Statistical Analysis Plan

Protocol Version 8.0

R2B36 - Efficacy and Safety of ICD Remote Monitored Exercise Testing to improve Heart Failure Outcomes:

REMOTE HF-ACTION (Pilot Randomized Controlled Trial)

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1 LIST OF ABBREVIATIONS

ACC	American College of Cardiology
AE	Adverse Event
AHA	American Heart Association
CI	Confidence Interval
CR	Cardiac Rehabilitation
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy Device
DCRI	Duke Clinical Research Institute
DUHS	Duke University Health System
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HF	Heart Failure
HIPAA	Health Insurance Portability and Accountability Act
ICD	Implantable cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITT	Intention To Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
MLM	Multilevel Modeling
NESTcc	National Evaluation System for health Technology Coordinating Center
NIH	National Institutes of Health
NYHA	New York Heart Association
PA	Physical Activity
PHI	Protected Health Information
PHQ-9	Patient Health Questionnaire 9
PI	Principal Investigator
PP	Per Protocol
PRO	Patient-Reported Outcome
QC	Quality Control
QOL	Quality of Life
SA	Safety Analysis
SAP	Statistical Analysis Plan
SD	Standard Deviation
US	United States

2 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to give a brief overview of the study design and study objectives, outline the types of analyses and presentations of data relevant to the study objectives, and provide a detailed description of the method in which the statistical analyses will be conducted to meet protocol objectives.

The analyses described in this SAP as well as the production of tables and listings will be performed using Version 9.4 or newer of SAS® (Cary, North Carolina) on Linux operating system. Additional statistical software may be used as needed.

3 STUDY OBJECTIVES

3.1 Primary Objective(s)

Compare the effects of remote cardiac rehabilitation (CR) on daily device measured physical activity (PA) over 12 weeks versus usual management.

- *Primary Outcome Measure*: Trajectory of the median Abbott ICD and CRT-D device measured daily PA obtained over the 1 month before randomization (baseline) and week 4, week 8, and week 12 after randomization among patients randomized to remote CR versus usual management.

3.2 Secondary Objectives

3.2.1 Secondary Objective #1 Compare the effect of remote cardiac rehabilitation on baseline and 12 week Kansas City Cardiomyopathy Questionnaire (KCCQ) HF symptom severity scores versus usual management.

- *Outcome Measure*: Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) HF symptom severity scores from the baseline to the 12 week

3.2.2 Secondary Objective #2 Report Adverse Events of the remote cardiac rehabilitation during the intervention period

- *Outcome Measure*: Adverse Events: heart failure hospitalization, fracture, myocardial infarction, serious adverse arrhythmia, and ICD therapy

3.2.3 Secondary Objective #3 Association between daily PA measured by the Abbott ICD or CRT-D device and in KCCQ HF symptoms severity score measured between baseline and end of follow up.

- *Outcome Measure*: Change in daily PA measured by the Abbott ICD or CRT-D device between baseline and week 12 of treatment period and change in KCCQ HF symptoms severity score measured between baseline and end of follow up

4 STUDY DESIGN

4.1 Overall Design

This pilot study will be a single center randomized controlled trial involving 13 medically stable outpatients with HF, reduced ejection fraction, and previously implanted ICD or CRT-D devices followed longitudinally on the Abbott Medical Merlin remote patient monitoring network. Patients will be randomized in a 1:1 fashion to usual care plus a remotely administered home based weekly prescription for aerobic exercise or usual care alone. Patients will be screened based on inclusion and exclusion criteria which are located in Section 5 of protocol.

4.1.1 Analysis Population

Effectiveness will be assessed in the Intent-To-Treat (ITT) population and in the As-treated (AT) populations. Both analysis populations will be examined for all objectives, however, the success of the trial will be based on the analysis of the ITT population.

- Intent-to-Treat (ITT) Population: All participants who were randomized. Subjects will be analyzed according to the treatment group to which they were randomized, regardless of whether they received that intervention. This population will include participants who may have received the wrong intervention and have protocol violations.
- Safety Analysis (SA) Population: All participants who had at least one session on the study app.
- As-Treated (AT) Population: The treatment assignment of this population will be based on the actual treatment patients received, not the treatment the patients were randomized to receive.

  Deviations related to treatment compliance with randomized intervention: Participants not meeting the adherence requirement of completing at least 2/3 of expected app check in sessions will be considered a protocol deviation and excluded from the AT analysis population.

