Medtronic

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Clinical Investigation Plan Identifier	MDT
Study Product	ECG Belt
ClinicalTrials.gov Identifier	NCT03504020
Sponsor	Medtronic 8200 Coral Sea St NE Mounds View, MN 55112
Document Title	ECG Belt for CRT Response – Statistical Analysis Plan
Document Version (Date)	1.0 (14 Dec 2021)

Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	ECG Belt for CRT Response
Clinical Investigation Plan Identifier	NA
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Sponsor/Local Sponsor	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN 55112 U.S.A. +1-800-328-2518 Local Sponsor: Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands
Document Version	Version 1.0

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1. Version History

Version	Summary of Changes	Author(s)/Title
1	Not Applicable, New Document	Cory Jensen, Statistician
2	• Medtronic Bakken Research Center added as sponsor • Clarifications throughout that "CRT-implanted" means the subject must have an active CRT device and active LV lead • Clarification that 6 month results will be analyzed prior to completion of all 9-month follow-ups • Section 7.9.1.5 edited to allow for more LVESV data to qualify as 6-month LVESV. Also used the same rules for Ancillary Objective #1 • Section 7.9.1.6 added to pre-specify sensitivity analysis for the primary objective • Section 7.9.1.7 added to pre-specify subgroup analysis for the primary objective • Added additional subgroup analysis to 7.9.7 • Added section 7.13 pre-specifying additional analysis	Jeff Cerkvenik, Distinguished Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AF	Atrial Fibrillation
CIP	Clinical Investigation Plan (AKA: the protocol)
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CSR	Clinical Study Report
Echo	Echocardiogram
ECG	Electrocardiogram
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICD	Implantable Cardioverter Defibrillator
IPG	Implantable Pulse Generator
LBBB	Left Bundle Branch Block
LV	Left Ventricular

Abbreviation	Definition
AE	Adverse Event
AF	Atrial Fibrillation
CIP	Clinical Investigation Plan (AKA: the protocol)
LVAT	Left Ventricular Activation Time
LVEF	Left Ventricular Ejection Fraction
LVEDD	Left Ventricular End Diastolic Diameter
LVESV	Left Ventricular End-Systolic Volume
MPP	Multiple Point Pacing
NYHA	New York Heart Association
RV	Right Ventricular
SDAT	Standard Deviation of Activation Times
SAP	Statistical Analysis Plan

3. Introduction

This Statistical Analysis Plan (SAP) has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports. This SAP does not limit the analysis in reports, and additional analysis of the study data beyond this plan is expected. This SAP is developed based on Version 5 of the CIP ECG Belt dated 02MAY2019.

ECG Belt for CRT Response (ECG Belt) study is a prospective, interventional, randomized, multi-center, investigational, pre-market research study. The primary purpose of this study is to evaluate the ECG Belt Research System as an additional diagnostic tool for optimizing CRT therapy. The ECG Belt Research System will be used to inform placement of the Left Ventricular (LV) lead while satisfying the EHRA/HRS published guidelines for LV lead implantation, and for optimizing pacing programming parameters in CRT patients. The ECG Belt Research System will provide real-time on-site feedback on CRT efficacy at the time of implant and follow-up.

The first 6 months of follow-up will focus on using the ECG Belt Research System to help choose pacing site, vector and pacing programming. From 6 to 9 months the ECG Belt Research System will be used to further investigate more personalized programming and post-implant optimization at follow-ups.

The study will focus on CRT patients that are known to have a lower likelihood of response to CRT with typical LV lead placement and device programming. These are CRT-indicated patients with a QRS duration $\geqslant$130 ms and LVEDD $\geqslant$55 mm who meet at least one of the following criteria:

- QRS duration <150 ms
- Prior documented Myocardial Infarction
- Non-LBBB

Data analysis will be performed by Medtronic-employed statisticians or designees. Data analysis will occur after 6-month follow-up data is collected and once final study data is collected. A modified intention-to-treat analysis will be performed and will serve as the primary analysis for all objectives in this study. The modified intention-to-treat cohort will include all CRT-implanted (must have active CRT device and active LV lead) randomized subjects in the group to which they were randomized. Since this is a research study, there are no sample size requirements for these data analyses.

All tests of treatment effects will be conducted at a two-sided alpha level of 0.05 unless otherwise stated.

The primary objective will be analyzed once the final 6-month follow-up is collected. Ancillary objectives may or may not be reported on at that time. The analysis of all objectives will appear in the study's final report.

4. Study Objectives

The study comprises two phases. The first phase through the 6-month follow-up has the purpose to investigate use of the ECG Belt Research System to help choose pacing site, vector and pacing programming.

The second phase of the study from 6 to 9 months has the purpose to further investigate use of the ECG Belt Research System for more personalized programming at follow-ups.

a. Primary Objectives

- Demonstrate benefit of using the ECG Belt Research System on reducing LVESV from baseline to 6 months post-implant compared to standard CRT.

b. Ancillary Objectives

1. To estimate the benefit of using the ECG Belt Research System on LVEF compared to standard CRT.
2. To estimate the benefit of using the ECG Belt Research System on change in quality of life compared to standard CRT.
3. To estimate the benefit of using the ECG Belt Research System on change in Six-Minute Walk Test distance compared to standard CRT.
4. To estimate the benefit of using the ECG Belt Research System on the Clinical Composite Score compared to standard CRT.
5. To characterize ECG Belt Research System-related AEs.
6. To assess the changes in LVESV from 6-9 months between subjects who have and have not used the ECG Belt Research System at 6 months.
7. To assess the extent of ECG Belt Research System guided programming changes across study visits.

5. Investigation Plan

a. Study Design

ECG Belt for CRT Response (ECG Belt) study is a prospective, interventional, randomized, multi-center, investigational, pre-market research study.

The study is expected to be conducted at approximately 48 centers located in the United States, Europe, and Canada. Centers will be initiated in phases to ensure optimal implementation of the ECG Belt Research System.

