Statistical Analysis Plan

[redacted]

VICTOR

Val**I**dation of **C**ardioMEMS HF Sys**T**em Cardiac **O**utput Algo**R**ithm IDE

NCT05428384

Statistical Analysis Plan (SAP)

Version B

June 8, 2022

[redacted]

Statistical Analysis Plan

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1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is intended to provide a detailed and comprehensive description of the planned methodology and analysis to be used for Clinical Investigational Plan (CIP) [redacted], the Validation of CardioMEMS HF System Cardiac Output Algorithm (VICTOR) IDE clinical investigation. This plan is based on Version B Clinical Investigation Plan.

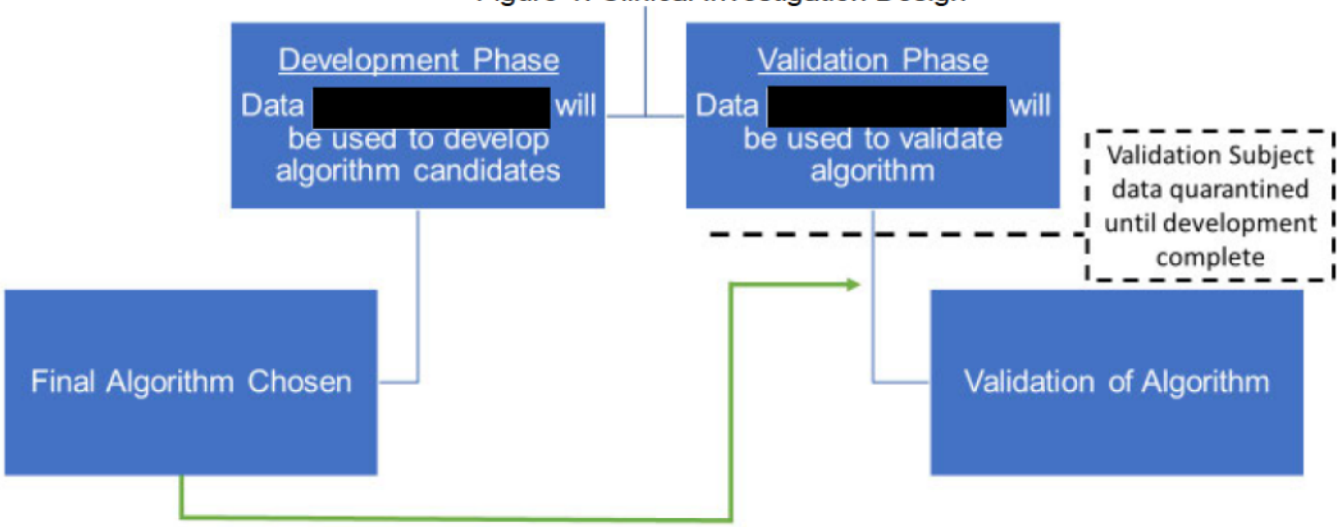
1.2 Clinical Investigation Objectives

There are two primary objectives of this clinical investigation. The first objective is to finalize development of the algorithm estimating CO by collecting paired cardiac Magnetic Resonance Imaging (cMRI) measurements of CO, as well as other parameters of heart function, and CardioMEMS HF System readings in the same subject. The second objective of this clinical investigation is to use data collected during the validation phase, distinct from the subjects within the development phase, to evaluate the agreement between the CardioMEMS HF System-derived CO and the CO values from cMRI CO values in patients previously implanted with the commercially available CardioMEMS HF System.

1.3 Clinical Investigation Design

This is a prospective, multi-center, clinical study of patients previously implanted with the commercially available CardioMEMS PA Sensor. [redacted]. Each subject will have six CardioMEMS HF System readings paired with three cMRI scans at each study visit and measurements completed for each subject will be under nominally the same conditions. The measurements will be taken in patients who already have the CardioMEMS PA Sensor implanted and subject data will be collected in two, sequential phases, (Figure 1): 1) Data used to develop an algorithm to estimate CO, termed the development phase; and 2) Data used to validate the CO algorithm, termed the validation phase. [redacted] During the development phase potential algorithms will be assessed to determine the optimal algorithm for estimating CO. Once identified, the selected algorithm will then undergo validation [redacted] Additional subjects may be added to both the development and validation cohorts based on development needs, [redacted]

Figure 1: Clinical Investigation Design



During validation, measurement data from a distinct subject cohort to subjects included in the development phase will be used to determine if the chosen algorithm meets the validation criteria.