Any additional exclusion of any subject from a data presentation, other than those described above and in the section on handling of missing data, will be considered on a case-by-case basis, and will be described in the final study report.

4.1.2 Study Periods

For each enrolled participant, the study will consist of 3 Periods as follows:

- Screening/Enrollment Period – screening/enrollment begins after IRB approval prior to Baseline.
- Baseline Period - the first month (Day -30 – Day -1) of the study prior to the treatment period.
- Treatment Period - Following the baseline period, patients will be randomized 1:1 to either remote CR or usual care through the CR app and will be followed up for 12 weeks (Day 1 – Day 84).

4.2 Sample Size and Power

Sample size was determined based on the following power calculations:

For aim 1, a sample size of 28 subjects with 1:1 randomization each measured at 4 time points provides 81.1% power to detect a 15 minute per day difference in PA between groups at week 12 with a standard deviation of 19 minutes per day within each group and a within subject correlation of 0.7. A test based on a mixed-model analysis is anticipated at a significance level of 0.05.

For aim 2, a sample size of 50 subjects with 1:1 randomization provides 80.2% power to detect an 8% difference in KCCQ score between groups with a standard deviation of 10 in KCCQ score within each group and an alpha of 0.05.

4.3 Randomization and Blinding

Treatment assignment will be randomized in a 1:1 fashion. Randomization will be performed in the Pattern Health App. Neither the patient nor the study team will be blinded to treatment assignment. Randomization will be stratified based on patient sex and non-ischemic versus ischemic cardiomyopathy etiology.

5 MODIFICATIONS

5.1 Modifications to the Approved Clinical Study Protocol

There are no modifications from the clinical study protocol (Version 8, dated June, 24 2022) that impact statistical analysis.

5.2 Modifications to the Approved Statistical Analysis Plan

This is the first version of the SAP for the analysis.

6 STATISTICAL ANALYSIS

6.1 General Considerations

6.1.1 General Analysis Conventions

Categorical variables will be presented as counts and percentages of non-missing values. Continuous variables will be presented as means, standard deviations, medians, as well as minimums and maximums, and the number of non-missing values. Missing data will be handled as outlined in section 6.8. Unscheduled assessments will not be included in analyses, but may be included in listings. Appropriate rounding will be performed for the summary statistics. The number of significant digits for the mean and standard deviation will be one and two more than the number for the reported values, respectively. Minimum and maximum values will be presented with the same precision as the original data. Percentages will be presented with one decimal. All statistical tests will be two sided unless stated otherwise. Histograms will be used to assess the normality of the data. Unless otherwise specified below, baseline values will be the last collected value prior to device use.

Statistical tests used will be two-sided, with α=0.05 as the level of significance. An absolute magnitude of the correlation coefficient that is 0.1-0.29 indicating weak correlation, 0.3-0.49 as moderate correlation and 0.5-1.0 as strong correlation.

6.1.2 Documentation conventions

The analyses described in this SAP as well as production of tables and listings will be performed using Version 9.4 (or newer) of SAS on Linux operating system. Additional statistical software may be used as needed.

6.1.3 Verification of results

All tables, listings, and graphs will be verified and reviewed before considered final. The verification process will ensure that the numbers are produced by a statistically valid method and that the execution of the computations is correct. Suitably qualified personnel will perform the verification procedures.

6.2 Background Characteristics

6.2.1 Subject Disposition

The number of subjects in the study population the number of subjects who completed and prematurely discontinued the study will be presented. Reasons for premature discontinuation or withdrawal from the study will be summarized in a listing.

6.2.2 Demographics and Medical History

Baseline demographic and medical history data will be summarized by treatment group with descriptive statistics [non-missing values (n), mean, standard deviation (SD), standard error of mean (SEM), median value, maximum value, and minimum value] for quantitative parameters and with counts and percentages

(or proportions) for categorical parameters using both the ITT and AT populations including appropriate p values to test the effectiveness of randomization. A listing will also be provided.

6.3 Primary Endpoint Analyses

P1: Compare the trajectory of the median Abbott ICD and CRT-D device measured daily PA obtained over the 1 month before randomization (baseline) and week 4, week 8, and week 12 after randomization among patients randomized to remote CR versus usual management.