Approximately 500 subjects will be enrolled in the study to ensure 400 randomized subjects. Centers are expected to randomize 8 subjects on average during the course of the study. Centers that enroll faster than others will be allowed to do so in order to maintain an adequate enrollment rate, with a maximum of 40 randomized subjects at one center to limit bias.

Study subjects will be followed for 9 months, unless there is a decision by Medtronic or regulatory authority to end the study early. The expected study duration is approximately 3.5 years representing approximately 32 months of enrollment and 9 months of subject follow-up.

b. Subject selection criteria and enrollment

Subjects will be screened to ensure they meet all of the inclusion and none of the exclusion criteria prior to study enrollment. Ethics Committee approval of the ECG Belt CIP and Informed Consent Form (ICF) must be obtained prior to enrolling subjects in the study. The subject is considered enrolled upon confirmation of the subject's inclusion/exclusion criteria and signing of the ICF.

i. Inclusion criteria

- Indicated for CRT, with QRS duration $\geqslant$130 ms, and planned to be implanted with a market-released Medtronic CRT device with AdaptivCRT and a Medtronic quadripolar LV lead.
- Meets at least one of the following criteria:
  - QRS duration < 150 ms
  - Prior documented Myocardial Infarction
  - Non-LBBB
- LVEDD $\geqslant$ 55 mm, as determined by site

ii. Exclusion criteria

- Permanent/persistent AF or presenting with AF
- Pre-existing or previous LV lead or other confounding devices e.g. Left Ventricular Assist Device, Vagal Nerve Stimulator
- Currently implanted with IPG or ICD with > 10% RV pacing
- Permanent complete AV block
- Enrolled in a concurrent study that may confound the results of this study. Pre-approval from the study manager is required for enrollment of a subject that is in a concurrent study.
- Less than 1-year life expectancy
- Vulnerable adults
- Younger than 18 years of age

c. Randomization

Eligible subjects will be randomized 2:1:1 to either the ECG Belt arm, control arm A, or control arm B respectively. The latter two arms are identically treated up until the 6-month follow-up and will be called the control arm as a whole. Randomization schedules will be created for each site by a statistician using randomized blocks and stratified by center to ensure relatively equal randomization within each center.

After verification that a subject meets all inclusion/exclusion criteria and core lab confirmation that LVESV can be determined from the subject's echocardiogram, subjects will undergo randomization prior to any implant attempt. Centers will receive each subject's assignment electronically via the study database.

d. Blinding

Due to the use of the ECG Belt during implant and follow-up, it is difficult to blind subjects or physicians to the treatment assignment. The echo core lab will be blinded to the randomization assignment.

e. CIP Revisions

ISO 14155:2020 7.5.1 requires that if a CIP amendment impacts the integrity of a study, the data collected before and after the amendment shall be analyzed statistically to assess the effect of the amendment on performance, effective or safety analysis. The first enrollment in the study was under CIP version 4, dated 29NOV2017. Version 5 was dated 02MAY2019. Changes consisted of EU MDR requirements, clarifications, and one new study requirement (to collect blinded ECG Belt data in control arm subjects). None of these changes would affect enrollment or study objective results. Therefore, there are no plans to do any comparison of results under version 4 and version 5 of the CIP.

6. Determination of Sample Size

The sample size of the study will be 400 randomized subjects. It will require approximately 500 enrolled to acquire 400 randomized, but enrollment will end once 400 are randomized. It is allowable to go over 400 randomized if the final randomizations occur within a week. As this is a research study, the sample size was based on budget, however power calculations can be found in the primary objective below.

Table 1 shows data from previous studies. The first row of the table shows that, among the subjects meeting this study's inclusion criteria, the mean relative change in LVESV at 6 months is -7.1 ± 27.5.

So, it can be assumed that the control group without ECG Belt Research System management will decrease by a mean 7.1% over 6 months, with a standard deviation of 27.5%.

Table 1: LVESV Results from Previous CRT Studies' CRT Subjects

Study	n	Mean ± S.D. Relative Change at 6 months in LVESV (%)
All studies	583	-7.1 ± 27.5
MIRACLE	125	-9.2 ± 22.8
MIRACLE ICD	142	-5.1 ± 25.1
REVERSE	124	-8.2 ± 28.0
Adaptive CRT control	62	-9.2 ± 32.3

Study	n	Mean ± S.D. Relative Change at 6 months in LVESV (%)
Adaptive CRT aCRT	130	-5.0 ± 31.3

Note: To be included in Table 1, subjects must meet current indications for CRT (NYHA II with LVEF≤30% or NYHA III/IV), and have QRS≥130, LVEDD≥55, and (QRS<150 or Ischemic or non-LBBB)

Figure 1 shows the power of the study under various values of improvement in LVESV due to the ECG Belt Research System under the following assumptions:

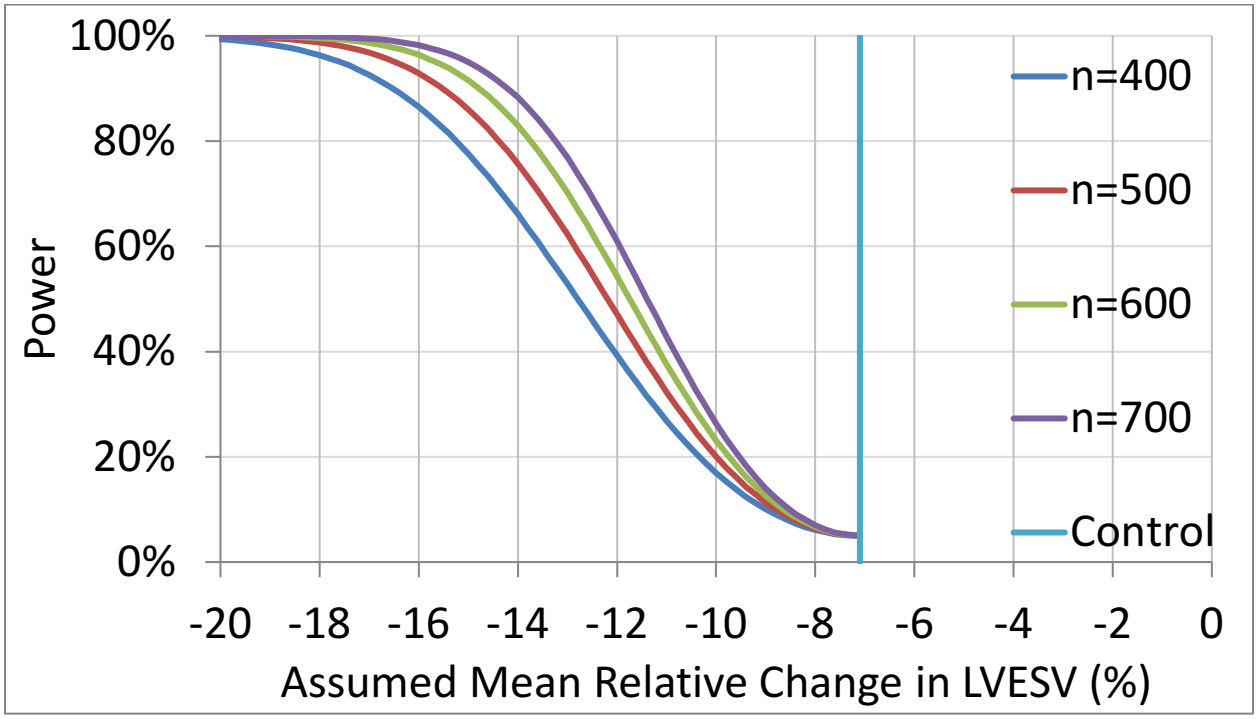
- Alpha=0.05
- Power = 80%
- Mean LVESV change in control population at 6 months is –7.1 ± 27.5%
- ECG Belt Research System population subjects also have a standard deviation of 27.5%
- 180 subjects in the ECG Belt arm will have paired LVESV data, along with 180 subjects in the control arm (10% attrition primarily due to deaths and unreadable echo's at 6 months)

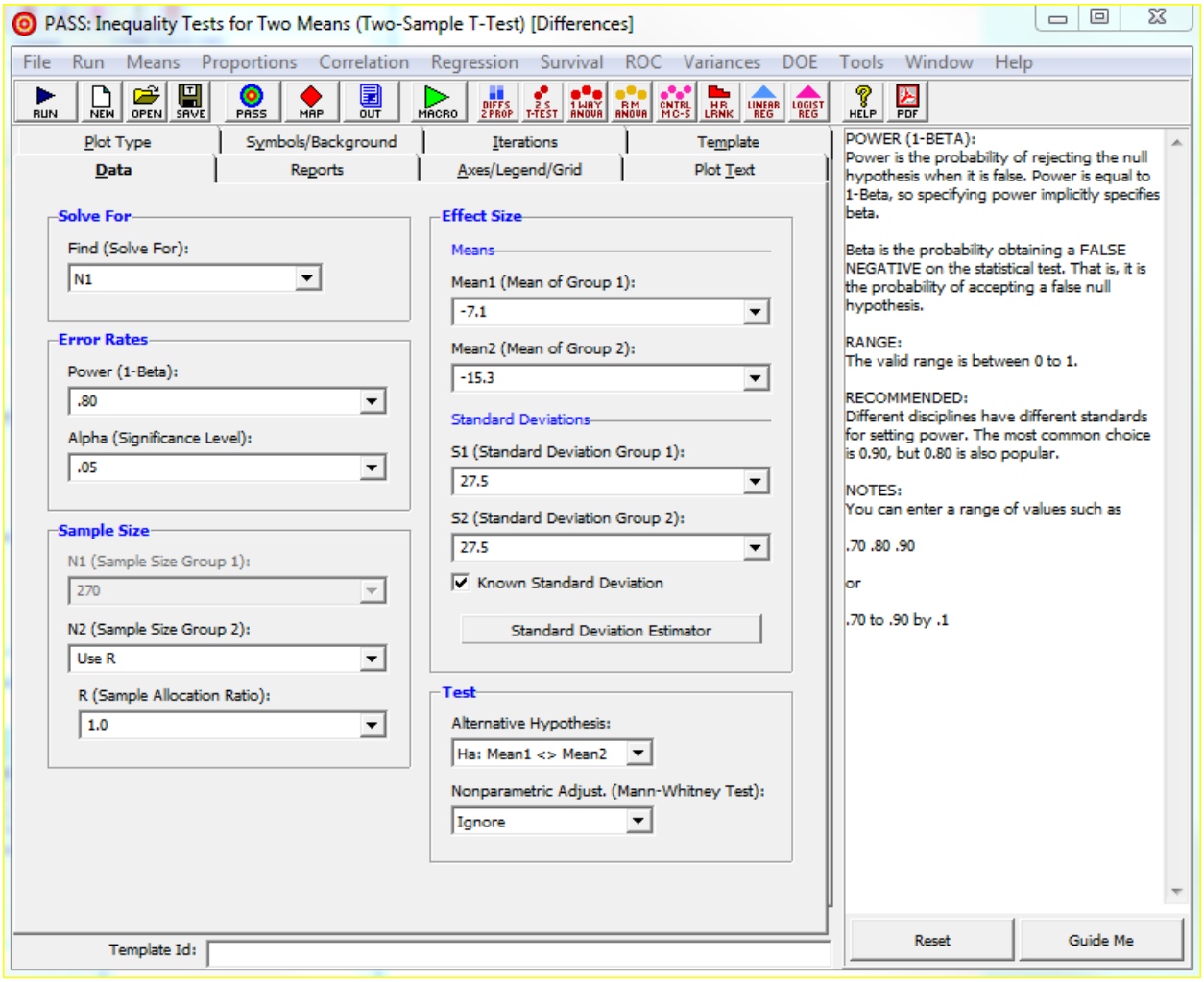
Figure 1 shows a vertical bar at -7.1% corresponding to the expected mean LVESV change in the control arm. The curves show the power of the study under different assumptions of sample size and the expected mean LVESV change in the ECG Belt arm.

