Reports collected*				
Vascular Imaging (CTA/MRA/doppler)	X	*Reports collected*				
ECG	X	*Reports collected*	X	X		
Informed consent, randomization		X				
Demographics		X				
Medical History		X			X	X
Vital signs		X*	X	X		
Antithrombotic and thrombolytic therapy		X	X	X	X	X
NIHSS		X				
CHA2DS2-VASc		X				
Stroke Subtype / Etiology (OCSS/TOAST)		X	X	X	X	X
Modified Rankin		X		X		
EQ-5D		X		X		
Adverse event assessment		X	X	X	X	X
New stroke/TIA, cardiac events		X	X	X	X	X
Return monitor / compliance diary			X			

1.5 Blinding

The study is conducted in an open-label non-blinded manner.

1.6 Definitions

Baseline: A subject's baseline value for a given endpoint or parameter is defined as his/her latest measurement taken prior to randomization.

Prior and Concomitant Medications: Prior medications are defined as those taken within three days of treatment initiation. Concomitant medications are defined as those taken during study follow-up. All prior and all concomitant medications will be recorded on the electronic case report form (e-CRF).

2.0 ANALYSIS POPULATIONS

2.1 Intent-to-Treat Population

The study will be analysed by intention to treat (intention to monitor, in this case).

2.2 Per Protocol (PP) Population

The PP population will include all patients who underwent monitoring according to protocol and completed at least 1 month of follow-up.

3.0 INTERIM ANALYSES

There will be no interim analysis.

4.0 MISSING DATA AND DATA TRANSFORMATION

All efforts will be undertaken to avoid missing data. No planned imputation will be undertaken.

5.0 STATISTICAL METHODS

The software used for all summary statistical analyses will be STATA v16.1.

Percentages will be rounded to one decimal place, except 0% and 100% will be displayed without any decimal places. Minima and maxima will be rounded to the precision of the original value; means and medians will be rounded to one decimal place greater than the precision of the original value; SDs will be rounded to two decimal places greater than the precision of the original value. P-values will be reported to four decimal places (0.xxxx), with values less than 0.0001 presented as <0.0001.

Inferential analyses will generally include statistics such as 2-sided 95% confidence intervals (CI), and p-values. Unless stated otherwise, all statistical tests will be 2-sided Subject Disposition.

The primary outcome (atrial fibrillation) and the first composite secondary outcome (atrial fibrillation or death) will be analysed by intention to treat, using time-to-event analysis. Secondary outcomes will be reported as proportions.

5.1 Protocol Deviations and Protocol Violations

5.2 Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized with descriptive statistics for each treatment group. Demographic variables include, but are not limited to: age, sex, race-ethnicity, weight as determined in hospital (in kg). Baseline characteristics include but are not limited to: prior use of alteplase (tPA), intended first thrombectomy approach (stent retriever or thrombus aspiration

6.0 EFFICACY ANALYSIS

6.1.1 Primary Outcome

The primary outcome will be the rate of detection of an atrial arrhythmia (AF / atrial flutter) that results in initiation of additional anti-platelet or OAC therapy as per usual clinical practice.

The first secondary outcome will be the composite of detection of an atrial arrhythmia (AF / atrial flutter) that results in initiation of additional anti-platelet or OAC therapy as per usual clinical practice or death (whichever occurs first).

Secondary Outcomes:

1. Recruitment rates.
2. Compliance with assigned therapy (accept ILR, conduct at least 80% of ELR assessments)
3. Time to detection of first episode of atrial fibrillation / atrial flutter ≥ 30 seconds.
4. Costs for all cardiac and non-cardiac investigations related to etiologic workup of index stroke / TIA.

5. Total duration of any detected atrial fibrillation / atrial flutter.
6. Study related adverse events / serious adverse events.
7. Clinical recurrence of ischemic stroke / TIA, death, hemorrhagic stroke, major adverse bleeding, or death.
8. Relationship between duration detected AF and clinically silent strokes, volume of leukoaraiosis, numbers of cerebral microbleeds
9. Presence of cognitive impairment, progression of 12 months
   Association between baseline clinical characteristics (e.g. comorbidities, burden of supraventricular ectopy on Holter, left atrial dimension) and subsequent detection of AF

6.1.2 Statistical Hypothesis

The primary hypothesis is: the rate of the primary outcome is 2-fold or more greater in the ILR group compared to the ELR group at 1 year (HR > 2.0)

6.1.3 Primary Efficacy Analysis

Two sample comparison of proportions or patients reaching the primary outcome at one year, unadjusted.

6.2 Secondary Efficacy Analyses

Two sample comparison of proportions or patients reaching the secondary outcome at one year, unadjusted.

Time to event analysis on the primary and secondary outcome.

Safety analyses by proportion of adverse events.