Analysis strategy for P1: The outcome variable for this objective is the median Abbott ICD and CRT-D device measured daily PA obtained over the 1 month before randomization (baseline) and week 4, week 8, and week 12 after randomization. This endpoint represents a summary measure. The hypothesis test will evaluate whether the trajectory of the mean Abbott ICD and CRT-D device measured in the remote CR treatment group is different from the trajectory in the usual management group. The test will be a multilevel modeling (aka mixed models) on trajectories of the outcomes over the study period. In the multilevel model, time (week of study), treatment group, and the interaction between treatment group and time will be handled as fixed effects. Time will be modeled as a continuous variable. The model will include random effects for subject-specific intercepts and slopes, with unstructured covariance for random intercepts and slopes.

Reporting for P1: Descriptive summaries of the median physical activity at baseline and 4 weeks, 8 weeks, and 12 weeks after randomization will be presented by treatment group. The estimated difference in slopes of trajectories from the CR and usual care treatment groups will be presented, along with the p-value for comparing the trajectories over the study period. If differences are noted with regard to baseline covariates adjusted analyses will be performed for the primary endpoint.

6.4 Secondary Endpoint Analysis

S1: Compare the change in mean HF symptom severity scores at baseline and 12 week as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ) among patients randomized to remote CR versus usual management.

Analysis Strategy for S1: The outcome variable for this objective is the mean change in HF symptom severity scores from 1 week before randomization (baseline) to 12 weeks, calculated as the HF symptom severity scores in week 12 minus the mean of baseline period. The hypothesis test will evaluate whether the mean change in the remote CR treatment group is different from the mean change in the usual management group. The test will be a two-sample t-test allowing for unequal variances.

Reporting for S1: Descriptive summaries of the mean physical activity at baseline and 12 weeks, as well as the 12-week change mean will be presented by treatment group. The summary statistics of the score at baseline, at 12-weeks and change from baseline will be reported for each treatment group. The mean difference (95% CI) between the CR and usual care treatment groups for change from baseline will be presented, along with the t-test p-value. If differences are noted with regard to baseline covariates adjusted analyses will be performed for the Secondary endpoint.

S2: (Safety) Report Adverse Events of heart failure hospitalization, fracture, myocardial infarction, serious adverse arrhythmia, and ICD therapy among randomized patients .

Reporting for S2: A listing of Adverse Events will be produced for the study population.

S3: Investigate the correlation between change in daily PA as measured by the Abbott ICD or CRT-D device between baseline and week 12 after randomization and change in HF symptoms severity scores as measured by KCCQ during same time period.

Analysis Strategy for S3: The variables used for this objective are the change in median PA from baseline to week 12, and the change in HF symptom severity score from baseline to week 12. The hypothesis test will evaluate whether there is a correlation between these two variables, pooling subjects across treatment groups..

Reporting for S3: We will be reporting the strength of the correlation and related p value and 95% CI.

6.5 Multiplicity and Family-Wise Error

No methods to account for multiplicity (alpha sharing plan) will be used as this is a hypothesis generating rather than a confirmatory study.

6.6 Missing Data

When using weekly averages (P1), we will take the median of the existing values for that week and use that value to impute the missing values for patients.
Weekly missing values will be handled using Multiple Imputation (MI) approach.

No imputation for S1 and S3.

6.7 Sensitivity Analysis

The sensitivity Analysis will be considered for P1 ITT analysis:

Multilevel modeling after imputing missing data using MI: This sensitivity analysis will be performed with the same method as the main analysis, but with imputation for missing data as described above.

Multilevel modeling assumption not met: This sensitivity analysis will be performed if the Multilevel modeling assumptions are severely violated and data transformation is needed. If that is the case, we will run the multilevel model on the transformed data and the p-value will be compared to the main results. The estimated differences in slopes of trajectories and respective p-values will be presented.

Multilevel modeling of endpoints P1 after adjusting for baseline data: This sensitivity analysis will be performed using same methods as original analysis, but adjusting for the baseline mean in the model as a covariate. The significance of the treatment assignment variable will be tested. The estimated adjusted difference in slopes of trajectories and respective p-value will be presented and compared to the main results.

6.8 Confounding Variables

Patients entering weight loss programs which promote exercise, surgeries which reduce body fat by significant degree, getting a physical trainer during course of study.