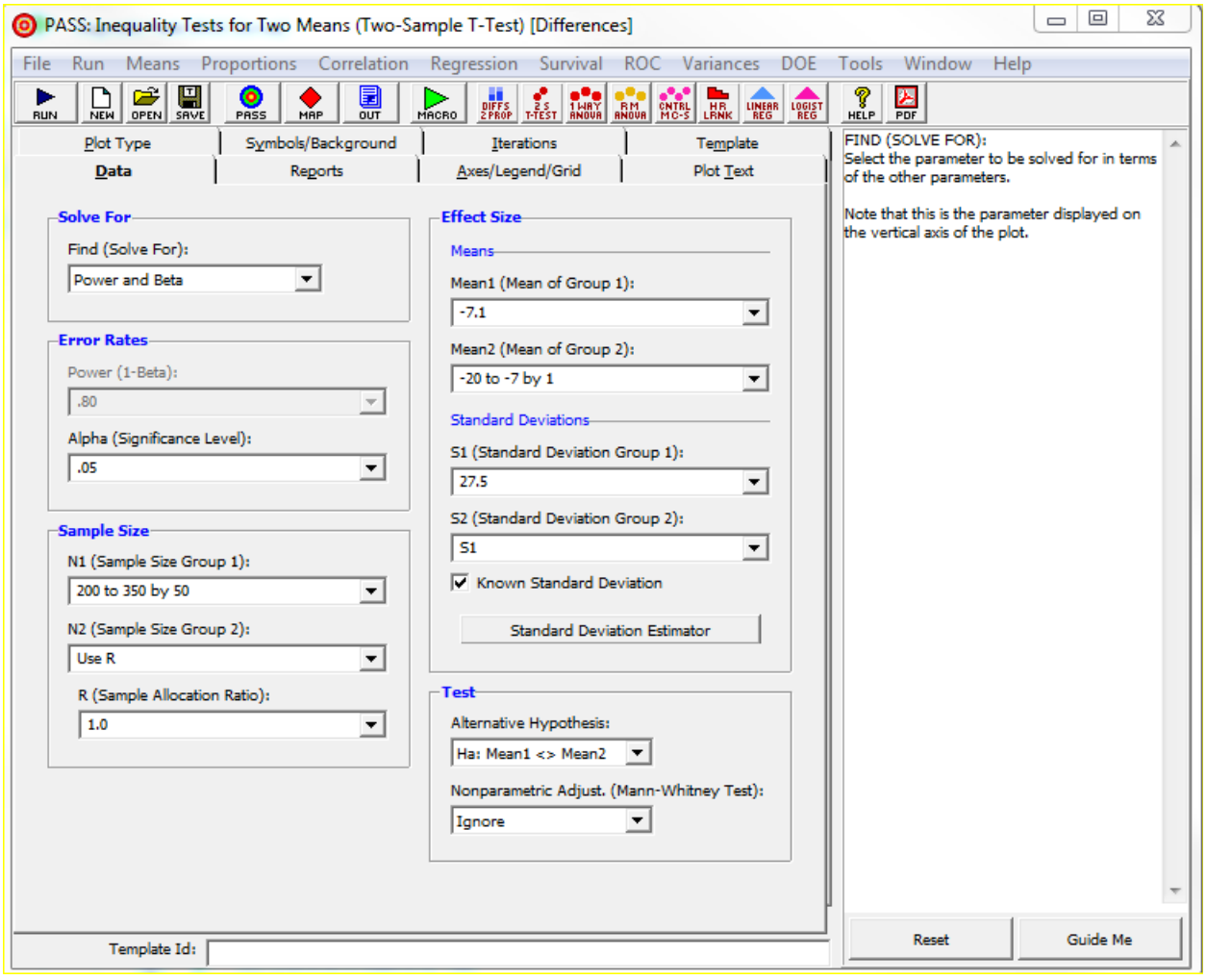
For example, for a sample size of 400, the graph shows that the power of the study is 80% under the assumptions above if the ECG Belt Research System population reduces its mean LVESV by 15.3% (a 8.2% increase over the assumed control population mean relative change of 7.1%). As another example, if the ECG Belt Research System population has a mean reduction of 14%, then the power of this objective is 66%.

The power calculations were performed using the inequality tests for two means (Two Sample T-Test) in PASS (2008).

Figure 1: Primary Objective #1 Power Curve


100%
80%
60%
40%
20%
0%
Power
-20
-18
-16
-14
-12
-10
-8
-6
-4
-2
0
Assumed Mean Relative Change in LVESV (%)
n=400
n=500
n=600
n=700
Control


