

Crome/Cobalt Respiration Study Statistical Analysis Plan

Revision 1.0

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Medtronic Statistical Analysis Plan

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1. Version History

Version	Summary of Changes	Author/Title
1.0	Not Applicable, New Document	Bryan Martin / Senior Statistician

2. List of Abbreviations and Definitions of Terms

Term	Definition
AE	Adverse Event
CIP	Clinical Investigation Plan
CRT-D	Cardiac Resynchronization Therapy Device
eCRF	Electronic Case Report Form
EDR	EGM-Derived Respiration
EGM	Electrogram
ICD	Implantable Cardioverter Defibrillator
ISO	International Organization for Standardization
RR	Respiration Rate
SAP	Statistical Analysis Plan

3. Introduction

The purpose of this study is to compare the measured respiration rates in various subject scenarios and use conditions between capnography and the Crome™ and Cobalt™ ICD and CRT-D MRI SureScan™ devices (derived using the mHolter Recorder).

This statistical analysis plan (SAP) is based on the Crome/Cobalt Respiration Study Clinical Investigation Plan (CIP) version 2.0.

The purpose of this SAP is to further clarify analysis methods beyond what is in the CIP.

4. Study Objectives

4.1 Primary Objective

Demonstrate an acceptable level of agreement between daily Crome and Cobalt ICD and CRT-D device-derived respiratory rate and daily capnography waveform-derived respiratory rate.

4.2 Ancillary Objective(s)

This study has three ancillary objectives, which are as follows:

1. Characterize respiration rate accuracy while subjects are participating in various levels of activity, pacing conditions, and body positions
2. Collect Heart sounds and Bio-impedance data for beat-by-beat respiration tracking to inform potential development of future algorithms
3. Collect at-home ambulatory EGM data while subjects are undergoing daily activities to serve as input to potential future algorithm development

5. Investigation Plan

The Crome/Cobalt Respiration Study is a prospective, observational, non-randomized, multi-center, non-significant risk device clinical study. The study is expected to be conducted at up to 5 study sites located in the United States and approximately 60 subjects will be enrolled. The target population will include adult subjects who are ≥ 18 years of age, have an existing active Crome or Cobalt ICD or CRT-D system that's been implanted for at least 30 days and which has not yet reached the Recommended Replacement Time (RRT), and who do not have any contraindications that would impact their ability to complete the required breathing and exercise activities.

Once consented, subjects will complete a baseline assessment. Following the Baseline Visit, subjects will have the mHolter recorder, capnography monitor and SpO2 sensor applied; the standard Holter telemetry mode will be turned on for 24 hours using the CareLink SmartSync™ Device Manager; the Sensor Research Holter Mode feature on their Crome or Cobalt device will be enabled to allow for data collection from additional sensors; and in-clinic testing will be completed by performing a series of breathing and exercise activities.

The subject-level study design diagram is shown in Figure 1 below.

