

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 1 of 82



Medtronic Clinical Investigation Plan	
Clinical Investigation Plan/Study Title	Crome/Cobalt Respiration Study
Clinical Investigation Plan Identifier	MDT22030
Study Product Name	Crome™ and Cobalt™ Implantable Cardioverter Defibrillator (ICD) and Cardiac Resynchronization Therapy Defibrillator (CRT-D) MRI SureScan™ Systems
Sponsor/Local Sponsor (funding source)	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112
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Table of Contents

Table of Contents	2
Table of Figures.....	6
Table of Tables	6
1. Glossary.....	6
2. Synopsis	9
3. Introduction	16
3.1 Background	16
3.2 Purpose.....	16
4. Objectives and/or Endpoints	17
4.1 Objectives	17
4.1.1 Primary Objective	17
4.1.2 Ancillary Objective(s).....	17
5. Study Design	18
5.1 Duration.....	19
5.2 Rationale.....	19
6. Product Description.....	21
6.1 General	21
6.1.1 Crome™ and Cobalt™ ICD MRI SureScan™ Systems.....	24
6.1.2 Crome™ and Cobalt™ CRT-D MRI SureScan™ Systems.....	24
6.1.3 mHolter™ Recorder and mHolter Test Support Kit.....	25
6.1.4 Investigational Software Application	26
6.1.5 Medtronic Model 24970A CareLink SmartSync™ Device Manager Base	26
6.1.6 Medtronic Model 24967 Patient Connector.....	27
6.1.7 Device Manager Application	28
6.1.8 Capnostream™ 35 Portable Respiratory Monitor and Accessories	28
6.1.9 Smart CapnoLine® Plus, Adult/Intermediate-Oral-Nasal	29
6.1.10 Nellcor Flexible SpO2 Sensor.....	29
6.2 Manufacturer	30
6.3 Packaging.....	30
6.4 Intended Population	30

Medtronic Business Restricted

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 3 of 82



6.5 Equipment.....	30
6.6 Product Use.....	31
6.7 Product Training Materials.....	32
6.8 Product Receipt and Tracking	32
6.9 Product Storage	33
6.10 Product Return.....	33
6.11 Product Accountability	33
7. Study Site Requirements	35
7.1 Investigator/Investigation Site Selection.....	35
7.2 Study Site Activation.....	35
7.3 Role of the Sponsor Representatives.....	36
8. Selection of Subjects.....	37
8.1 Study Population	37
8.2 Subject Enrollment.....	37
8.3 Inclusion Criteria.....	37
8.4 Exclusion Criteria.....	38
9. Study Procedures	38
9.1 Schedule of Events.....	38
9.2 Data Collection.....	38
9.3 Subject Screening	40
9.4 Prior and Concomitant Medications/Therapies.....	40
9.5 Subject Consent.....	40
9.6 Enrollment/Baseline.....	41
9.7 In-clinic Testing Visit	42
9.8 1-day Follow-up Visit/Study Exit	42
9.9 Device Interrogation.....	43
9.10 CareLink Data	43
9.11 Subject Diary	43
9.12 Assessment of Safety	43
9.13 Recording Data	44
9.14 Deviation Handling	45
9.15 Subject Exit, Withdrawal or Discontinuation.....	46

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 4 of 82



9.15.1	Study Exit/Early Withdrawal	46
9.15.2	Study Completed	46
9.15.3	Lost to Follow-up	46
9.15.4	Subject Chooses to Exit (i.e., Revokes Consent).....	46
9.15.5	Investigator Withdraws Subject	47
10.	Risks and Benefits.....	47
10.1	Potential Risks	47
10.2	Risk Minimization	47
10.3	Potential Benefits	53
10.4	Risk-Benefit Rationale.....	53
10.5	Risk Determination.....	54
11.	Adverse Events and Device Deficiencies.....	54
11.1	Adverse Events	54
11.2	Device Deficiency	54
11.3	Processing Updates and Resolution.....	54
11.4	Definitions/Classifications.....	55
11.5	Reporting of Adverse Events and Device Deficiencies	59
11.5.1	Adverse Event and Device Deficiency Classification.....	59
11.5.2	Adverse Event and Device Deficiency Reporting Requirements.....	60
11.6	Subject Death	62
11.6.1	Death Classification and Reporting.....	63
11.7	Product Complaint Reporting.....	63
12.	Data Review Committees.....	64
12.1	Core Lab	64
12.2	Data Monitoring Committee.....	64
13.	Statistical Design and Methods.....	65
13.1	General Aspects of Analysis.....	65
13.2	Analysis Execution.....	65
13.3	Interim Analysis	65
13.4	Primary Objective.....	65
13.5	Ancillary Objective(s).....	67

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 5 of 82



13.5.1	Ancillary Objective #1	67
13.5.2	Ancillary Objective #2	67
13.5.3	Ancillary Objective #3	67
13.6	Sample Size Determination	67
13.7	Minimization of Bias.....	69
14.	Ethics.....	69
14.1	Statement(s) of Compliance	69
15.	Study Administration	70
15.1	Monitoring	70
15.1.1	Monitoring Visits	70
15.2	Data Management.....	71
15.3	Direct Access to Source Data/Documents	71
15.4	Confidentiality.....	72
15.5	Liability/Warranty/Insurance Information	72
15.6	CIP Amendments	72
15.7	Record Retention	72
15.7.1	Investigator Records.....	73
15.7.2	Sponsor Records	73
15.8	Reporting Requirements	74
15.8.1	Investigator Reports	74
15.8.2	Sponsor Reports	76
15.9	Publication and Use of Information	77
15.9.1	Publication Committee.....	78
15.9.2	Management of Primary, Secondary, and Ancillary Publications	78
15.9.3	Criteria for Determining Authorship	78
15.9.4	Transparency	79
15.10	Suspension or Early Termination	79
15.10.1	Planned Study Closure.....	79
15.10.2	Early Termination or Suspension	79
15.10.3	Procedures for Termination or Suspension	80
16.	References	81
17.	Appendices	81

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 6 of 82



17.1 Participating Investigator and Institutions.....	81
17.2 Institutional Review Board (IRB) List.....	81
18. Version History.....	82

Table of Figures

Figure 1. Subject-level Study Design.....	19
Figure 2. Example of Method.	21
Figure 3. mHolter Recorder System	26
Figure 4. CareLink SmartSync™ Device Manager.....	27
Figure 5. Patient Connector	28
Figure 6. Capnostream 35 Portable Respiratory Monitor	28
Figure 7. Smart CapnoLine Plus	29
Figure 8. etCO2 Sampling Line Illustration.....	29
Figure 9. Nellcor Flexible SpO2 Sensor	29
Figure 10. Respiration Rate Accuracy Determination	66

Table of Tables

Table 1: System Product/Component Information.....	22
Table 2: Product Disposition.....	34
Table 3: Data Collection and Study Procedure Requirements at Subject Visits.....	39
Table 4: Potential Risks and Risk Minimization.....	48
Table 5: Adverse Event and Device Deficiency Definitions	55
Table 6: Adverse Event Classification Responsibilities.....	60
Table 7: Reporting Requirements.....	60
Table 8: Core Laboratory Information	64
Table 9: Tolerance Intervals (95%-80%) Under Varying Standard Deviations	68
Table 10: Investigator Reports Applicable per Medtronic Requirements.....	75
Table 11: Sponsor Reports for the United States.....	76

1. Glossary

Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 7 of 82



Term	Definition
AF	Atrial Fibrillation
AT	Atrial Tachycardia
ATP	Antitachycardia Pacing
ASADE	Anticipated Serious Adverse Device Effect
Bio-Z	Bio-impedance
CFR	Code of Federal Regulation
CIP	Clinical Investigation Plan
COPD	Chronic Obstructive Pulmonary Disease
CRO	Clinical Research Organization
CRT-D	Cardiac Resynchronization Therapy Defibrillator
CRF	Case Report Form
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
DMC	Data Monitoring Committee
DoH	Declaration of Helsinki
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGM	Electrogram
etCO2	End-tidal Carbon Dioxide
FAL	Foreseeable Adverse Event List
FD	Financial Disclosure
FDA	Food and Drug Administration

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CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 8 of 82



Term	Definition
FDAAA	Food and Drug Administration Amendments Act
FICO2	Fractional Inspired Carbon Dioxide
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IC	Informed Consent
ICF	Informed Consent Form
ICD	Implantable Cardioverter Defibrillator
IDE	Investigational Device Exemption
IFU	Instructions For Use
ISF	Investigator Site File
ISO	International Organization for Standardization
LBBB	Left Bundle Branch Block
MRI	Magnetic Resonance Imaging
NSR	Nonsignificant Risk
PHI	Protected Health Information
PR	Pulse Rate
PSA	Pacing Systems Analyzer
RA	Regulatory Authority
RDC	Remote Data Capture
RR	Respiration Rate
RRT	Recommended Replacement Time
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 9 of 82

Medtronic

Term	Definition
SAP	Statistical Analysis Plan
SID	Subject Identification
SpO2	Oxygen Saturation
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

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2. Synopsis

Title	Crome/Cobalt Respiration Study
Clinical Study Type	Prospective, observational, non-randomized, multi-center, non-significant risk device clinical study
Product Name	Crome and Cobalt Implantable Cardioverter Defibrillator (ICD) and Cardiac Resynchronization Therapy Defibrillator (CRT-D) MRI SureScan™ Systems
Sponsor / Funding Source	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112
External Organizations	Clinimark, LLC 80 Health Park Drive, Suite 20 Louisville, CO 80027 Phone: (303) 926-5432
Indication under investigation	The study will utilize commercially approved Crome and Cobalt ICD and CRT-D MRI SureScan™ systems, which will become investigational for a short period of time during this study when an investigational feature, the Sensor Research Holter Mode feature, is enabled. Only subjects who have already been implanted with a Crome or Cobalt implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator will be enrolled in the study. The Crome and Cobalt CRT-D MRI SureScan™ systems are indicated for use in patients who are at significant risk of developing atrial and/or life-threatening ventricular arrhythmias and who have heart failure with ventricular arrhythmias. Heart failure patients must have experienced one or more of the following conditions:

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CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 10 of 82