[redacted] The Sponsor has designed this clinical investigation to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risk Analysis in Section 15.0 of this clinical investigation plan for details.

1.4 Endpoints

1.4.1 Primary Endpoint and Rationale

The primary endpoint of this clinical investigation is to estimate CO from CardioMEMS HF System data. The estimated CO will be evaluated for agreement between the CardioMEMS HF System-derived CO and the CO values from cMRI in patients with the CardioMEMS HF System. Specifically, the primary endpoint will compare the two paired measurements taken at rest, collected during the 3-month follow-up visit from subjects allocated to the validation phase. Paired measurements will be compared using Deming regression. Agreement will be assessed through estimating the regression parameters of slope and intercept and evaluating their proximities to unity (slope=1 and intercept=0).

[redacted]

1.4.2 Descriptive Endpoints

Paired measurements will be evaluated for the following data samples:

1) Baseline measurements recorded at rest
2) Baseline measurements recorded following introduction of Dobutamine
3) All Baseline measurements
4) 3 Month measurements recorded at rest
5) 3 Month measurements recorded following introduction of Dobutamine
6) All 3 Month measurements
7) Baseline and 3 Month measurements recorded at rest
8) Baseline and 3 Month measurements recorded following introduction of Dobutamine
9) All Baseline and 3 Month measurements

Each data sample will be analyzed using Deming regression methods described for the primary endpoint, Bland-Altman methods, and relative error will be computed using the method proposed by Shoemaker et al.[4]

1.5 Blinding

Investigators and subjects will not be blinded.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Enrolled Population

The Enrolled population includes all enrolled subjects (development phase and validation phase),

- Informed Consent obtained
- Inclusion/Exclusion criteria satisfied

2.1.2 Per Protocol (PP) Population

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

Continuous variables will be summarized with the numbers of observations, means and standard deviations, with quartiles, minimum and maximum.

2.2.2 Descriptive Statistics for Categorical Variables

Categorical variables will be summarized with subject counts and percentages/rates.

2.3 Endpoint Analysis

2.3.1 Primary Endpoint

The primary endpoint of this clinical investigation is to estimate CO from CardioMEMS HF System data. The estimated CO will be evaluated for agreement between the CardioMEMS-derived CO and the CO values from cMRI in patients with the CardioMEMS HF System. Specifically, the primary endpoint will compare the two paired measurements taken at rest, collected during the 3-month follow-up visit from subjects allocated to the validation phase. [redacted]

[redacted]

[redacted]

2.4 Sample Size Calculations

[redacted]

[redacted]

[redacted]

2.5 Interim Analysis

No formal interim analyses are planned for this study. As such, no formal statistical rule for early termination of the trial is defined.

2.6 Timing of Analysis

[redacted]

2.7 Trial Success

The trial will be considered successful if Deming regression 95% confidence interval of the slope contains 1 and the 95% confidence interval of the intercept contains 0 for the primary endpoint.

2.8 Subgroups for Analysis

There are no planned subgroup analyses for this trial.

2.9 Handling of Missing Data

The purpose of this trial is to validate an algorithm by comparing measurements using two methods. In order to evaluate the primary endpoint, a physical measurement must be recorded from each method, and thus, there is no planned sensitivity analysis or imputation procedure for missing data.

2.10 Poolability

This trial is designed to be conducted in up to 15 centers in the United States. Given the sample size allocated for the primary endpoint, individual centers may not have adequate sample to assess individual center effect. Therefore, no formal poolability analysis is planned with overall results deemed poolable for interpretation of the study endpoints.

2.11 Multiplicity

This study includes a single primary endpoint. Thus, no Type I error adjustment is necessary.

2.12 Adjustments for Covariates

Unless otherwise specified, no adjustments for covariates will be made for any of the variables in the analyses.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized for the subjects in the Enrolled population: gender, age, ethnicity, race, cardiac disease history, medical history and co-morbidities, vital signs, and laboratory assessments.

3.2 Adverse Events

Adverse events are defined in Section 7.1 of the Clinical Investigational Plan. All adverse events will be summarized for all subjects in the Enrolled population as number and percentage of all subjects who experience the event and the total number of events.

3.3 Subject Early Termination

Subject early termination reasons including deaths, withdrawals, lost-to-follow-up, etc. will be summarized by analysis population at all scheduled visits.

3.4 Protocol Deviation

Protocol deviations will be summarized by major and minor categories for subjects in whom a protocol deviation was reported.