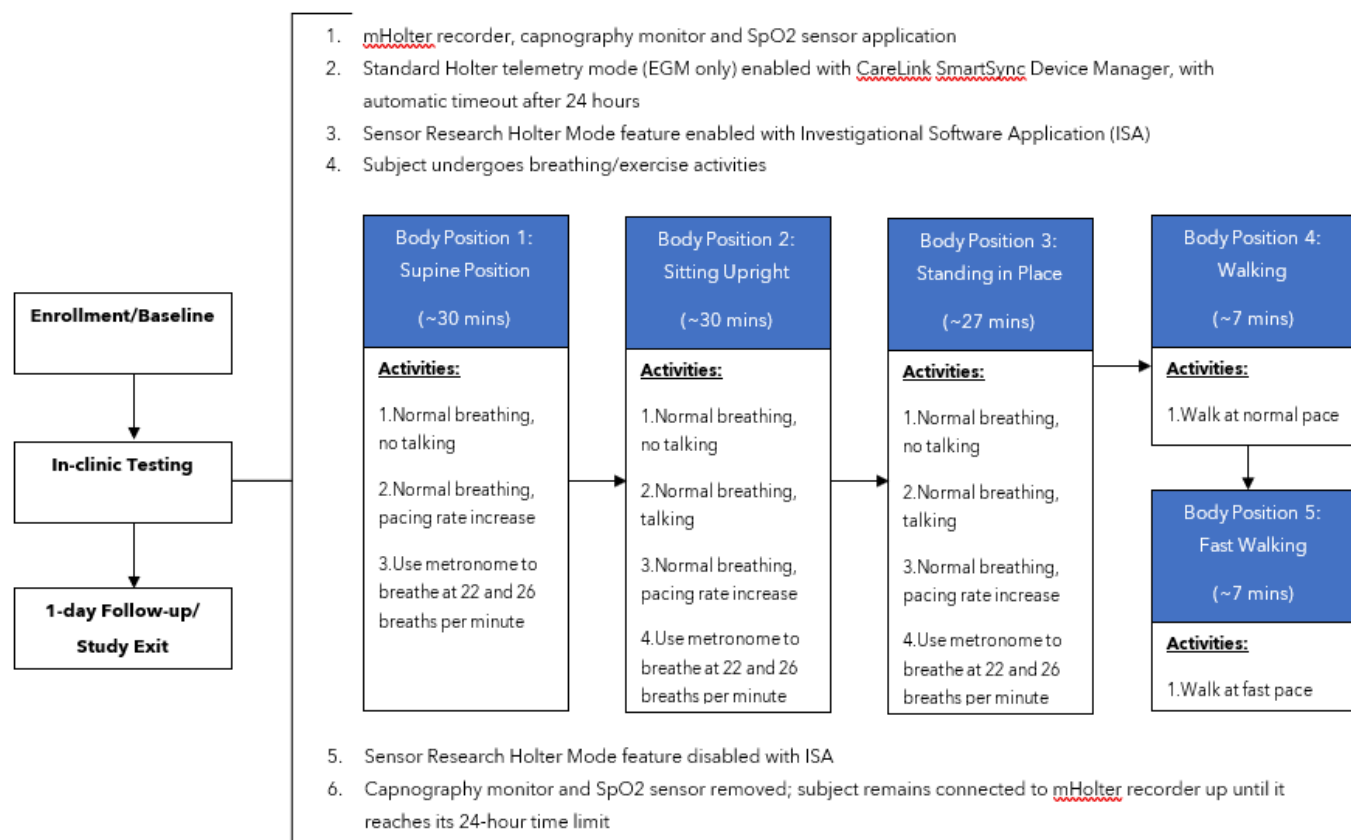


Figure 1. Subject-level Study Design

6. Determination of Sample Size

The study will enroll approximately 60 subjects. The first 15 will be used to modify the algorithm that calculates the respiration rate. The remaining 45 will be used in the primary objective. Table 1 shows what the 95% confidence and 80% probability tolerance interval would be with a sample size of 45, a mean of 0, and the standard deviation indicated in the first column. For example, if the standard deviation is 1.6, the tolerance interval is -2.5 – 2.5. This would meet the primary objective of being within ± 3 breaths per minute. With 45 subjects, as long as the mean daily RR difference is 0 and the standard deviation is 1.9 or less, the objective would be met.

Table 1: Tolerance Intervals (95%-80%) Under Varying Standard Deviations

Standard Deviation	Lower Tolerance Limit	Upper Tolerance Limit
1.5	-2.36557	2.36557
1.6	-2.52327	2.52327
1.7	-2.68098	2.68098
1.8	-2.83868	2.83868
1.9	-2.99638	2.99638
2.0	-3.15409	3.15409
2.1	-3.31179	3.31179
2.2	-3.46950	3.46950
2.3	-3.62720	3.62720
2.4	-3.78491	3.78491
2.5	-3.94261	3.94261
2.6	-4.10032	4.10032
2.7	-4.25802	4.25802
2.8	-4.41572	4.41572
2.9	-4.57343	4.57343
3.0	-4.73113	4.73113
3.1	-4.88884	4.88884