	• NYHA Functional Class III or IV patients who remain symptomatic despite stable, optimal medical therapy and have LVEF ≤ 35% and a prolonged QRS duration • NYHA Functional Class II patients who have left bundle branch block (LBBB) with a QRS duration ≥ 130 ms and a LVEF ≤ 30% • NYHA Functional Class I, II, or III who are on stable, optimal medical therapy (if indicated) and have LVEF ≤ 50%, atrioventricular block (AV block), and are expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize right ventricular pacing The Crome and Cobalt ICD MRI SureScan™ systems are indicated for the automated treatment of patients who have experienced, or are at significant risk of developing, atrial and/or life-threatening ventricular arrhythmias through the delivery of antitachycardia pacing, cardioversion, and defibrillation therapies.																																
Investigation Purpose	The Crome/Cobalt Respiration Study is designed to compare 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 a Holter recorder).																																
Product Status	<table><tr><th colspan="4">Components already present</th></tr><tr><th>Model Number / Identifier</th><th>Component</th><th>Manufacturer</th><th>Investigational or Market-released</th></tr><tr><td>DTPB2D1 DTPB2D4</td><td>Cobalt™ HF CRT-D MRI SureScan™</td><td>Medtronic</td><td>Market-Released*</td></tr><tr><td>DTPB2Q1 DTPB2QQ</td><td>Cobalt™ HF Quad CRT-D MRI SureScan™</td><td>Medtronic</td><td>Market-Released*</td></tr><tr><td>DTPA2D4 DTPA2D1</td><td>Cobalt™ XT HF CRT-D MRI SureScan™</td><td>Medtronic</td><td>Market-Released*</td></tr><tr><td>DTPA22QQ DTPA2Q1</td><td>Cobalt™ XT HF Quad CRT-D MRI SureScan™</td><td>Medtronic</td><td>Market-Released*</td></tr><tr><td>DTPC2D1 DTPC2D4</td><td>Crome™ HF CRT-D MRI SureScan™</td><td>Medtronic</td><td>Market-Released*</td></tr><tr><td>DTPC2Q1 DTPC2QQ</td><td>Crome™ HF Quad CRT-D MRI SureScan™</td><td>Medtronic</td><td>Market-Released*</td></tr></table>	Components already present				Model Number / Identifier	Component	Manufacturer	Investigational or Market-released	DTPB2D1 DTPB2D4	Cobalt™ HF CRT-D MRI SureScan™	Medtronic	Market-Released*	DTPB2Q1 DTPB2QQ	Cobalt™ HF Quad CRT-D MRI SureScan™	Medtronic	Market-Released*	DTPA2D4 DTPA2D1	Cobalt™ XT HF CRT-D MRI SureScan™	Medtronic	Market-Released*	DTPA22QQ DTPA2Q1	Cobalt™ XT HF Quad CRT-D MRI SureScan™	Medtronic	Market-Released*	DTPC2D1 DTPC2D4	Crome™ HF CRT-D MRI SureScan™	Medtronic	Market-Released*	DTPC2Q1 DTPC2QQ	Crome™ HF Quad CRT-D MRI SureScan™	Medtronic	Market-Released*
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DTPB2Q1 DTPB2QQ	Cobalt™ HF Quad CRT-D MRI SureScan™	Medtronic	Market-Released*																														
DTPA2D4 DTPA2D1	Cobalt™ XT HF CRT-D MRI SureScan™	Medtronic	Market-Released*																														
DTPA22QQ DTPA2Q1	Cobalt™ XT HF Quad CRT-D MRI SureScan™	Medtronic	Market-Released*																														
DTPC2D1 DTPC2D4	Crome™ HF CRT-D MRI SureScan™	Medtronic	Market-Released*																														
DTPC2Q1 DTPC2QQ	Crome™ HF Quad CRT-D MRI SureScan™	Medtronic	Market-Released*																														

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056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 11 of 82



	DDPB3D1 DDPB3D4	Cobalt™ DR ICD MRI SureScan™	Medtronic	Market-Released*
	DVPB3D1 DVPB3D4	Cobalt™ VR ICD MRI SureScan™	Medtronic	Market-Released*
	DDPA2D4 DDPA2D1	Cobalt™ XT DR ICD MRI SureScan™	Medtronic	Market-Released*
	DVPA2D4 DVPA2D1	Cobalt™ XT VR ICD MRI SureScan™	Medtronic	Market-Released*
	DVPC3D1 DVPC3D4	Crome™ VR ICD MRI SureScan™	Medtronic	Market-Released*
	DDPC3D1 DDPC3D4	Crome™ DR ICD MRI SureScan™	Medtronic	Market-Released*
	24970A	CareLink SmartSync™ Device Manager Base	Medtronic	Market-Released
	24967	Patient Connector	Medtronic	Market-Released
	M01A01	CareLink SmartSync™ Platform	Medtronic	Market-Released
	M01A02	CareLink SmartSync™ Common Application	Medtronic	Market-Released
	D00U001	CareLink SmartSync™ Host Application	Medtronic	Market-Released
	D00U002	Pacing System Analyzer Application	Medtronic	Market-Released
	Components Provided by Medtronic			
	Model Number / Identifier	Component	Manufacturer	Investigational or Market-released
	MH01	mHolter™ Recorder	Medtronic	Market-Released
	MHKIT	mHolter Test Support Kit	Medtronic	Market-Released
	24967	Patient Connector with attached USB Cable	Medtronic	Market-Released**

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056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 12 of 82



	1.0.0	Investigational Software Application located on Medtronic-owned, commercially available laptop	Medtronic	Investigational
	PM35MN02	Capnostream™ 35 Portable Respiratory Monitor	Medtronic	Market-Released
	009818	Smart CapnoLine® Plus, Adult/Intermediate-Oral-Nasal	Medtronic	Market-Released
	FLEXMAX	Nellcor™ Flexible SpO2 Sensor	Medtronic	Market-Released
	DOC10	Nellcor™ Pulse Oximetry Interface Cable	Medtronic	Market-Released
	Not Applicable	Capnostream Accessories - Vesa adapter assembly accessories (PM35VAA) - Clamp (PM35MNF) - External charger (PM35CHG) - Removable battery (PM35BTY)	Medtronic	Market-Released
*The Crome and Cobalt ICD and CRT-D devices are market-released, but once the investigational Sensor Research Holter Mode feature is enabled on the devices, they will be considered investigational until the feature is disabled. Although considered investigational during this time period, the Crome and Cobalt ICD and CRT-D devices will maintain market-released functionality. **The 24967 Patient Connector is market-released, however, when used with the Investigational Software Application for the purposes of this study, it will be considered investigational.				
Primary Objective(s) and/or Endpoint(s)	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.			

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056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 13 of 82

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Ancillary Objective(s)	• Characterize respiration rate accuracy while subjects are participating in various levels of activity, pacing conditions, and body positions • Collect Heart sounds and Bio-impedance data for beat-by-beat respiration tracking to inform future algorithms • Collect at-home ambulatory EGM data while subjects are undergoing daily activities to serve as input to potential future algorithm development
Study Design	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 in the United States and approximately 60 subjects will be enrolled, with no more than 30 subjects enrolled per site. In addition, a minimum of 30% of all enrolled subjects will have a documented history of heart failure and a minimum of 20% of all enrolled subjects will be female (as identified at birth). Once a subject is enrolled, they will undergo a Baseline Visit prior to completing the In-clinic Testing Visit. All enrolled subjects will have a Holter recorder, capnography monitor and SpO2 sensor applied at the beginning of the In-clinic Testing Visit. The standard Holter telemetry mode will be turned on for 24 hours using the CareLink SmartSync™ Device Manager. The Sensor Research Holter Mode feature will then be enabled, using the Investigational Software Application, on their Crome or Cobalt ICD or CRT-D device before undergoing a series of breathing and exercise activities. After completing the in-clinic testing, the Sensor Research Holter Mode feature will be disabled and the capnography monitor and SpO2 sensor will be removed. Subjects will go home with the Holter recorder for collection of ambulatory data up until the Holter recorder reaches its 24-hour time limit, which begins once it's turned on at the In-clinic Testing Visit. Subjects will be asked to complete a Subject Diary to track their activities during this at-home data collection period. Subjects will then complete the 1-day Follow-up Visit, either in-person or remotely via phone call, and will then be exited from the study. The expected duration of subject participation in the study (from start of study procedures to study exit) is approximately 2 days. The expected total study duration (from time of first enrollment to the exit of last enrolled subject) is approximately 8 months.
Sample Size	The study will enroll approximately 60 subjects at up to 5 study sites across the US, with no more than 30 subjects enrolled per site. In addition, a minimum of 30% of all enrolled subjects will have a documented history of heart failure and a minimum of 20% of all enrolled subjects will be female (as identified at birth).

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056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 14 of 82

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Inclusion/Exclusion Criteria	<u>Inclusion Criteria:</u> 1. Subject has an active Crome™ or Cobalt™ ICD or CRT-D MRI SureScan™ system which has been implanted for at least 30 days and which has not yet reached the Recommended Replacement Time (RRT) 2. Subject is implanted with one of the following models of a true bipolar right ventricular lead manufactured by Medtronic: - Model 6946M - Model 6947 - Model 6947M - Model 6935 - Model 6935M 3. Subject is ≥ 18 years of age 4. Subject (or subject's legally authorized representative) is willing and able to provide written informed consent 5. Subject is willing and able to comply with study procedures <u>Exclusion Criteria:</u> 1. Subject has existing condition that necessitates the use of supplemental oxygen 2. Subject has active acute respiratory infection or respiratory disorder that may affect ability to perform breathing or exercise activities, as assessed by the investigator 3. Any concomitant condition that might endanger the subject through participation in the study or interfere with study procedures, as assessed by the investigator 4. Subject has an active or suspected lead integrity issue, in the opinion of the investigator 5. Subject is enrolled in another study that could confound the results of this study 6. Subject has NYHA Class IV heart failure
Study Procedures and Assessments	When a subject, or legally authorized representative, and the investigator or approved designee have signed and dated the Informed Consent Form, the subject is considered enrolled in the study. There are three study visits. A baseline assessment will be completed prior to the subject undergoing in-clinic testing. Subjects will complete a 1-day Follow-up Visit and then will be exited from the study. The enrollment/baseline and in-clinic testing visits can be performed on the same day, but subjects must be consented prior to initiation of any study-specific procedures. • Enrollment/Baseline

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056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 15 of 82

Medtronic

- In-clinic Testing
- 1-day Follow-up Visit/Study Exit

Study Procedure/ Assessment	Enrollment/ Baseline	In-clinic Testing	1-day Follow- up Visit ¹ / Study Exit
Informed Consent	X		
Eligibility Assessment	X		
Medical History	X		
Vital Signs	X		
Demographics	X		
Medications	X		
NYHA Classification ²	X		
Holter application		X	
Capnography/SpO2 Sensor application		X	
Sensor Research Holter Mode feature enabled		X	
Breathing / Exercise Activities		X	
Device Interrogations (Save session)		X	
Removal of Capnography/SpO2 Sensor equipment		X	
Sensor Research Holter Mode feature disabled		X	
Removal of Holter equipment			X
Subject Diary			X
Study Exit			X
Adverse Events	As they occur		
Device Deficiencies	As they occur		
Protocol Deviations	As they occur		

¹Visit may be completed remotely via phone call. If completed remotely, the subject must remove the mHolter recorder and mail the mHolter recorder and Subject Diary back to the site.