PASS: Inequality Tests for Two Means (Two-Sample T-Test) [Differences]
File Run Means Proportions Correlation Regression Survival ROC Variances DOE Tools Window Help
RUN NEW OPEN SAVE PASS MAP OUT MACRO DIFFS 2 PROP 2 S T-TEST 1 WAY ANOVA RM ANOVA CNTRL M.C.-S HR LRNK LINEAR REG LOGIST REG HELP PDF
Plot Type Symbols/Background Iterations Template
Data Reports Axes/Legend/Grid Plot Text
Solve For
Find (Solve For):
N1
Error Rates
Power (1-Beta):
.80
Alpha (Significance Level):
.05
Sample Size
N1 (Sample Size Group 1):
270
N2 (Sample Size Group 2):
Use R
R (Sample Allocation Ratio):
1.0
Effect Size
Means
Mean1 (Mean of Group 1):
-7.1
Mean2 (Mean of Group 2):
-15.3
Standard Deviations
S1 (Standard Deviation Group 1):
27.5
S2 (Standard Deviation Group 2):
27.5
Known Standard Deviation
Standard Deviation Estimator
Test
Alternative Hypothesis:
Ha: Mean1 <> Mean2
Nonparametric Adjust. (Mann-Whitney Test):
Ignore
POWER (1-BETA):
Power is the probability of rejecting the null hypothesis when it is false. Power is equal to 1-Beta, so specifying power implicitly specifies beta.
Beta is the probability obtaining a FALSE NEGATIVE on the statistical test. That is, it is the probability of accepting a false null hypothesis.
RANGE:
The valid range is between 0 to 1.
RECOMMENDED:
Different disciplines have different standards for setting power. The most common choice is 0.90, but 0.80 is also popular.
NOTES:
You can enter a range of values such as
.70 .80 .90
or
.70 to .90 by .1
Template Id:
Reset
Guide Me


PASS: Inequality Tests for Two Means (Two-Sample T-Test) [Differences]
File Run Means Proportions Correlation Regression Survival ROC Variances DOE Tools Window Help
RUN NEW OPEN SAVE PASS MAP OUT MACRO DIFFS 2 PROP 2 S T-TEST 1 WAY ANOVA R M ANOVA CNTRL M C-S HR LRNK LINEAR REG LOGIST REG HELP PDF
Plot Type Symbols/Background Iterations Template
Data Reports Axes/Legend/Grid Plot Text
Solve For
Find (Solve For):
Power and Beta
Error Rates
Power (1-Beta):
.80
Alpha (Significance Level):
.05
Sample Size
N1 (Sample Size Group 1):
200 to 350 by 50
N2 (Sample Size Group 2):
Use R
R (Sample Allocation Ratio):
1.0
Effect Size
Means
Mean1 (Mean of Group 1):
-7.1
Mean2 (Mean of Group 2):
-20 to -7 by 1
Standard Deviations
S1 (Standard Deviation Group 1):
27.5
S2 (Standard Deviation Group 2):
S1
Known Standard Deviation
Standard Deviation Estimator
Test
Alternative Hypothesis:
Ha: Mean1 <> Mean2
Nonparametric Adjust. (Mann-Whitney Test):
Ignore
FIND (SOLVE FOR):
Select the parameter to be solved for in terms of the other parameters.
Note that this is the parameter displayed on the vertical axis of the plot.
Template Id:
Reset
Guide Me

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

The patient is considered enrolled upon confirmation of the subject's inclusion/exclusion criteria and signing of the ICF.

Centers will receive each subject's randomization assignment electronically via the Oracle Clinical database upon confirmation of the subject's inclusion/exclusion criteria and baseline echo readability.

After randomization, subjects remain enrolled until the 9-month follow up visit or exit.

The numbers of subjects enrolled, randomized and received therapy (active CRT device and active LV lead post-implant) will be summarized.

7.1.2. Clinical Investigation Plan (CIP) Deviations

Study deviations will be summarized in the study reports based on deviation type, and details of individual study deviations will be listed.

7.1.3. Analysis Sets

A modified intention-to-treat analysis will be performed and will serve as the primary analysis for all objectives in this study. The modified intention-to-treat cohort will include all CRT-implanted randomized subjects in the group to which they were randomized.

7.2. General Methodology

All tests of treatment effects will be conducted at a two-sided alpha level of 0.05 unless otherwise stated. The two-sided, two-sample t test will be used to compare continuous endpoints between the ECG Belt and control arms. Chi-square tests will be used to compare categorical endpoints between the ECG Belt and control arms. Mantel-Haenszel chi-square tests will be used to compare ordinal endpoints between the ECG Belt and control arms The primary objective will be analyzed once the final 6-month follow-up is collected. Ancillary objectives may or may not be reported on at that time. The analysis of all objectives will appear in the study's final report.

7.3. Center Pooling

The study will include approximately 48 centers in the US, Europe, and Canada. All data will be pooled for the analysis.

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

All available data will be included in the data listings and tabulations. For the main analysis of each study objective, the modified intention-to-treat cohort will be used, in which missing data (if any) will not be imputed and subjects with missing data will be excluded from analysis. If missing data becomes a concern, a sensitivity analysis may be conducted.

For the primary objective of the study, analysis accounting for all subjects with a summary of the reasons for missing data will be included in the analysis of the objective.

7.5. Adjustments for Multiple Comparisons

Because there is only one primary objective in the study, there will be no adjustment for multiple comparisons.

7.6. Demographic and Other Baseline Characteristics

Subjects' demographic and other baseline characteristics will be summarized using descriptive statistics. For continuous variables, descriptive statistics such as mean and standard deviation will be presented. For categorical variables, counts and percentages will be reported.

7.7. Treatment Characteristics

N/A. All subjects will undergo CRT implant, which is not the focus of this study.

7.8. Interim Analyses

There is no planned interim analysis for this study. The 6-month study objectives will be analyzed once 6-month follow-up is complete, and the 9-month objectives will be analyzed when all the study data is collected.

7.9. Evaluation of Objectives

7.9.1 Primary Objective

Demonstrate benefit of using the ECG Belt Research System on reducing LVESV from baseline to 6 months post-implant compared to standard CRT.

7.9.1.1. Hypothesis

H_0: Δ $LVESV_{ECG\ Belt} = \Delta\ LVESV_{control}$

H_A: Δ $LVESV_{ECG\ Belt} \neq \Delta\ LVESV_{control}$

Where Δ LVESV is the relative (%) change in LVESV from baseline to 6 months post-implant calculated as 100 x (6-month LVESV – baseline LVESV) / baseline LVESV.

The null hypothesis will be rejected if the p-value is less than 0.05. This is a research study, therefore if the ECG Belt arm has a better change in LVESV than the control arm, even if it is not statistically significant, the results could be interpreted as positive.