3.5 Descriptive Endpoints or Additional Data

Descriptive endpoints will evaluate data for the following data samples:

1) Baseline measurements recorded at rest
2) Baseline measurements recorded following introduction of Dobutamine
3) All Baseline measurements
4) 3 Month measurements recorded at rest
5) 3 Month measurements recorded following introduction of Dobutamine
6) All 3 Month measurements
7) Baseline and 3 Month measurements recorded at rest
8) Baseline and 3 Month measurements recorded following introduction of Dobutamine
9) All Baseline and 3 Month measurements

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

[redacted]

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
CI	Confidence Interval
cMRI	Cardiac Magnetic Resonance Imaging
CIP	Clinical Investigation Plan
CO	Cardiac Output
MRI	Magnetic Resonance Imaging
OLR	Ordinary Least-squares Regression
SAP	Statically Analysis Plan
SD_a	Analytical Standard Deviation

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7.0 APPENDICES

[redacted]

APPENDIX B: SAMPLE SIZE CALCULATION DETAILS

[redacted]

[redacted]

[redacted]

[redacted]

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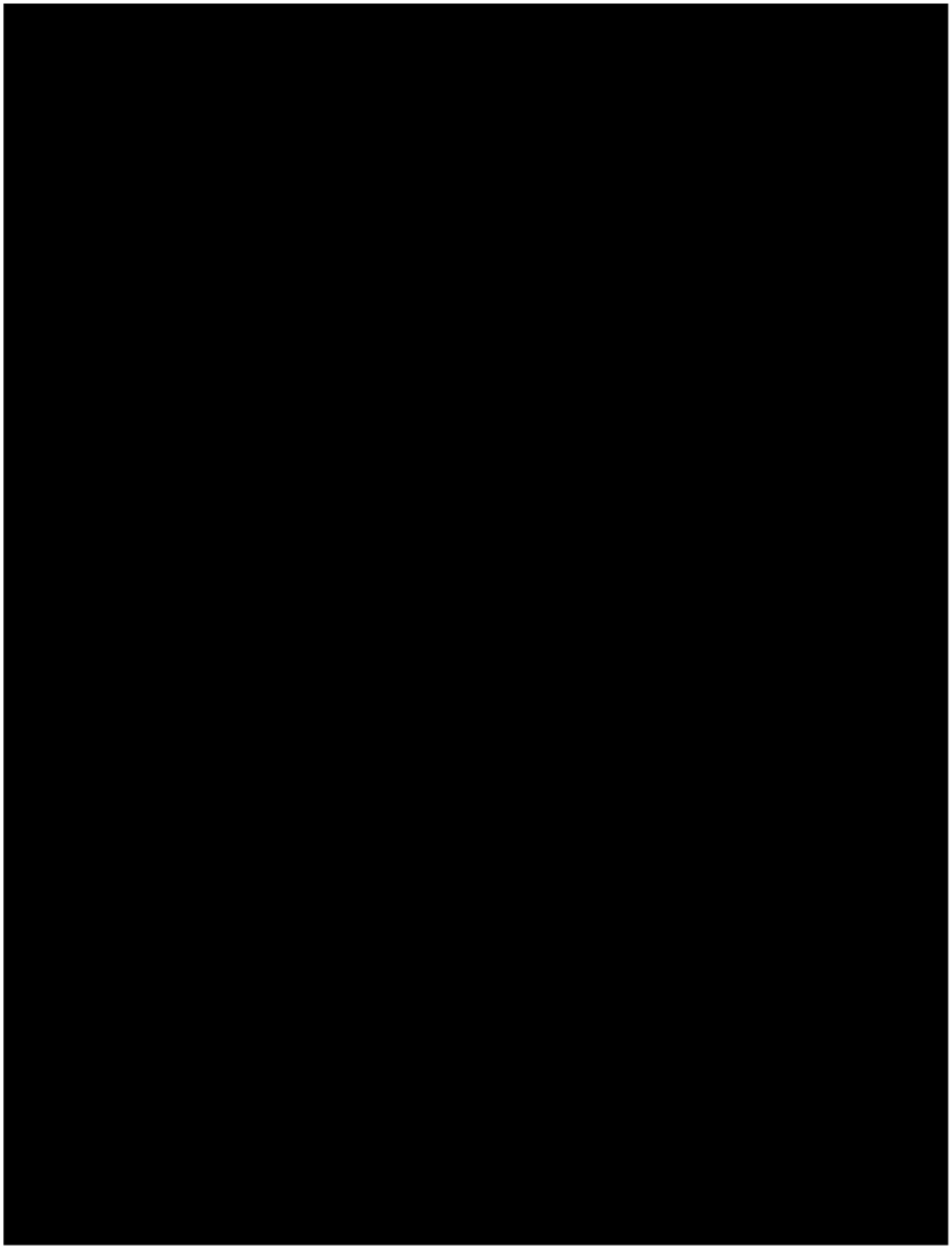