²NYHA Classification needs to be completed for all subjects with heart failure

Safety Assessments

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.

Statistics

For the primary objective, daily respiration rates will be calculated using a series of paired device-derived respiration rates and capnography waveform-derived respiration rates. The difference in daily respiration rate between the two methods will be summarized by a 95%-80% tolerance interval. If the entire tolerance interval is within ± 3 breaths per minute, then it will be demonstrated that there is 95% confidence that 80% of daily respiration rates are within ± 3 breaths per minute of the actual breaths per minute, and

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	therefore, device-derived respiration rate accuracy is acceptable. Other types of statistics may be reported as well.
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3. Introduction

3.1 Background

Respiratory rate is one of the key vital signs and elevated respiration rate has been shown to be a predictor of increased risk for heart failure hospitalization and mortality. Respiration rate is also useful in monitoring other diseases such as COPD, sleep apnea, and other neurological conditions that affect breathing (e.g., stroke). Published literature from cardiovascular implantable electronic devices (CIED) demonstrated the effect of respiration sensing in the HeartLogic algorithm in the MultiSENSE study. For the Boston Scientific COGNIS CRT-D system in NYHA class II, III, and IV patients, with the respiration sensor on, it improved the sensitivity of the alerts for the prediction of early detection of worsening heart failure [1]. Early developmental data sets have shown an increased sensitivity to heart failure related events with the addition of respiration rate. Being able to derive respiratory rates from an implantable device could lead to a reliable and automatic technique for measuring respiration and ultimately, allow for the continuous monitoring of patients for various disease states outside the clinic setting.

In this study, respiration-derived measures from the Crome™ and Cobalt™ ICD and CRT-D SureScan™ devices will be validated against the gold standard of capnography through a series of varying use conditions such as body position, exercise/breathing activities, and pacing rate. The ability to derive measures of respiration from an implantable device could overcome the current limitations and provide a reliable automated technique for measuring respiration.

The data and results from this study will be used to support the release of Respiration Rate (RR) being displayed in Cardiac Compass primarily for Crome and Cobalt ICD and CRT-D devices. The results may also inform a subsequent study and serve as clinical evidence for future features.

3.2 Purpose

Medtronic is sponsoring the Crome/Cobalt Respiration Study, a prospective, observational, non-randomized, multi-center, non-significant risk device clinical study. 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).

4. Objectives and/or Endpoints

4.1 Objectives

4.1.1 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.

The endpoint of interest is the difference between daily respiration rates. 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 difference of these daily RRs is of interest. 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.

4.1.2 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

The endpoints for this objective are the paired RRs measured by the device EGM and capnography during various activities.

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

The endpoints to be collected include amplitude and duration of heart sounds to correlate with heart failure status and Bioimpedance to measure inspiration and expiration timing for pacing algorithms. They will only be collected for further research purposes and not summarized as part of this study's report.

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

The endpoints for this objective are device-derived respiration rates over different time periods of ambulatory data.

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5. Study Design

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. If a subject exits without completing the required study procedures, the subject may be replaced. In addition, a minimum of 30% of all enrolled subjects will have a documented history of heart failure and a minimum of 20% of all enrolled subjects will be female (as identified at birth). 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. Approximately five Investigational Software Applications and five Model 24967 Patient Connectors with attached USB cables will be used in this study, as one of each is anticipated to be provided to each study site and used across all subjects at their site. The Crome and Cobalt ICDs and CRT-Ds used in the study are only considered investigational when the Sensor Research Holter Mode feature is enabled and approximately 60 subjects are anticipated to participate in the study. As the Crome and Cobalt ICDs and CRT-Ds are already implanted in the study participants, no additional devices will be required for this study.

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 Enrollment/Baseline and In-clinic Testing visits may occur on the same day, but subjects must be consented prior to initiation of any study-specific procedures. Once the in-clinic testing has been completed, the capnography monitor and SpO2 sensor will be removed and the Sensor Research Holter Mode feature on the subject's Crome or Cobalt device will be disabled. The subject's Crome or Cobalt device will be returned to its original settings, with the exception of the Holter telemetry mode parameter, which will remain set to 24 hours. Subjects will remain connected to the mHolter recorder when they leave the clinic up until the mHolter recorder reaches its 24-hour time limit, which begins once it's turned on at the In-clinic Testing Visit. All subjects will complete a 1-day Follow-up Visit, which may be done in person or remotely via phone call. Completion of the 1-day Follow-up Visit marks completion of the study and the subject will be exited from the study at this visit.

Participating sites that enroll faster than others will be allowed to do so in order to maintain an adequate enrollment rate. However, to ensure a widespread distribution of data and minimize study site bias in study results, the maximum number of subjects to be enrolled at a single study site is 30 subjects.

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

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056-F275 Rev E Clinical Investigation Plan Template

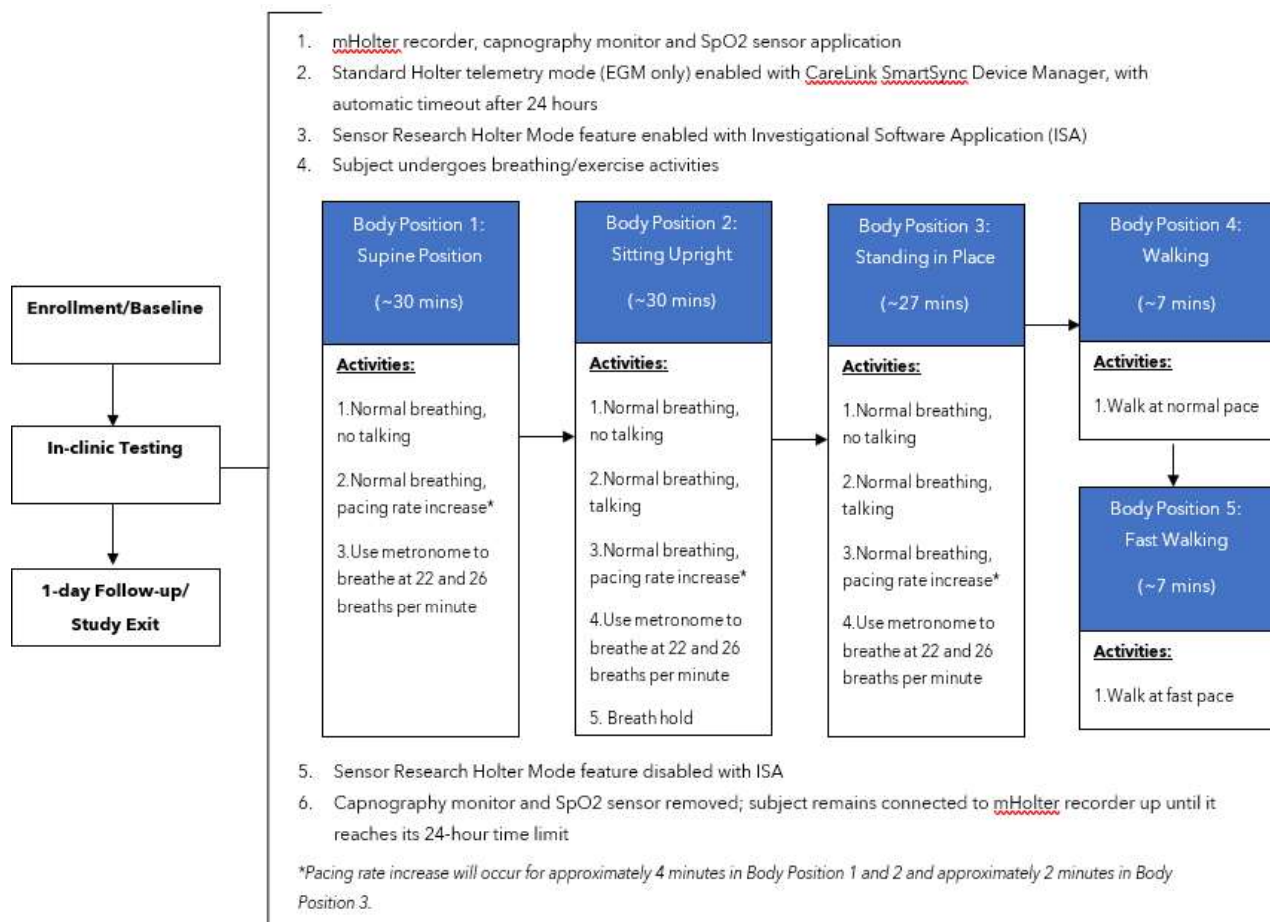


Figure 1. Subject-level Study Design

5.1 Duration

The expected total study duration is approximately 8 months, representing approximately 8 months of enrollment from the time of first site being activated, and 1 day of subject follow-up. Total subject participation (from enrollment to study exit) is approximately 2 days.

5.2 Rationale

It is well established that respiration (rate) can be derived from (surface) ECG recordings using the variation of the amplitude of the R-peak with respiration. The goal of this study is to evaluate if respiration (rate) can also be determined from intracardiac EGM data.

The rationale for the design is based on preliminary work using EGM peak amplitude detection to measure respiratory rate in two clinical studies using earlier ICD and CRT devices, and in an acute preclinical study in swine using the Crome/Cobalt dual chamber device.