7.9.1.2. Performance Criteria and Rationale

A reduction in LVESV has been shown to predict lower mortality rates in CRT patients[i], and changes are seen soon after implant. An alpha level of 0.05 is a standard statistical criterion.

7.9.1.3. Endpoint Definition

The endpoint is the relative change in LVESV from baseline to 6 months calculated as below.

100 x (6-month LVESV – baseline LVESV) / baseline LVESV.

See section 7.9.1.5 for details on using 9-month values in some cases.

7.9.1.4. Analysis Methods

The relative change in LVESV from baseline to 6 months will be calculated and compared using a two-sided, two-sample t-test.

The analysis will be performed with SAS code similar to:

```
proc ttest data=ECG;
    class RAND;
    var LVESV_CHG;
run;
```

where RAND is a variable coding whether the subject is in ECG Belt arm or control arm and LVESV_CHG is a variable coding the result of the LVESV change from baseline to 6 months visit. The null hypothesis will be rejected if the p-value is less than 0.05.

7.9.1.5. Determination of Subjects/Data for Analysis

All randomized subjects in the modified intention-to-treat cohort with a non-missing LVESV value at both baseline and the 6-month visit will be included if their 6-month follow-up is within 365 days of implant. Additionally, subjects who are missing their 6-month LVESV but have a 9-month LVESV will be included by using their 9-month LVESV as the 6-month value if they meet the following criteria:

- Their 9-month echo was within 365 days of implant
- They were not reprogrammed at the 6-month follow-up, or did not perform a 6-month follow-up visit

In all cases, contrast images will be used over non-contrast if both are available. Subjects exiting, dying, or with missing LVESV will not be included, and their data will not be imputed.

7.9.1.6. Sensitivity Analysis

The following sensitivity analyses will be performed. They address the cases where contrast was used for one echo and no contrast was used for the other echo. Results will be reported in the final report. Their inclusion in presentations and publications is at the discretion of authors.

1. The same primary analysis inclusion rules, except subjects with different use of contrast at the two timepoints (e.g., no contrast at baseline and contrast at 6 months) will be excluded. If a subject has values for both contrast and no contrast at a visit, only the contrast value will be considered.
2. The same primary analysis inclusion rules, however, when both non-contrast and contrast LVESV values are available, use the one that matches the other timepoint.
3. Same as sensitivity analysis #2, except only use a matching non-contrast image if the core lab did not enter a cautionary comment on its quality on the CRF. If there is a cautionary comment, the paired LVESV data will be considered missing for that subject.
4. The same primary analysis inclusion rules will be used. In cases where contrast was used, subtract 13.6 from the LVESV value. The correction factor of 13.6 is based on Igata[1] If a subject has values for both contrast and no contrast at a visit, only the contrast value will be used.

The following are additional sensitivity analyses independent of contrast use.

[1] Sachiyo Igata, Megan Kraushaar et al. Systematic Assessment of the Impact of Ultrasound-Enhancing Agents upon Measurements of Cardiac Size and Function by Echocardiography, Journal of the American Society of Echocardiography, March, 2020: 313-321.

The same primary analysis, but only including subjects whose 6-month echo occurred within the pre-specified follow-up window (182-196 days post-implant).

To determine the effect of missing data on the primary analysis, another sensitivity analysis will use multiple imputation to impute relative change in LVESV when missing. Variables used in the multiple imputation will be

- LVESV % change baseline to 6 months
- Baseline variables: age, sex, QRS duration, LVESV, LBBB, RBBB, ischemic, NYHA, hypertension, myocardial infarction, diabetes, renal dysfunction
- Change from baseline to 6 months: 6-minute hall walk, and Minnesota Living with Heart Failure Questionnaire
- Randomization arm (ECG Belt or control)

Example SAS code:

```
PROC MI DATA=AN.ALLDATA NIMPUTE=5 OUT=MI_PRIMARY SEED=1013;
WHERE IMPDT NE .;
CLASS SEX LBBB RBBB ISCH NYHA0 HTN MI DIABETES RENALDYS RAND2;
VAR LVESV6DPCT AGE SEX QRS LVESV0 LBBB RBBB ISCH NYHA0 HTN MI DIABETES
RENALDYS DWALK6D MNQOL6D RAND2;
FCS LOGISTIC(SEX LBBB RBBB ISCH NYHA0 HTN MI DIABETES RENALDYS RAND2);
RUN;

*PROC GLM GIVES SAME P-VALUES AS T-TEST AND OUTPUTS (ESTIMATE STDERR) IN THE
FORMAT NEEDED FOR MIANALYZE;
PROC GLM DATA=MI_PRIMARY;
BY _Imputation_;
CLASS RAND2;
MODEL LVESV6DPCT=RAND2 / SOLUTION;
ODS OUTPUT ParameterEstimates=MIGLM;
RUN;

DATA MIGLM2;
SET MIGLM;
IF PARAMETER NE 'RAND2      CONTROL' THEN DELETE;
PARAMETER='RAND2';
RUN;

PROC MIANALYZE PARMS=MIGLM2;
MODELEFFECTS RAND2;
RUN;
```

7.9.1.7. Subgroup Analysis

Change in LVESV by randomization arm will be reported by the following subgroups:

- LBBB
- RBBB
- IVCD
- ischemic
- non-ischemic
- subjects with underlying intrinsic dyssynchrony (SDAT>25 ms)
- subjects without underlying intrinsic dyssynchrony (SDAT<25 ms)
- subjects with Attain Stability (4798)
- subjects with Attain Performa (4298, 4398, or 4598)

Additionally, the following will be plotted against change in LVESV by randomization arm to see if ECG Belt can be used as a predictor of response. A simple linear regression of each will also be incorporated.