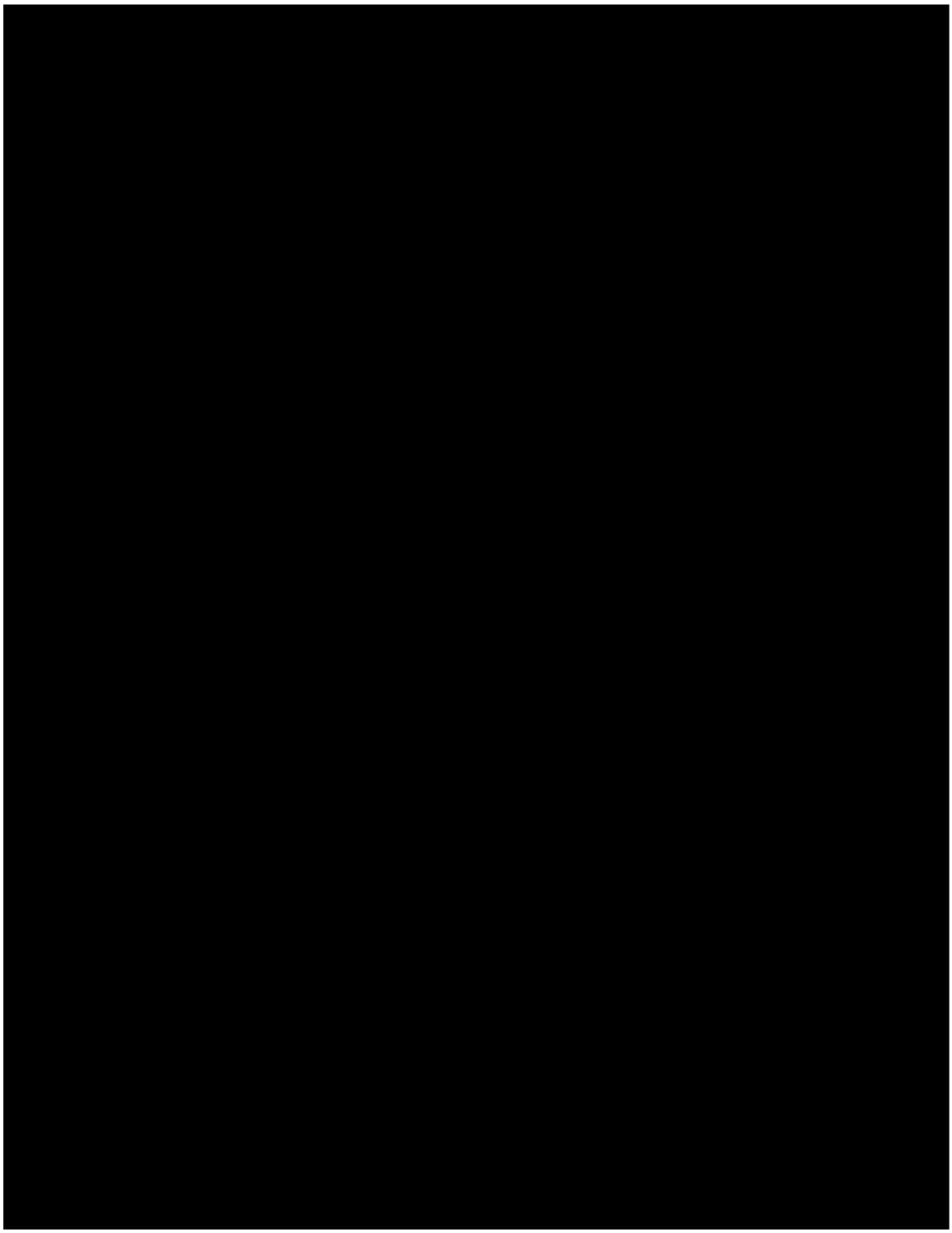

APPENDIX D: STATISTICAL ANALYSIS PLAN REVISIONS

Ver	Details	Rationale
A	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Statistical Analysis Plan

Ver	Details	Rationale
[redacted]	[redacted]	[redacted]