The two clinical studies and their data sets are described below:

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- The REDUCEHF/PDR Study [2] with 24-hour Holter recording of 20 heart failure patients (NYHA Class II and III). The patients were implanted with Chronicle ICDs, and the RV coil – CAN EGM was used. The respiration rate calculated from the EGM was compared to truth via measurement using a respiration band (Braebon Medibyte). The EGM detection method resulted in an average (absolute) difference of 2.37 breaths per minute during the day, and 0.95 breaths per minute at night as compared to the respiration band. See Figure 2 for an example of the EGM detection method.
- In the Medtronic REST-HF Study (NCT03087084, 2018) 24-hour recordings of EGM were collected in 14 heart failure patients indicated for ICD or CRT implant or replacement (6 ICD + 8 CRT). Respiration rate calculated from the RV coil-CAN EGM was compared to true respiration rate derived from a respiration band (Biopac). The average (absolute) difference was 0.4 breaths per minute for valid EGM data collected during the night (0-6AM). The validity of the EGM was determined based on a set of objective criteria.

The preclinical work using the Crome/Cobalt dual chamber device in an acute, anesthetized swine (N=1) and the same detection algorithm showed good correlation with the signal derived by the EGM sense amplifier (sampled at 1kHz and filtered with the Tachy bandpass filter of 13-39Hz) and the ventilator rate. Additionally, the signals from holtered EGM derived from the EGM amplifiers in the device (sampled at 256Hz and filtered with the EGM bandpass filter of 2.5-100H) also correlated well with the ventilation signal.

An example of the EGM detection method is illustrated in Figure 2. The EGM-derived respiration rate is calculated by interpolating the time series of the peak amplitudes (red dots) and applying a breath detection algorithm on the filtered waveform. The breath detection algorithm is based on detecting the peaks in the filtered, interpolated waveform.

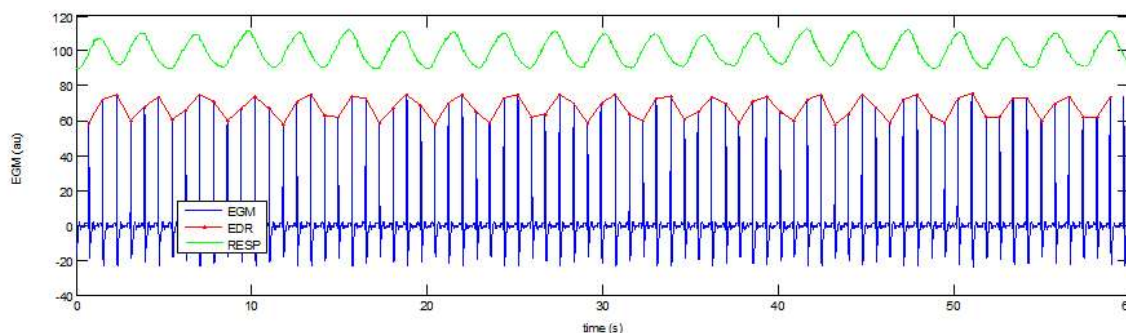


Figure 2. Example of Method. Respiration (red) derived from the RV coil-CAN EGM (blue) after interpolation and filtering, as compared to the true respiration rate (green) from an external respiratory band.

6. Product Description

6.1 General

Only subjects who have already been implanted with an active Crome or Cobalt ICD or CRT-D for at least 30 days, which has not yet reached the Recommended Replacement Time (RRT), will be enrolled in this study. The Crome and Cobalt ICDs and CRT-Ds are approved, programmable devices that provide treatment in patients who have experienced or are at significant risk of developing atrial and/or life-threatening ventricular arrhythmias. The Crome and Cobalt devices have the following approved indications:

US Indications:

- Crome™ and Cobalt™ CRT-D MRI SureScan™ systems are indicated for use in patients who are at significant risk of developing atrial and/or life-threatening ventricular arrhythmias and who have heart failure with ventricular arrhythmias. Heart failure patients must have experienced one or more of the following conditions:
 - o NYHA Functional Class III or IV patients who remain symptomatic despite stable, optimal medical therapy and have LVEF $\leq$ 35% and a prolonged QRS duration
 - o NYHA Functional Class II patients who have left bundle branch block (LBBB) with a QRS duration $\geq$ 130 ms and a LVEF $\leq$ 30%
 - o NYHA Functional Class I, II, or III who are on stable, optimal medical therapy (if indicated) and have LVEF $\leq$ 50%, atrioventricular block (AV block), and are expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize right ventricular pacing
- Crome™ and Cobalt™ ICD MRI SureScan™ systems are indicated for the automated treatment of patients who have experienced, or are at significant risk of developing, atrial and/or life-

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CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 22 of 82



threatening ventricular arrhythmias through the delivery of antitachycardia pacing, cardioversion, and defibrillation therapies.

The study will be conducted using the products/components described in Table 1 below, which includes the products that will be provided by Medtronic to complete the In-clinic Testing Visit. In addition, this study will use an investigational feature, the Sensor Research Holter Mode, which already exists in the Medtronic Crome and Cobalt ICD and CRT-D devices, however, is not market-released. Instructions for use (IFU) of the market-released devices used in this study are provided within their respective manuals. Instructions for use of the Investigational Software Application (ISA), the Sensor Research Holter Mode and the Patient Connector with attached USB cable provided by Medtronic specifically for use with the ISA will be provided in the User Manual specifically developed for this study. These products are intended for use by a trained Medtronic representative only, under the supervision of the investigator or appropriately delegated site personnel, at the In-clinic Testing Visit.

Table 1: System Product/Component Information

Components already present			
Model Number / Identifier	Component	Manufacturer	Investigational or Market-released
DTPB2D1 DTPB2D4	Cobalt™ HF CRT-D MRI SureScan™	Medtronic	Market-Released*
DTPB2Q1 DTPB2QQ	Cobalt™ HF Quad CRT-D MRI SureScan™	Medtronic	Market-Released*
DTPA2D4 DTPA2D1	Cobalt™ XT HF CRT-D MRI SureScan™	Medtronic	Market-Released*
DTPA22QQ DTPA2Q1	Cobalt™ XT HF Quad CRT-D MRI SureScan™	Medtronic	Market-Released*
DTPC2D1 DTPC2D4	Crome™ HF CRT-D MRI SureScan™	Medtronic	Market-Released*
DTPC2Q1 DTPC2QQ	Crome™ HF Quad CRT-D MRI SureScan™	Medtronic	Market-Released*
DDPB3D1 DDPB3D4	Cobalt™ DR ICD MRI SureScan™	Medtronic	Market-Released*
DVPB3D1 DVPB3D4	Cobalt™ VR ICD MRI SureScan™	Medtronic	Market-Released*
DDPA2D4 DDPA2D1	Cobalt™ XT DR ICD MRI SureScan™	Medtronic	Market-Released*
DVPA2D4	Cobalt™ XT VR ICD MRI SureScan™	Medtronic	Market-Released*

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 23 of 82



DVPA2D1			
DVPC3D1 DVPC3D4	Crome™ VR ICD MRI SureScan™	Medtronic	Market-Released*
DDPC3D1 DDPC3D4	Crome™ DR ICD MRI SureScan™	Medtronic	Market-Released*
24970A	CareLink SmartSync™ Device Manager Base	Medtronic	Market-Released
24967	Patient Connector	Medtronic	Market-Released
M01A01	CareLink SmartSync™ Platform	Medtronic	Market-Released
M01A02	CareLink SmartSync™ Common Application	Medtronic	Market-Released
D00U001	CareLink SmartSync™ Host Application	Medtronic	Market-Released
D00U002	Pacing System Analyzer Application	Medtronic	Market-Released
Components Provided by Medtronic			
Model Number / Identifier	Component	Manufacturer	Investigational or Market-released
MH01	mHolter™ Recorder	Medtronic	Market-Released
MHKIT	mHolter Test Support Kit	Medtronic	Market-Released
24967	Patient Connector with attached USB Cable	Medtronic	Market-Released**
1.0.0	Investigational Software Application located on Medtronic-owned, commercially available laptop	Medtronic	Investigational
PM35MN02	Capnostream™ 35 Portable Respiratory Monitor	Medtronic	Market-Released
009818	Smart CapnoLine® Plus, Adult/Intermediate-Oral-Nasal	Medtronic	Market-Released
FLEXMAX	Nellcor™ Flexible SpO2 Sensor	Medtronic	Market-Released
DOC10	Nellcor™ Pulse Oximetry Interface Cable	Medtronic	Market-Released
Not Applicable	Capnostream Accessories - Vesa adapter assembly accessories (PM35VAA) - Clamp (PM35MNF) - External charger (PM35CHG)	Medtronic	Market-Released

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CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 24 of 82

Medtronic

- Removable battery (PM35BTY)

*The Crome and Cobalt ICD and CRT-D devices are market-released, but once the investigational Sensor Research Holter Mode feature is enabled on the devices, they will be considered investigational until the feature is disabled. Although considered investigational during this time period, the Crome and Cobalt ICD and CRT-D devices will maintain market-released functionality.

**The 24967 Patient Connector is market-released, however, when used with the Investigational Software Application for the purposes of this study, it will be considered investigational.

6.1.1 Crome™ and Cobalt™ ICD MRI SureScan™ Systems

Implantable Cardioverter Defibrillator (ICD) systems are implantable heart devices which consist of a defibrillator and leads. The defibrillator, or ICD, is housed in the device can and continuously monitors the heart and automatically delivers therapies to correct fast heart rhythms when necessary. Leads are thin, soft insulated wires which carry the electrical impulse from the defibrillator to the heart and relay information about the heart's natural activity back to the implantable defibrillator. An external computer, or programmer, is used to program the heart device and retrieve information from the defibrillator, which will assist in arrhythmia and heart failure treatment.

The Medtronic Crome and Cobalt ICDs are multiprogrammable cardiac devices that monitor and regulate the patient's heart rate by providing single chamber or dual chamber (model-dependent), rate-responsive bradycardia pacing and ventricular tachyarrhythmia therapies. The devices can detect ventricular tachyarrhythmias (VT/VF) automatically and provide treatment with defibrillation, cardioversion, and antitachycardia pacing therapies. The device responds to bradyarrhythmias by providing bradycardia pacing therapy. The device also provides diagnostic and monitoring information that assists with system evaluation and patient care. For additional information regarding each ICD models' capabilities, please reference the commercially available product manual at <https://manuals.medtronic.com/manuals/main/region>.