The table was constructed using SAS code similar to the following:

```
*CALCULATE TOLERANCE INTERVAL;
*https://www.afil.edu/STAT/statcoe_files/Tolerance%20Intervals%20Demystified.
pdf;
%MACRO TI (DATASET=, PARAM=, P=, ALPHA=);
PROC MEANS DATA=&DATASET;
VAR &PARAM;
OUTPUT OUT=DDD N=N MEAN=MEAN STD=STD;
RUN;

DATA TI;
SET DDD;
```

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```
P=&P/100;
ALPHA=&ALPHA/100;

* calculate K factor***;
Z=PROBIT((1+P)/2);
K1= Z*(SQRT(1+(1/N)));
CHISQ=CINV(ALPHA, N-1);
K2=SQRT((N-1)/CHISQ);
K=K1*K2;
TILOWER = MEAN - K*STD;
TIUPPER = MEAN + K*STD;
RUN;

PROC PRINT;
VAR N MEAN STD P ALPHA K TILOWER TIUPPER;
RUN;
%MEND;

/*data ten;*/
/*set med2;*/
/*if _n_>10 then delete;*/
/*run;*/
/**/
/*%TI(DATASET=ten,PARAM=DIFF,P=90,ALPHA=10);*/

DATA FORTY5;
DO X=1 TO 45;
DIFF=RAND("NORMAL",0,1);
OUTPUT;
END;
RUN;

%TI(DATASET=FORTY5,PARAM=DIFF,P=80,ALPHA=5);

DATA TOLLIM;
SET TI;
DO X=1.5 TO 3.1 BY 0.1;
LOWERTL=-K*X;
UPPERTL=K*X;
OUTPUT;
END;
FORMAT LOWERTL UPPERTL 8.2;
RUN;