6.9 Bias

The study sample size is reasonably small introducing the possibility of selection bias. To minimize this risk, we are employing simple, straightforward inclusion and exclusion criteria and minimizing the total number of criteria to make our study population as similar to a general HF population as possible. Other sources of bias, including misclassification bias will be minimized by the direct electronic dataflow from randomization to data capture from the Pattern Health App, and direct data streams from Abbott medical to the Pattern Health app. Recall bias will be minimized because questions regarding symptoms will be asked to reflect the current symptoms, not a recollection pf prior symptoms. Observer bias will be minimized by the objective nature of the physical activity measurement used in the primary endpoint.

7 TABLES, FIGURES, AND LISTINGS

Table	Title	Population
1. Disposition		
Table 1	Subject Enrollment and Status Summary	All enrolled
2. Demographics and Past Medical History		
Table 2.1	Demographics and Baseline Characteristics	ITT
Table 2.2	Demographics and Baseline Characteristics	AT
Table 2.3	Medical History at Baseline	ITT
Table 2.4	Medical History at Baseline	AT
3. Primary Endpoint Analysis		
Table 3.1.1	Primary Endpoint P1: Trajectory of the median Abbott ICD and CRT-D device measured daily PA obtained over baseline and treatment period	ITT
Table 3.1.2	Primary Endpoint P1: Descriptive statistics of the median Abbott ICD and CRT-D device measured daily PA obtained over baseline and treatment period	ITT
Table 3.2.1	Primary Endpoint P1: Trajectory of the median Abbott ICD and CRT-D device measured daily PA obtained over baseline and treatment period	AT
Table 3.2.2	Primary Endpoint P1: Descriptive statistics of the median Abbott ICD and CRT-D device measured daily PA obtained over baseline and treatment period	AT
Table 3.3	P1: Sensitivity Analysis for Imputed Data	ITT
Table 3.4*	P1: Sensitivity Analysis for Transformed Data	ITT
4. Secondary Endpoint Analysis		
Table 4.1.1	Secondary Endpoint S1: Change from baseline KCCQ HF symptom severity score to the last week of study	ITT
Table 4.1.2	Secondary Endpoint S1: Change from baseline KCCQ HF symptom severity score to the last week of study	AT
List 4.2	Secondary Endpoint S2: Adverse Events: heart failure hospitalization, fracture, myocardial infarction, serious adverse arrhythmia, and ICD therapy	ITT and AT
Table 4.3.1	Secondary Endpoint S3: Association between daily PA measured by the Abbott ICD or CRT-D device and in KCCQ HF symptoms severity score measured between baseline and end of follow up	ITT
Table 4.3.2	Secondary Endpoint S3: Association between daily PA measured by the Abbott ICD or CRT-D device and in KCCQ HF symptoms severity score measured between baseline and end of follow up	AT

*These tables will be intentionally blank if sensitivity analysis unnecessary.

Figure	Title	Population
Figure 3.1.1	Predicted Trajectories of the Mean Abbott ICD and CRT-D Device Measured Daily PA by Random Group	ITT
Figure 3.1.2	Trend of the Median Abbott ICD and CRT-D Device Measured Daily PA by Random Group	ITT
Figure 3.2.1	Predicted Trajectories of the Mean Abbott ICD and CRT-D Device Measured Daily PA by Random Group	AT
Figure 3.2.2	Trend of the Median Abbott ICD and CRT-D Device Measured Daily PA by Random Group	AT

Patient-level data listings will be produced to accompany the above tables and figures

8 LIST OF APPENDICES

8.1 Appendix A: Schedule of Activities (SOA)

	Screening / Baseline	Randomization	Initial Remote Physical Activity Session	Follow up Sessions	13 Weeks post Randomization (Completion)
Frequency	1	1	1	11	1
Type of Visit	Chart Review, Written Communication through EMR ± App ± Phone Call	Written Communication through App± Phone Call	Written Communication through App± Phone Call	Written Communication through App± Phone Call	Written Communication through App ± Phone Call
General eligibility criteria	•	•*			
Informed consent	•	•*			
Demographics	•				
Medical history	•	•*	•		
NYHA Assessment	•		•		•
KCCQ QoL Assessment			•		•
Remote Device Interrogation			•	•	•
Medication Review	•		•		•
Adverse Events			•	•	•
Weight, Blood Pressure, Glucose*	•			•	•
Patient Satisfaction Survey**					•

**Diabetes Patients only*
***Remote Cardiac Rehab Patients only*

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Final Audit Report 2022-06-27

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