The MRI SureScan feature permits a mode of operation that allows a patient with a SureScan system to be safely scanned by an MRI machine while the device continues to provide appropriate bradycardia pacing.

The Sensor Research Holter Mode that exists on the Medtronic Crome and Cobalt ICDs is not market-released and will be enabled during the study using the Investigational Software Application. The Sensor Research Holter Mode is an extensibility feature which allows streaming of sensor data (i.e., heart sounds and bio-impedance) that will be collected during the study. Data collection from these additional sensors is not possible for devices outside of this study. The Sensor Research Holter Mode feature will be disabled prior to the subject leaving the study site. Although the subject's Crome or Cobalt ICD will be considered investigational during the time period when the Sensor Research Holter Mode is enabled, the Crome and Cobalt ICD devices will maintain their market-released functionality when the feature is enabled.

6.1.2 Crome™ and Cobalt™ CRT-D MRI SureScan™ Systems

Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are implantable devices that send small electrical impulses to both lower chambers of the heart to help them beat together in a more synchronized pattern. The intent is to improve the heart's ability to pump blood and oxygen to the body.

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056-F275 Rev E Clinical Investigation Plan Template

The CRT-D is made up of two parts: the device can and the insulated wires or leads. The device can contains the battery and heart device. The leads carry information signals from the heart to the heart device and carry electrical impulses to the heart. An external computer, or programmer, is used to program the heart device and retrieve information from the heart device, which will assist in arrhythmia and heart failure treatment.

The Medtronic Crome and Cobalt CRT-Ds are multiprogrammable cardiac devices that monitor and regulate the patient's heart rate by providing single or dual chamber, rate-responsive bradycardia pacing, sequential biventricular pacing, ventricular tachyarrhythmia therapies, and atrial tachyarrhythmia therapies. The device can detect ventricular tachycardia and ventricular fibrillation (VT/VF) automatically and provide treatment with cardioversion and antitachycardia pacing therapies. The device can also detect atrial tachycardia and atrial fibrillation (AT/AF) automatically and provide treatment with cardioversion and antitachycardia pacing therapies. Simultaneous or sequential biventricular pacing is used to provide patients with cardiac resynchronization therapy. The device responds to bradyarrhythmias by providing bradycardia pacing therapies. The device also provides diagnostic and monitoring information that assists with system evaluation and patient care. For additional information regarding each ICD models' capabilities, please reference the commercially available product manual at <https://manuals.medtronic.com/manuals/main/region>.

The MRI SureScan feature permits a mode of operation that allows a patient with a SureScan system to be safely scanned by an MRI machine while the device continues to provide appropriate bradycardia pacing.

The Sensor Research Holter Mode that exists in the Medtronic Crome and Cobalt CRT-Ds is not market-released and will be enabled during the study using the Investigational Software Application. The Sensor Research Holter Mode is an extensibility feature which allows streaming of sensor data (i.e., heart sounds and bio-impedance) that will be collected during the study. Data collection from these additional sensors is not possible for devices outside of this study. The Sensor Research Holter Mode feature will be disabled prior to the subject leaving the study site. Although the subject's Crome or Cobalt CRT-D will be considered investigational during the time period when the Sensor Research Holter Mode is enabled, the Crome and Cobalt CRT-D devices will maintain their market-released functionality when the feature is enabled.

6.1.3 mHolter™ Recorder and mHolter Test Support Kit

The mHolter recorder is a non-medical device for use only in this clinical study and is not intended to be used to manage, diagnose, or treat patients. Pictured in Figure 3, the Medtronic mHolter recorder is an external, battery-powered, ambulatory recorder designed to record ECG and telemetered implantable device data continuously for up to 24 hours. It is a passive data recorder that provides no real time calibration, testing or quality control support information for any implanted devices. The recorded data is saved to a removable memory card and must be downloaded to a compatible Holter analysis system to be reviewed. The mHolter connects to the patient via cables and ECG electrodes. The mHolter accepts five patient ECG leads and records the patient's telemetered implantable device data via an external antenna adhered to the patient's skin directly over the implanted device.

The mHolter recorder package contents include the mHolter recorder, wearable pouch and strap, storage bag, and product documentation. The mHolter recorder performs no cardiac assessment or analysis of the patient's cardiac condition.

The mHolter Test Support Kit is a non-sterile kit that contains all the necessary tools for the proper application and use of the mHolter recorder.



Figure 3. mHolter Recorder System

6.1.4 Investigational Software Application

The Investigational Software Application (ISA) will be used to enable and disable the Sensor Research Holter Mode (SRHM) extensibility feature, which already exists in the Medtronic Crome and Cobalt ICD and CRT-D devices. Enabling the SRHM feature will allow for collection of data from additional sensors in the already implanted Crome and Cobalt ICD and CRT-D devices, such as impedance and heart sounds measurements. The ISA will also allow for the appropriate device configurations to be set, after the SRHM feature has been enabled, in order to obtain the desired data points. The Investigational Software Application will be located on a Medtronic-owned laptop for use during the study. This investigational application was developed by Medtronic strictly for use as defined in this study and is not intended to be market approved. The use of the ISA will not inhibit the normal operating functions of the implanted devices and will not modify any internal device parameters except those defined in this study. Once the study is over and the Medtronic-owned laptop has been received back by Medtronic, it will be wiped, and the application will be removed so that the Investigational Software Application is no longer available for use. A trained Medtronic representative is the only intended user of the Investigational Software Application, under the supervision of the investigator or appropriately delegated site personnel, and a separate User Manual will be developed for the Medtronic representative to follow for use in the study.

6.1.5 Medtronic Model 24970A CareLink SmartSync™ Device Manager Base

The CareLink SmartSync™ Device Manager is shown in Figure 4 and is intended to be used to interrogate and program Medtronic implantable devices and conduct a cardiac lead analysis session during Medtronic heart device implant or invasive troubleshooting. During the study, the CareLink SmartSync™ Device Manager will be used to obtain device interrogations and to increase the pacing parameters of the subject's Cobalt or Crome ICD or CRT-D device when the SRHM feature is enabled.

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The base is intended to be used as part of the CareLink SmartSync™ Device Manager system. The base provides the analyzer and ECG hardware for use during device implant, invasive troubleshooting, and implanted device follow-up procedures. Clinicians use the base's ECG connections along with the app display to view, measure, and record live cardiac waveforms. The base also provides a charge cradle and USB port to charge the patient connector. Additionally, the USB port is used to transmit data between the patient connector and the device manager app.



Figure 4. CareLink SmartSync™ Device Manager

6.1.6 Medtronic Model 24967 Patient Connector

The patient connector is shown in Figure 5 and is a hand-held, battery-operated telemetry device that is intended to be used with Medtronic apps to interrogate, analyze, and/or program implantable Crome or Cobalt ICDs and CRT-Ds. The patient connector uses Bluetooth® technology to transmit data to a Medtronic app for further processing.

Although commercially available, when the 24967 Patient Connector provided by Medtronic is used with the Investigational Software Application for the purposes of this study, it will be considered investigational as it will be used outside its approved indications for use. The Patient Connector will be used to enable communication between the subject's Crome or Cobalt ICD or CRT-D device and the ISA. The 24967 Patient Connector with attached USB cable provided by Medtronic for use in this study with the ISA will be labelled for investigational use.



Figure 5. Patient Connector

6.1.7 Device Manager Application

The device manager application is the primary interface of the device manager. The device manager app provides access to the implantable device apps and to the CareLink SmartSync™ Pacing System Analyzer (PSA) Application. The implantable device app is intended to be used as part of the device manager. Clinicians use the implantable device app with the patient connector to adjust programmable parameters and evaluate the performance of implantable Crome and Cobalt systems.

6.1.8 Capnostream™ 35 Portable Respiratory Monitor and Accessories

The Capnostream™ 35 monitor and its accessories provide continuous, non-invasive measurement and monitoring of:

- End-tidal carbon dioxide (etCO₂) – level of carbon dioxide in exhaled breath
- Respiratory rate (RR) – breaths per minute
- Fractional inspired carbon dioxide (FiCO₂) – level of carbon dioxide present during inhalation
- Peripheral oxygen saturation of arterial hemoglobin (SpO₂)
- Pulse rate (PR) – pulsatile cycle in beats per minute via pulse oximeter technology



Figure 6. Capnostream 35 Portable Respiratory Monitor

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056-F275 Rev E Clinical Investigation Plan Template

6.1.9 Smart CapnoLine® Plus, Adult/Intermediate-Oral-Nasal

A sample of the exhaled gases are delivered from the subject (via a cannula) into the Capnostream 35 Portable Respiratory Monitor for etCO₂ measurement, from which the respiratory rate will be derived. The etCO₂ sample line (also referred to as a filter line) is a disposable single use sampling line. Each study subject will be connected to the Capnostream monitor with an etCO₂ sampling line.

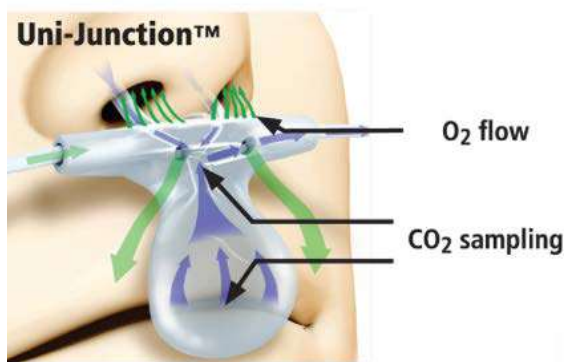


Figure 8. etCO₂ Sampling Line Illustration



Figure 7. Smart CapnoLine Plus

6.1.10 Nellcor Flexible SpO₂ Sensor

Pulse oximetry is a non-invasive method of measuring the amount of hemoglobin saturated with oxygen or SpO₂. Light emitting diodes (LEDs) emit red and infrared light. Changes in light absorption during the pulsatile cycle determine the SpO₂. Each study subject will be connected to the Capnostream 35 Portable Respiratory Monitor with a non-invasive, reusable SpO₂ disposable sensor applied to a finger (index finger preferred), which is inserted into the capnography monitor using the pulse oximetry interface cable.