PROC PRINT;
VAR X LOWERTL UPPERTL;
RUN;
```

6.1 Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subjects will be screened to ensure they meet all of the inclusion criteria and none of the exclusion criteria prior to being enrolled
- All sites will use the same version of the Clinical Investigation Plan and electronic Case Report Forms (eCRFs)
- All study site personnel will be trained to the study using standardized training materials prior to being allowed to participate
- Financial Disclosures will be collected from all investigators
- Maximum number of 30 subjects allowed to be contributed by a given site
- Monitoring visits will be conducted to verify CIP compliance and verification of source data

In summary, potential sources of bias that may be encountered in this clinical study have been considered and minimized by careful study design.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be summarized with at least the number of subjects enrolled.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Study deviations are collected as part of the study and will be summarized in the final report.

7.1.3 Analysis Sets

Subjects who are enrolled but do not undergo any of the respiration rate measurements will be excluded from all analyses.

Due to the study's sample size, subgroup analysis will be limited. The subgroups of most interest are heart failure / non-heart failure and gender.

The first 15 enrolled subjects' data will be used to refine the algorithm that converts EGM data to respiration rate to create a final algorithm. If any of the 15 subjects are missing data, they will not be replaced. The final algorithm will be applied to the final (~45) subjects' EGMs. Because they contributed to algorithm enhancement, the first 15 subjects will be excluded from the primary and ancillary objectives.

7.2 General Methodology

Not applicable

7.3 Center Pooling

Not applicable

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

Generally, missing data will not be included in analyses and will not be imputed, but will be reported (e.g., x% of data was missing).

7.5 Adjustments for Multiple Comparisons

No adjustments for multiple comparisons will be made.

7.6 Demographic and Other Baseline Characteristics

Demographics (e.g., age, sex, race, ethnicity, etc.) and other baseline characteristics will be summarized.

7.7 Treatment Characteristics

There is no treatment in this study.

7.8 Interim Analyses

No interim analysis is planned, though because this is a feasibility study, data may be looked at while the study is ongoing.

7.9 Evaluation of Objectives

7.9.1 Primary Objective

The endpoint of interest is the difference between the daily capnography respiration rate and the device-derived respiration rate. For each subject in the study, a daily respiration rate (RR) using a series of device-derived respiration rates will be calculated. Using capnography RRs from the same time periods, a daily capnography RR will be calculated. The daily capnography RR represents the true RR for the subject, and the goal is to demonstrate the daily device-derived RR is consistently within ± 3 breaths per minute of the true RR.

The data from this study is intended to be used to enable nightly median respiration rate to be available in future device iterations, where the device will calculate the daily respiratory rate by recording EGM

during a 60-second window every hour from 11pm – 6am and combine all non-active EGM-derived respiratory rates into a nightly median respiration rate. This study will replicate the 11pm – 6am measurements by measuring multiple respiratory rates while each subject is sitting and lying down.

Each subject will have RR measured by capnography and device in 52 one-minute increments under various use conditions or configurations (e.g., sitting/supine, normal/fast breathing, different device settings). Eight (8) of these minutes will be in supine position with normal breathing, no talking, and normal pacing, and another 4 will be in sitting position with normal breathing, no talking, and normal pacing. These likely best represent the nighttime 11pm – 6am hours.

To represent these 8 hours, 6 supine and 2 sitting minutes from each patient will be used. The 6 supine minutes will be the 2nd minute of the first configuration, both minutes from the second configuration, the 2nd minute of the third configuration, and both minutes from the fourth and final normal breathing, no talking, normal pacing configuration. The 2 sitting minutes will be the second minute of each of the two configurations. Decisions for the 8 measurements to use were based on the following thoughts:

- The second minute of a pair of measurements is more likely to be run correctly by the site and patient.
- The very first minute of data collection could be affected by events/activity prior.
- The first minute of the third configuration could have leftover effects from pacing in the immediately preceding configuration.

Missing measurements (not done, missing capnography RR, and/or missing device RR) will be replaced:

1. If sitting measurements are missing, use the first valid measurements from: The first minute of the second sitting configuration; then the first minute of the first sitting configuration.
2. If supine measurements are missing, use the first valid measurements from: The first minute from the first supine configuration; then the first minute from the third normal breathing, no talking, normal pacing supine configuration; then (if not used already), the first minute of the second sitting configuration; then the first minute of the first sitting configuration.
3. If there are still not 8 usable minutes of data, perform the daily RR calculation with less than 8 minutes as measurements could be unusable in future patients.

Table 2 Examples of Measurements to Use in Daily RR Calculation

Configuration					Example #1		Example #2		Example #3	
Position	Breathing	Talking	Pacing Increase	M e a s.	Meas. Available	Use in daily RR	Meas. Available	Use in daily RR	Meas. Available	Use in daily RR
Supine	Normal	No	No	1	Yes		Yes		Yes	
Supine	Normal	No	No	2	Yes	Yes	Yes	Yes	Yes	Yes
Supine	Normal	No	No	1	Yes	Yes	No		Yes	Yes
Supine	Normal	No	No	2	Yes	Yes	Yes	Yes	Yes	Yes
Supine	Normal	No	Yes	1	Yes		Yes		Yes	
Supine	Normal	No	Yes	2	Yes		Yes		Yes	
Supine	Normal	No	Yes	1	Yes		Yes		Yes	
Supine	Normal	No	Yes	2	Yes		No		Yes	
Supine	Normal	No	No	1	Yes		Yes	Yes	Yes	
Supine	Normal	No	No	2	Yes	Yes	Yes	Yes	Yes	Yes
Supine	Normal	No	No	1	Yes	Yes	Yes	Yes	Yes	Yes
Supine	Normal	No	No	2	Yes	Yes	Yes	Yes	Yes	Yes
Sitting	Normal	No	No	1	Yes		Yes	Yes	No	
Sitting	Normal	No	No	2	Yes	Yes	Yes	Yes	No	
Sitting	Normal	No	No	1	Yes		No		No	
Sitting	Normal	No	No	2	Yes	Yes	No		No	
Sitting	Normal	Yes	No	1	Yes		Yes		No	
Sitting	Normal	Yes	No	2	Yes		Yes		No	
Sitting	Normal	Yes	No	1	Yes		Yes		No	
Sitting	Normal	Yes	No	2	Yes		Yes		No	
Sitting	Normal	No	Yes	1	Yes		Yes		No	
Sitting	Normal	No	Yes	2	Yes		Yes		No	
Sitting	Normal	No	Yes	1	Yes		Yes		No	
Sitting	Normal	No	Yes	2	Yes		Yes		No	

The daily RR will be the median of the 8 (or fewer) selected RRs. It will be computed based on the RRs from the core lab's capnography analysis and the EGM-Derived Respiration (EDR)-algorithm using EGM2 (Rvcoil-can).

Using the difference in daily RRs (one per subject) between capnography and the device, a normal-distribution tolerance interval will be constructed, with 95% confidence and 80% reliability using standard methods involving the mean, standard deviation, and sample size of the observations in the study. The tolerance interval determines x and y for the statement, "There is 95% confidence that at least 80% of differences in daily RR are within x and y breaths per minute". If x is greater than -3, and y is less than 3, the objective will be met.

SAS code for the tolerance interval calculation:

```
*CALCULATE TOLERANCE INTERVAL;  
*https://www.ait.edu/STAT/statcoe_files/Tolerance%20Intervals%20Demystified.  
pdf;  
%MACRO TI (DATASET=, PARAM=, P=, ALPHA=);  
PROC MEANS DATA=&DATASET;  
VAR &PARAM;  
OUTPUT OUT=DDD N=N MEAN=MEAN STD=STD;  
RUN;  
  
DATA TI;  
SET DDD;  
  
P=&P/100;  
ALPHA=&ALPHA/100;  
  
* calculate K factor***;  
Z=PROBIT ( (1+P) / 2 ) ;  
K1= Z * (SQRT (1 + (1/N) ) ) ;  
CHISQ=CINV (ALPHA, N-1) ;  
K2=SQRT ( (N-1) / CHISQ ) ;  
K=K1*K2;  
TILOWER = MEAN - K*STD;  
TIUPPER = MEAN + K*STD;  
RUN;  
  
PROC PRINT;  
VAR N MEAN STD P ALPHA K TILOWER TIUPPER;  
RUN;  
%MEND;  
  
%TI (DATASET=MED2, PARAM=DIFF, P=80, ALPHA=5) ;
```

7.9.2 Ancillary Objective #1

Characterize respiration rate accuracy while subjects are participating in various levels of activity, pacing conditions, and body positions

The absolute difference in RR between capnography (based on the core lab reading) and device data (based on EDR using EGM2) will be calculated for each minute of paired capnography and device data. For the absolute difference in RR, means, standard deviations, and medians will be reported stratified by patient position, breathing technique, talking (yes/no), and increased pacing (yes/no).

7.9.3 Ancillary Objective #2

Collect Heart sounds and Bio-impedance data for beat-by-beat respiration tracking to inform potential development of future algorithms

This data is collected for future research purposes and will not be analyzed as part of the SAP.

7.9.4 Ancillary Objective #3

Collect at-home ambulatory EGM data while subjects are undergoing daily activities to serve as input to potential future algorithm development

This data is collected for future research purposes and will not be analyzed as part of the SAP.

7.10 Safety Evaluation

There are no defined safety endpoints for the study. All adverse events (AEs) will be collected throughout the duration of the study, beginning at the time of the subject signing informed consent through study exit.

To comply with ISO 14155 requirements, a summary of all adverse events and adverse device effects, including a discussion of the severity, treatment needed, resolution, and relevant principal investigator's judgment concerning the causal relationship with the investigational devices or procedure will be provided. All device deficiencies will be listed.

A listing of all deaths, including reason for death will be provided.

7.11 Health Outcomes Analyses

Not applicable

7.12 Changes to Planned Analysis

Not applicable

8. Validation Requirements

All analysis output going into reports or publications must be validated at either level I (independent programming) or level II (review by a second programmer).

9. References

Not applicable