- Intrinsic SDAT
- Intrinsic LVAT
- Intrinsic LV dispersion

7.9.2 Ancillary Objective #1

To estimate the benefit of using the ECG Belt Research System on LVEF compared to standard CRT.

i. Endpoint Definition

Absolute LVEF change from baseline to 6 months.

ii. Analysis Methods

The mean changes in LVEF will be compared between ECG Belt arm and control arm using a two-sided, two-sample t-test.

iii. Determination of Subjects for Analysis

All randomized subjects in the modified intention-to-treat cohort with a non-missing LVEF value at both baseline and the 6-month visit will be included if their 6-month follow-up is within 365 days of implant. Additionally, subjects who are missing their 6-month LVEF but have a 9-month LVEF will be included by using their 9-month LVEF as the 6-month value if they meet the following criteria:

- Their 9-month echo was within 365 days of implant
- They were not reprogrammed at the 6-month follow-up, or did not perform a 6-month follow-up visit

In all cases, contrast images will be used over non-contrast if both are available. Subjects exiting, dying, or with missing LVEF will not be included, and their data will not be imputed.

7.9.3 Ancillary Objective #2

To estimate the benefit of using the ECG Belt Research System on change in quality of life compared to standard CRT.

i. Endpoint Definition

Quality of life will be measured using the Minnesota Living with Heart Failure Questionnaire. The endpoint is change from baseline to 6 months. Questionnaires with fewer than 11 questions answered will not be included.

ii. Analysis Methods

The mean changes in quality of life will be compared between ECG Belt arm and control arm using a two-sided, two-sample t-test.

iii. Determination of Subjects for Analysis

All randomized subjects in the modified intention-to-treat cohort with paired Minnesota Living with Heart Failure Questionnaire data.

7.9.4 Ancillary Objective #3

To estimate the benefit of using the ECG Belt Research System on change in Six-Minute Walk Test distance compared to standard CRT.

i. Endpoint Definition

Six-Minute Walk Test distance will be measured at baseline and 6 months. The endpoint is change from baseline to 6 months. If the test at either time point was not done due to heart failure reasons, the distance will be considered to be 0.

ii. Analysis Methods

The mean changes in Six-Minute Walk Test distance will be compared between ECG Belt arm and control arm using a two-sided, two-sample t-test.

iii. Determination of Subjects for Analysis

All randomized subjects in the modified intention-to-treat cohort with paired Six-Minute Walk Test distances, including those with a 0 distance on either or both the baseline and six-month visit due to heart failure.

7.9.5 Ancillary Objective #4

To estimate the benefit of using the ECG Belt Research System on the Clinical Composite Score compared to standard CRT.

i. Endpoint Definition

Clinical Composite Response[ii] will be evaluated at both 6 and 9 months post-implant. The description below is for 6 months, 9 months is analogous, but using 274 days instead of 182.

A subject will be considered "worsened" if he/she experiences any of the following between randomization and the earlier of 182 days post-implant or his/her 6-month follow-up:

- Death from any cause.
- Hospitalization duration >24 hours due to or associated with worsening heart failure.
- Discontinues CRT due to or associated with worsening heart failure, treatment failure, or lack of/ insufficient therapeutic response.

A subject will also be considered "worsened" if either of the following occurs:

- A worsening in NYHA class at 6 months (compared to baseline).
- Moderate or marked worsening of the subject global assessment score at 6 months compared to baseline.

A subject will be considered "improved" if he/she is not "worsened" and one of the following is true:

- An improvement in NYHA class at 6 months (compared to baseline).
- Moderate or marked improvement of the subject global assessment score at 6 months compared to baseline.

If a subject is neither "worsened" nor "improved", and the subject has a 6-month follow-up, then he/she will be considered "unchanged".

ii. Analysis Methods

Clinical Composite Response results will be reported at 6 months by randomization arm and compared using a Mantel-Haenszel chi-squared test.

iii. Determination of Subjects for Analysis

All randomized subjects in the modified intention-to-treat who either worsen or have a 6-month follow-up will be included.

7.9.6 Ancillary Objective #5

To characterize ECG Belt Research System related AEs.

i. Endpoint Definition

An AE will be considered related to the ECG Belt Research System if it is classified as system-related.

ii. Analysis Methods

The percentage of ECG Belt Research System uses with an AE related to them will be reported. The denominator for this calculation will be the number of times the ECG Belt Research System was used. For example, this is expected to be 4 times (during implant, post-implant, 6 months, and 9 months) for a subject randomized to the ECG Belt arm and completing the study. The numerator will be the number of ECG Belt Research System uses with at least one adverse event. A 95% confidence interval will be applied to the estimate as well using GEE methods with subject as a repeated variable.

In addition, similar methods will be used to calculate the percentage of ECG Belt Research System uses with a serious adverse event related to the use of the ECG Belt Research System.

iii. Determination of Subjects for Analysis

All ECG Belt Research System uses will be included.

7.9.7 Ancillary Objective #6

To assess the changes in LVESV from 6-9 months between subjects who have and have not used the ECG Belt Research System at 6 months.

i. Endpoint Definition

Relative LVESV change from 6 months to 9 months.

ii. Analysis Methods

The relative change in LVESV from 6 months to 9 months will be calculated and compared between control arm A and B using a two-sided, two-sample t-test.

iii. Determination of Subjects for Analysis

Only subjects in the control arm and in the modified intention-to-treat cohort with paired LVESV data at 6 and 9-month follow up visits will be included. In all cases, contrast images will be used over non-contrast if both are available.

iv. Additional Analysis

The Minnesota Living with Heart Failure questionnaire, six-minute hall walk, and LVEF will be analyzed similarly to the LVESV analysis.

The LVESV treatment arm results from 6 to 9 months will be reported.