Figure 9. Nellcor Flexible SpO₂ Sensor

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6.2 Manufacturer

All products and accessories that will be used in the study are manufactured by Medtronic. Additional manufacturing information can be found in the product manuals for each of the market-released items.

6.3 Packaging

All market-released products will be labeled according to their approved labeling.

The Investigational Software Application, located on a Medtronic-owned laptop, and the Model 24967 Patient Connector with attached USB cable provided by Medtronic for use with the ISA will both be labeled for investigational use only. The Crome/Cobalt Respiration Research System User Manual will be provided under separate cover.

6.4 Intended Population

The target population consists of 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 RRT, and who do not have any contraindications that would impact their ability to complete the required breathing and exercise activities.

The Crome™ and Cobalt™ CRT-D MRI SureScan™ systems are indicated for use in patients who are at significant risk of developing atrial and/or life-threatening ventricular arrhythmias and who have heart failure with ventricular arrhythmias. Heart failure patients must have experienced one or more of the following conditions:

- NYHA Functional Class III or IV patients who remain symptomatic despite stable, optimal medical therapy and have LVEF $\leq 35\%$ and a prolonged QRS duration
- NYHA Functional Class II patients who have left bundle branch block (LBBB) with a QRS duration ≥ 130 ms and a LVEF $\leq 30\%$
- NYHA Functional Class I, II, or III who are on stable, optimal medical therapy (if indicated) and have LVEF $\leq 50\%$, atrioventricular block (AV block), and are expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize right ventricular pacing

The Crome™ and Cobalt™ ICD MRI SureScan™ systems are indicated for the automated treatment of patients who have experienced, or are at significant risk of developing, atrial and/or life-threatening ventricular arrhythmias through the delivery of antitachycardia pacing, cardioversion, and defibrillation therapies.

6.5 Equipment

As there will be no test site equipment critical to be used for assessing endpoints for this study, no maintenance/calibration reports will be necessary by the site for this study. Medtronic will be responsible to ensure the equipment provided to sites are properly calibrated and maintained per the product manuals.



The CareLink SmartSync™ device manager must be available at each study site to support study activities. The CareLink SmartSync™ device manager consists of the following components:

- Medtronic Model 24970A CareLink SmartSync™ Device Manager Base
- Medtronic Model 24967 Patient Connector
- CareLink SmartSync™ Device Manager Application

Medtronic will provide the study sites with the following required equipment intended for use in the study by both trained site personnel and Medtronic personnel, as applicable:

- Capnostream™ 35 Portable Respiratory Monitor and Accessories
- Smart CapnoLine® Plus, Adult/Intermediate-Oral-Nasal
- mHolter™ Recorder
- mHolter Test Support Kit
- Nellcor™ Flexible SpO2 Sensor
- Nellcor™ Pulse Oximetry Interface Cable

Medtronic will also provide the study sites with the following required investigational equipment intended to be used by trained Medtronic personnel only for study purposes, under the supervision of the investigator or appropriately delegated site personnel:

- Investigational Software Application (located on Medtronic-owned laptop)
- Medtronic Model 24967 Patient Connector with attached USB cable (specifically for use with the ISA only)

In addition, Medtronic will provide the site with the appropriate data transfer equipment (e.g., USB, flash drive, etc.) and metronome, which will not be required to be tracked on the Product Accountability Log. The data transfer equipment and metronome are required to be provided back to Medtronic at the end of the study.

6.6 Product Use

Detailed instructions for use of the required market-approved equipment are available in their commercially approved device/user manuals.

The Investigational Software Application and Patient Connector with attached USB cable provided to the study site by Medtronic are both intended to be used by a qualified Medtronic Representative only, under the supervision of the investigator or appropriately delegated site personnel, and in accordance to the Crome/Cobalt Respiration Research System User Manual that has been developed for this study. In addition, the Sensor Research Holter Mode feature will only be enabled and disabled by a qualified Medtronic Representative and used in accordance to the User Manual.

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056-F275 Rev E Clinical Investigation Plan Template

6.7 Product Training Materials

All selected investigators must be qualified by training, education, and experience. All study site personnel participating in the study will be required to complete all study-specific training, as required in the Crome/Cobalt Respiration Study Training Plan and have proper delegation by the Principal Investigator (PI) on the Delegation of Authority Log maintained at the site. All study training will be documented.

Due to the non-interventional nature of this study and the fact that the Investigational Software Application is intended for Medtronic personnel use only, required training will be minimal.

6.8 Product Receipt and Tracking

Distribution of study products and components to study sites will be managed by Medtronic and will only occur when Medtronic has received all required documentation and has notified the site of their site activation and authorization to enroll.

The Sensor Research Holter Mode is an investigational feature that already exists in the market-released Medtronic Crome and Cobalt ICD and CRT-D devices that are already implanted in the study subjects and thus, will not be specifically tracked on the site's product accountability logs. Instead, the device information for each subject's Crome or Cobalt ICD or CRT-D device will be collected on a separate eCRF and the start/stop time the Sensor Research Holter Mode feature is enabled and disabled during the In-clinic Testing Visit will be recorded on the In-clinic Testing Visit eCRF.

Product accountability for all products provided to the study sites will be required to be tracked. Product accountability will be documented on the Device Accountability eCRF, which will be maintained in the Remote Database Capture (RDC) system. The Device Accountability eCRF will track, at a minimum, the following information:

- Model Number
- Lot, Serial or Kit Number
- Expiration Date, if applicable
- Receipt Date
- Received by Name
- Subject ID
- Date Used
- Date and reason for return, if applicable
- Method of return, if applicable
- Name of person responsible for return, if applicable

The following products will not be tracked by Subject ID or Date Used, which is considered an exception to ISO 14155:2020, due to the fact that products will be used across all subjects at the study site throughout the duration of the study:

- Investigational Software Application (located on Medtronic-owned laptop)
- 24967 Patient Connector with attached USB cable

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- Capnostream™ 35 Portable Respiratory Monitor
- Capnostream™ accessories
- Nellcor™ FLEXMAX SpO2 Sensor
- Nellcor™ Pulse Oximetry Interface Cable

6.9 Product Storage

The Investigational Software Application, which is located on a Medtronic-owned laptop, and the Model 24967 Patient Connector with attached USB cable provided by Medtronic for use with the ISA, once received at the study site, must be stored in a secure location at the study site. It is the responsibility of the investigator to correctly store and track the investigational products maintained at the study site. Investigational products will be used by a qualified Medtronic representative only, under the supervision of the investigator or appropriately delegated site personnel, and only in accordance with the User Manual.

It is the responsibility of the investigator to correctly handle, store and track market-released product, as applicable. These products will be used according to their approved labeling.

6.10 Product Return

All explanted devices or potentially defective products should be returned to Medtronic for analysis when permissible by local laws and regulations. If the products are explanted but not returned, a justification will be reported on the Device Accountability eCRF. To receive a Returned Product Mailer Kit, please contact your local Medtronic field personnel.

6.11 Product Accountability

Product delivery

Market released products:

Distribution of the market-released products to study sites during the study will be managed by Medtronic and can only be ordered by Medtronic personnel.

Investigational products:

The Investigational Software Application and the Model 24967 Patient Connector with attached USB cable provided by Medtronic for use with the ISA are considered investigational and are only intended for use by a qualified Medtronic Representative, under the supervision of the investigator or appropriately delegated site personnel. The ISA will be located on a Medtronic-owned laptop and both the ISA and Patient Connector will be distributed to a study site only when Medtronic has received all required documentation and has notified the study site of study site activation. Distribution of investigational product to study sites during the study will be managed by Medtronic and can only be ordered by Medtronic personnel.

The Sensor Research Holter Mode is an investigational feature that already exists in the market-released Medtronic Crome and Cobalt ICD and CRT-D devices that are already implanted in the study subjects and as such, does not require distribution to study sites.

Product receipt and tracking

Market released products:

Medtronic Business Restricted

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 34 of 82

Medtronic

Except for the Investigational Software Application, the Model 24967 Patient Connector with attached USB cable provided by Medtronic for use with the ISA, and the Sensor Research Holter Mode feature, all other components used in this study will be market released in the United States. As Medtronic is providing the market-released products to study sites, all products received at the study site must be tracked. These products will be tracked on the Device Accountability eCRF. Please see Table 2 below for the disposition of study products that Medtronic will provide to sites.

Table 2: Product Disposition

Model / Identifier	Component	Return to MDT at Study/Site Closure	Disposal After Each Use
MH01	mHolter™ Recorder	X	
MHKIT	mHolter Test Support Kit		X
24967	Patient Connector with attached USB cable	X	
1.0.0	Investigational Software Application located on Medtronic-owned laptop	X	
PM35MN02	Capnostream™ 35 Portable Respiratory Monitor and its accessories	X	
009818	Smart CapnoLine® Plus, Adult/Intermediate-Oral-Nasal		X
FLEXMAX	Nellcor™ FLEXMAX SpO2 Sensor	X	
DOC10	Nellcor™ Pulse Oximetry Interface Cable	X	
N/A	Metronome	X	
N/A	Data transfer equipment (i.e., USB, flash drive, etc.)	X	

Investigational products:

The study site is responsible for maintaining tracking of the Investigational Software Application, located on a Medtronic-owned laptop, and the Model 24967 Patient Connector with attached USB cable provided by Medtronic for use with the ISA during the study. These products will be tracked on the Device Accountability eCRF, which must be maintained at each study site and updated when the investigational product is received from or returned to Medtronic. In addition to tracking the date of events, the Device Accountability eCRF tracks product information including, but not limited to, date received, model/serial number, and expiration date for the received product, if applicable, and name of the person responsible for return.

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

The Sensor Research Holter Mode is an investigational feature that already exists in the market-released Medtronic Crome and Cobalt ICD and CRT-D devices that are already implanted in the study subjects and thus, will not be tracked on the site's Device Accountability eCRF. Instead, the device information for each subject's Crome or Cobalt device will be collected on a separate eCRF and the start/stop time the Sensor Research Holter Mode feature is enabled and disabled during the In-clinic Testing Visit will be recorded on the In-clinic Testing Visit eCRF.

Medtronic will perform periodic reconciliation of the investigational products to ensure traceability.

7. Study Site Requirements

7.1 Investigator/Investigation Site Selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be experienced in the field of application and training in the use of the Cobalt™ and Crome™ ICD and CRT-D MRI SureScan™ Systems
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results
- Be able to demonstrate that the proposed investigational study site:
 - Has the required number of eligible subjects needed within the recruitment period
 - Has one or more qualified investigators, a qualified investigational study site team and adequate facilities for the foreseen duration of the clinical investigation

Study site personnel training will be completed and documented prior to participation in this study.

7.2 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train study site personnel on the clinical investigation plan, on relevant standards and regulations, informed consent, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB approval (and voting list, as required by local law) of the current version of the CIP and ICF
- Fully executed Clinical Trial Agreement
- Financial disclosure of investigators

Medtronic Business Restricted

- Curriculum Vitae of investigators and key members of the investigation study site team (as indicated on the Delegation of Authority), signed and dated
- Signed Investigator Statement from investigators
- Documentation of delegated tasks
- Documentation of study training
- Additional requirements imposed by local regulations, the IRB and regulatory authorities shall be followed, if appropriate

In addition, all participating study site staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the principal investigator to perform study related activities.

Due to the non-interventional nature of the study and the fact that the Investigational Software Application was developed for purposes of this study only, an Investigator's Brochure will not be developed; this is considered an exception to ISO 14155:2020.

All activation related requirements will be conducted/collected in separate parts with the exception of a formal Site Initiation Visit (SIV)/SIV Report, in deviation from ISO 14155:2020. Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study related activities.

7.3 Role of the Sponsor Representatives

In addition to performing monitoring and auditing activities, sponsor representatives may provide support at the study site as required for the study under supervision of the Principal Investigator, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Provide technical support at visits under the supervision of a study investigator

In addition, for this study, sponsor representatives may be authorized by the principal investigator to perform the following significant trial related duties:

- Provide data collection/technical support during the In-clinic Testing Visit
- Perform device programming and device interrogation, as applicable

Sponsor representatives may not perform the following:

- Practice medicine, provide medical diagnoses or make decisions related to subject treatment/care
- Discuss a subject's condition or medical treatment with the subject or a member of the subject's family
- Complete source documents or entry into the electronic medical record
- Enter data on eCRFs, with the exception of Medtronic Use Only fields/forms

Medtronic Business Restricted

Any data collection completed by Medtronic personnel will be clearly identified.

8. Selection of Subjects

8.1 Study Population

The target population will include adult subjects who are ≥ 18 years of age, who have an active, implanted Crome or Cobalt ICD or CRT-D system that's been implanted for at least 30 days and which has not yet reached the RRT, and who do not have any contraindications that would impact their ability to complete the required breathing and exercise activities, which aligns with the key eligibility criteria for the study. The study will enroll approximately 60 subjects, with no more than 30 subjects enrolled per site. In addition, a minimum of 30% of all enrolled subjects will have a documented history of heart failure and a minimum of 20% of all enrolled subjects will be female (as identified at birth).

Subjects who meet the eligibility criteria listed in [Sections 8.3](#) and [8.4](#) are eligible to participate in the study.

8.2 Subject Enrollment

When a subject and the principal investigator or authorized designee, as required, have personally signed and dated the ICF, the subject is considered enrolled in the study. The date the subject signed the ICF and data protection authorization, if applicable, must be documented in the subject's medical records.

Subjects will be screened to ensure they meet all of the inclusion and none of the exclusion criteria prior to study enrollment. Informed consent must be obtained prior to performing any study-related procedures.

8.3 Inclusion Criteria

1. Subject has an active Crome™ or Cobalt™ ICD or CRT-D MRI SureScan™ system which has been implanted for at least 30 days and which has not yet reached the Recommended Replacement Time (RRT)
2. Subject is implanted with one of the following models of a true bipolar right ventricular lead manufactured by Medtronic:
 - Model 6946M
 - Model 6947
 - Model 6947M
 - Model 6935
 - Model 6935M
3. Subject is ≥ 18 years of age
4. Subject (or subject's legally authorized representative) is willing and able to provide written informed consent

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5. Subject is willing and able to comply with study procedures

8.4 Exclusion Criteria

1. Subject has existing condition that necessitates the use of supplemental oxygen
2. Subject has active acute respiratory infection or respiratory disorder that may affect ability to perform breathing or exercise activities, as assessed by the investigator
3. Any concomitant condition that might endanger the subject through participation in the study or interfere with study procedures, as assessed by the investigator
4. Subject has an active or suspected lead integrity issue, in the opinion of the investigator
5. Subject is enrolled in another study that could confound the results of this study
6. Subject has NYHA Class IV heart failure

9. Study Procedures

9.1 Schedule of Events

Following signing of the informed consent, enrolled subjects will complete a baseline assessment, which will consist of collection of their medical history and demographics. Following the completion of the baseline assessment, subjects will complete an In-clinic Testing Visit where they will perform various breathing and exercise activities after the application of the mHolter recorder, capnography monitor, and SpO2 sensor and the Sensor Research Holter Mode feature has been enabled with the Investigational Software Application (ISA). The baseline assessment and In-clinic Testing Visits may occur on the same day, as long as the required baseline assessments are completed prior to beginning the in-clinic testing procedures with the subject. Following the In-clinic Testing Visit, subjects will remain connected to the mHolter recorder when they leave the clinic and will continue to provide ambulatory data up until the mHolter recorder reaches its 24-hour time limit. After at least 24 hours and not more than 48 hours have passed, subjects will complete a 1-day Follow-up Visit, which may be completed in person or remotely via phone call. If completed via phone call, subjects will be responsible to remove their mHolter recorder and return it to the study site via mail, along with their Subject Diary. Completion of the 1-day Follow-up Visit marks completion of the subject's study participation and the subject will be exited from the study at this visit. The study procedures outlined in this Clinical Investigation Plan are not standard practice for this patient population, however, are study-driven procedures required to be completed by those enrolled in the study.

9.2 Data Collection

The requirements for data collection and study procedures associated with each visit are summarized in Table 3 below.

Should a subject miss the 1-day Follow-up Visit or the 1-day Follow-up Visit falls outside the pre-specified window (i.e., at least 24 hours and not more than 48 hours post In-clinic Testing Visit), a study deviation must be reported. Data analyses include follow-up visits, regardless of whether the visit occurs on time. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation report via eCRF.

Medtronic Business Restricted

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 39 of 82

Medtronic

Table 3: Data Collection and Study Procedure Requirements at Subject Visits

Study Procedure	Enrollment/ Baseline	In-clinic Testing	1-day Follow- up Visit ¹ / Study Exit
Informed consent	X		
Eligibility assessment	X		
Medical history	X		
Vital Signs	X		
Demographics	X		
Medications	X		
NYHA Classification ²	X		
Holter application		X	
Capnography/SpO2 sensor application		X	
Sensor Research Holter Mode feature enabled		X	
Breathing / exercise activities		X	
Device interrogations (Save session)		X	
Removal of capnography/SpO2 sensor equipment		X	
Sensor Research Holter Mode feature disabled		X	
Removal of Holter equipment			X
Subject diary			X
Study Exit			X
Adverse Events	As they occur		
Device Deficiencies	As they occur		
Protocol Deviations	As they occur		

¹Visit may be completed remotely via phone call at least 24 hours and not more than 48 hours following the In-clinic Testing Visit. If completed remotely, the subject is responsible for removal of the mHolter recorder and mailing the mHolter recorder and their Subject Diary back to the study site.

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

²NYHA Classification needs to be completed for all subjects with heart failure

9.3 Subject Screening

All subjects will be screened to ensure they meet all of the inclusion criteria and none of the exclusion criteria prior to study enrollment. The subject will be considered enrolled after both the subject and the investigator (or authorized designee) have each personally signed and dated the ICF.

9.4 Prior and Concomitant Medications/Therapies

There are no medication/therapy restrictions in the study. All cardiovascular, pulmonary and anti-diabetic medications already prescribed to the subjects at baseline will be documented on the Medication eCRF.

9.5 Subject Consent

Informed consent is defined as a legally effective documented confirmation of a subject's, or their legally authorized representative's, voluntary agreement to participate in a particular clinical study after information has been given and explained to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining an ICF and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law that has been approved by the study site's Institutional Review Board (IRB) and signed and dated by the subject or their legally authorized representative.

Investigators shall consider all subjects who meet eligibility requirements for study participation to avoid any bias in the subject population. Prior to enrolling subjects, approval of the CIP, ICF and any other written study information to be provided to the subjects must have been obtained from each site's IRB. The document(s) must be controlled (i.e., versioned and/or dated) to ensure it is clear which version(s) were approved by the IRB. Any adaptation of the sample ICF must be reviewed and approved by Medtronic and the IRB reviewing the application prior to enrolling subjects. The template ICF will be provided under separate cover.

The investigator must notify the subject, or their legally authorized representative, of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, consent may be requested from subjects to confirm their continued participation.

Prior to initiation of any study-specific procedures, informed consent must be obtained from the subject or their legally authorized representative. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize study sites to submit subject information to the study sponsor. The informed consent process must be conducted by the principal investigator or an authorized designee, and the ICF and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be given to the subject, or their legally authorized representative, in a language they are able to read and understand. The process of obtaining informed consent must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other study site personnel. The informed consent process shall not waive or appear to waive the subject's legal rights. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

The subject must have ample time and opportunity to read and understand the ICF, to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the study, the ICF must be signed and personally dated by the subject, or their legally authorized representative, acknowledging that their participation is voluntary, and signed and personally dated by the investigator or authorized designee.

In the event the subject cannot read and/or write, a witnessed (impartial third party) informed consent will be allowed. In this situation, an independent witness must be present throughout the informed consent process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject. Whenever possible, either the subject or their legally authorized representative shall sign and personally date the informed consent form. The witness must sign and personally date the ICF attesting that the information was accurately explained, and that informed consent was freely given. Detailed documentation of the consent process must be recorded in the subject's case history. The ICF should document a supervised oral process was used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original, signed ICF must be filed in the hospital/clinical chart and/or with the subject's study documents. A copy of the ICF and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, signed and dated as required by law, must be provided to the subject and their legally authorized representative, if applicable.