Subgroup Analysis

LVESV results for control arms A and B will be reported by the subgroups

- Those with increased LVESV between baseline and 6 months
- Those with LVESV decreased from 0-15% between baseline and 6 months
- Those with LVESV decreased by >15% between baseline and 6 months
- LBBB
- RBBB
- IVCD
- ischemic
- non-ischemic
- subjects with underlying intrinsic dyssynchrony (SDAT>25 ms)
- subjects without underlying intrinsic dyssynchrony (SDAT<25 ms)
- subjects with Attain Stability (4798)
- subjects with Attain Performa (4298, 4398, or 4598)

7.9.8 Ancillary Objective #7

To assess the extent of ECG Belt Research System guided programming changes across study visits.

i. Endpoint Definition

Any change in programming due to use of the ECG Belt Research System. This includes vector selection, Adaptive CRT programming mode, and A-V and V-V timing.

ii. Analysis Methods

The percentage of subjects whose programming is changed due to the ECG Belt Research System will be reported at each visit where the ECG Belt Research System is used. Additionally, frequencies of types of changes (e.g., vectors, V-V timing) will be reported.

iii. Determination of Data for Analysis

All subject visits where the ECG Belt Research System was used post-implant will be included.

7.10.Safety Evaluation

All ECG Belt Research System-related and all Serious Adverse Events (including Unanticipated Serious Adverse Device Events and Unanticipated Adverse Device Events) will be collected throughout the study duration, starting at the time of signing the ICF. This ensures any AEs which could potentially be relevant will be collected. Subject deaths are also required to be reported. A listing of deaths (including reason) will be reported in the annual report and the final report. The percentage of ECG Belt Research System uses with an AE related to them and serious adverse events related to them will be reported. A 95% confidence interval will be applied to the estimate using GEE methods with subject as a repeated variable. Section 7.9.6 describes in detail the methods that evaluate the safety of this system.

Device deficiencies will be summarized in a table, and a listing of all events will be included in the final report.

7.11. Health Outcomes Analyses

N/A. All outcomes of interest are part of a study objective.

7.12. Changes to Planned Analysis

This SAP has been developed prior to data being analyzed to further describe the statistical methods and planned analyses of the study data to be included in the clinical study report. Any change to the data analysis methods described in the CIP will require a CIP amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP or SAP, and the justification for making the change, will be described in the clinical study report.

7.13.Additional Analysis

The following analyses, while not part of the official objectives of the study, are pre-specified for possible use in manuscripts. They will not necessarily be included in the final report of the study or in the primary manuscript.

7.13.1 SDAT/LVAT Change vs Response

Variables used in this analysis will include

- SDAT change: ECG Belt arm - SDAT of the final programmed settings from the ECG Belt Mgmt Post-implant CRF minus SDAT of Underlying ventricular rhythm from the Implant ECG Belt CRF. Control arm – SDAT change will be provided by the research group
- LVAT change: ECG Belt arm - LVAT of the final programmed settings from the ECG Belt Mgmt Post-implant CRF minus LVAT of Underlying ventricular rhythm from the Implant ECG Belt CRF. Control arm – LVAT change will be provided by the research group
- LV Dispersion change: computed from the activation times measured by ECG Belt. This data is not collected on the CRF's and will come from the research group. Just like SDAT and LVAT, there will be a LV dispersion for intrinsic/baseline and post-implant, so a change can be determined

- LVESV change: from baseline to 6 months
- LVEF change: from baseline to 6 months
- QoL change: baseline to 6 month change in Minnesota living with Heart Failure questionnaire score

This exploratory analysis will compare each of the 3 predictor variables (SDAT, LVAT, and LV dispersion) against the outcome variables (LVESV, LVEF, and QoL). Each pair (a total of 9 pairs) will be put in a scatter plot with a simple linear regression line added. If, in any of the 9 comparisons, the slope of the regression line has a p-value of <0.15, further analysis on that pair will be performed.

This further analysis will entail dividing the predictor variable into quartiles (rounding to sensible cut-offs where possible) and reporting results (mean ± s.d. of change) within each quartile.

Where the sample size is adequate, the same analysis as above will be repeated for each of these subgroups:

- LBBB subjects
- RBBB
- IVCD
- Ischemic
- Non-ischemic

All implanted subjects with data will be included. Missing data will not be imputed. Those subjects will simply be excluded from the analyses where their data is missing.

7.13.2 SDAT Compared to Other Measures

Variables used in this analysis will include the changes from pre-implant to post-implant of SDAT, RV-LV timing (from device), and QRS width change (from ECG Belt). The latter two are not collected on CRF's and will be provided by the research group.

The purpose of this analysis is to show the value of SDAT over standard clinical metrics like RV-LV timing or QRS width change.

SDAT vs. RV-LV and SDAT vs. QRS will be plotted on a scatter plot.

Each of the 3 predictor candidates will be plotted on a scatter plot vs. % change in LVESV from baseline to 6 months. Using linear regression, R^2 will be calculated for each to determine the best predictor.

Only implanted ECG Belt arm subjects will be used in the analysis. For each analysis, all subjects with data will be included. Missing data will not be imputed.

8. Validation Requirements

Levels of validation required for the different elements of the clinical study report are specified in the table below.

Level I	A peer reviewer independently programs output and then compares the output with that generated by the original author of the program to be validated	All TLGs in the CSR pertaining to the primary and secondary objectives of the study
Level II	A peer reviewer reviews the program, and where appropriate, performs calculations or programming checks to verify the output	All other TLGs in the CSR (not pertaining to the primary and secondary objectives of the study) *

*Level II validation is the minimum requirement here; alternatively, level I validation can be performed if desired since it is more rigorous.

i Gold MR, Daubert C, Abraham WT, Ghio S, Sutton MSJ, Hudnall JH, Cerkvenik J, Linde C. The effect of reverse remodeling on long-term survival in mildly symptomatic patients with heart failure receiving cardiac resynchronization therapy: Results of the REVERSE study. Heart Rhythm, 2015; 12(3):524-530.
ii Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure J Card Fail. 2001; 2:176-82.