If the ICF is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the informed consent process to be documented in the subject's case history, regardless of circumstance.

The ICF and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be available for monitoring and auditing. Any Medtronic Field personnel who support the in-clinic testing procedures must be able to review the subject's signed and dated ICF and verify its completeness prior to proceeding with the testing. In the event the Medtronic Field personnel identify the ICF as being incomplete, the in-clinic testing will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

9.6 Enrollment/Baseline

A subject is considered enrolled when the consent process has been finalized. The date the subject, or the subject's authorized representative, signed the ICF and Data Protection Authorization, as required by law, must be documented in the subject's medical records. A log of all subjects enrolled in the study should be maintained. Once consent is obtained, report adverse events/deaths, device deficiencies, study deviations and subject exits as they occur.

Following subject enrollment, a baseline assessment will be completed. The baseline assessment can be completed on the same day as subject enrollment and must occur prior to the in-clinic testing.

The following procedures/data collection are required to be collected at the enrollment/baseline visit:

- Informed consent
- Eligibility criteria assessment

Medtronic Business Restricted

- Demographics
- Vital Signs
- Medications
- Medical History
- NYHA Classification, if subject has heart failure
- Assessment for AEs/DDs

9.7 In-clinic Testing Visit

Once the baseline visit has been completed, it is preferred for the In-clinic Testing Visit to occur within a week post-baseline visit completion, which could be the same day as the baseline visit. The following procedures/data collection are required for the in-clinic testing visit:

- A minimum of two device interrogations/save sessions will be obtained, with one being a full “Interrogate ALL” device interrogation
 - The first interrogation/save session should be obtained prior to the Sensor Research Holter Mode feature being enabled and the final interrogation/save session should be obtained after the Sensor Research Holter Mode feature has been disabled
 - If it is determined on the initial device interrogation that the subject has received high-voltage or Antitachycardia Pacing (ATP) therapy from their ICD or CRT-D device within the past 24 hours or has a new onset arrhythmia, the subject should not undergo the In-clinic Testing Visit and should be exited from the study.
- Study Testing Procedure Steps:
 - Application of mHolter recorder, capnography monitor and SpO2 sensor
 - Standard Holter telemetry mode turned on for 24 hours with CareLink SmartSync™ Device Manager
 - Sensor Research Holter Mode feature enabled
 - Breathing/exercise activities (Please reference Figure 1 above for additional details)
 - ☐ Some activities will be repeated in the same body position in order to capture specific sensor data
 - ☐ Subjects will be asked to perform each activity for approximately 2 minutes
 - Removal of capnography monitor and SpO2 sensor
 - Sensor Research Holter Mode feature disabled
 - Subject remains connected to mHolter recorder for collection of ambulatory data up until the mHolter recorder reaches its 24-hour time limit, which begins once it’s turned on at the beginning of the In-clinic Testing visit
- Assessment for AEs/DDs

9.8 1-day Follow-up Visit/Study Exit

All enrolled subjects will be required to complete a 1-day Follow-up Visit to allow for the collection of ambulatory at-home data and the assessment of subject status. The 1-day Follow-up Visit should be

Medtronic Business Restricted

completed at least 24 hours and not more than 48 hours post In-clinic Testing Visit. This visit may be completed in-person or remotely via phone call. If completed remotely, the subject is responsible to remove their mHolter recorder and mail it back to the study site, along with their Subject Diary.

The following information is required to be collected at the 1-day follow-up visit:

- Subject Diary
- mHolter recorder removed from subject and returned to study site
- Assessment for AEs/DDs
- Study Exit eCRF

9.9 Device Interrogation

For the In-clinic Testing Visit, at minimum, an initial and final interrogation/save session will need to be obtained, with at least one of them being a full “Interrogate ALL” device interrogation. Both device interrogations must be performed and saved to the SmartSync tablet via SAVE SESSION. The save operation generates a PKG file that includes the implantable device data (.pdd file) and any reports generated during the session. The saved session data are then exported from the SAVED REPORTS on the SmartSync tablet via SEND TO... of the PKG file, of which the .pdd file will be extracted and saved in a digital format. The original file should be stored at the study site and a copy should be sent to Medtronic. It is recommended that data are not cleared during any interrogation.

9.10 CareLink Data

CareLink transmissions are not required as part of the study data collection efforts. However, if CareLink is available, transmissions are recommended to occur per the study site’s standard of care. In the US, CareLink transmitted data may be used to help study management and assist event review, however, they will not serve as a substitution of follow-up visits.

9.11 Subject Diary

While subjects are at home wearing the mHolter recorder, they will be asked to complete a Subject Diary in order to collect the activities they undergo while wearing the mHolter recorder following the In-Clinic Testing Visit. The following information will be collected on this diary, which is expected to be provided to the site personnel at the 1-day Follow-up / Study Exit Visit:

- Time of activity (start and stop)
- Description of activity
 - The following activities should be recorded in the Subject Diary:
 - Going to sleep
 - Waking up
 - Any significant, sustained change in physical activity

9.12 Assessment of Safety

There are no defined safety endpoints for this study, however, AE information is collected in this study. See [Section 11](#) for further information on the collection of AEs and safety information.

9.13 Recording Data

Data entered must be traceable to source documents. Source documentation is defined as the first time data appear, and may include original documents, data, and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory notes, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, subject files, device data, etc.). Subject records must be clearly marked to indicate the subject participation in the study.

Subject data will be collected on electronic Case Report Forms (eCRFs) via a web-based remote data capture (RDC) system. The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs. Only authorized persons can complete and sign eCRFs, as specified on the Delegation of Authority Log included in the Investigator Site File (ISF). In general, eCRFs (or paper copies) may not serve as source documents. Source documentation for data elements not routinely captured in medical records may vary from study site to study site; the study site may use source document worksheets if identified as source documents.

The investigator must ensure the availability of source documents from which the information on the eCRFs were derived. The type and location of source documents should be documented. Where printouts of electronic medical records are provided as source documents, or where copies of source documents are retained as source documents, those should be certified. Certification must contain (1) the signature of the individual making the copy and (2) the date the copy was made.

Data will be collected from the Capnostream 35 Portable Respiratory Monitor, mHolter recorder and the CareLink SmartSync™ Device Manager during the study. A USB will be used to collect the capnography waveforms from the Capnostream Monitor and the device interrogations. The mHolter recorder uses an SD card to collect and store data, which will be downloaded by the site personnel or a Medtronic representative while on-site.

The source documents must be made available for monitoring or auditing by Medtronic's representative or representatives of other applicable regulatory agencies. The eCRF may be considered source for the following data collection elements:

- Enrollment Notification
 - Study site assigned subject reference
- Baseline
 - Administrative information
- Device Accountability eCRF
 - All fields on this eCRF may be considered source
- AE eCRF
 - Date study site became aware of event
 - Relatedness of adverse event
- Non-Subject AE
 - Date study site became aware of event
 - Relatedness of adverse event

Medtronic Business Restricted

- DD eCRF
 - Date study site became aware of event
- Deviations
 - Reason for deviation

9.14 Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g., subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply for study duration. This may also apply for other unforeseen situations (e.g., the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on the Protocol Deviation eCRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. Multiple deviations of the same type at the same visit may be reported on one eCRF.

In the event the deviation involves a failure to obtain a subject's consent or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB/EC as well as Medtronic within five (5) working days. Reporting of all other study deviations must comply with IRB policies and/or local laws and must be reported to Medtronic as soon as possible upon the study site becoming aware of the deviation. Refer to [Section 15.8](#) for required investigator reports and other deviation reporting requirements and timeframes for reporting to Medtronic and/or other regulatory agencies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g., amend the CIP, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and study site, and in some cases, may necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic will provide site-specific reports to investigators summarizing information on deviations that occurred at the investigational study site on a periodic basis.

Examples of study deviations include but are not limited to:

- Failure to obtain proper informed consent
- Failure to collect required study data (e.g., required device data)
- Inclusion/exclusion criteria not met

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9.15 Subject Exit, Withdrawal or Discontinuation

9.15.1 Study Exit/Early Withdrawal

Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system and/or study testing procedure related AEs are resolved or unresolved with no further actions planned. A study exit eCRF is required to be completed for all subjects and the study site is required to document the reason for exit on the study exit eCRF. Following exit, subjects will continue to receive standard medical care.

Upon exiting from the study, no further study data will be collected, or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.

Subjects are urged to remain in the study through the 1-day Follow-up Visit, but may be exited from the study for any of the following situations:

- Subject lost to follow-up
- Subject death
- Subject did not meet inclusion/exclusion criteria
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)

The following information is required to be collected at study exit:

- Date of exit
- Reason for exit
- Assessment for AEs/DDs

9.15.2 Study Completed

At the completion of the 1-day Follow-up Visit, subjects will be exited from the study. The 1-day Follow-up and Study Exit Visits should be combined, and the 1-day Follow-up / Study Exit eCRF needs to be completed. Following study completion, subjects will continue to receive standard medical care.

9.15.3 Lost to Follow-up

Before documenting a subject as lost to follow-up on the study exit eCRF, the investigator should make efforts to confirm the health status of the subject through documenting at least two attempts to contact the subject, subject's relatives or other persons associated with the subject (e.g., phone, email, mailed letter). The method of attempt must be documented in the subject's medical record. The investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. In addition, regulation set forth by the governing IRB must be followed.

9.15.4 Subject Chooses to Exit (i.e., Revokes Consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e., the subject revokes consent), the study site is required to document the reason for exit on the Study Exit eCRF. In addition, study sites shall follow the regulations set forth by the governing IRB.

Medtronic Business Restricted

Permission may be requested to follow up with the subject outside of the study due to withdrawal based on problems related to the investigational feature, safety, or performance. If possible, the following data should be collected prior to subject withdrawal:

- Reason for exit
- All ongoing AEs are resolved or unresolved with no further actions planned

9.15.5 Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study team prior to withdrawing subjects. If an Investigator Withdrawal is necessary, the date and reason for subject withdrawal should be collected.

10. Risks and Benefits

10.1 Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. The risk analysis process for the Crome/Cobalt Respiration Study is being performed in accordance with ISO 14971 and will ensure that the level of risk is acceptable prior to starting the study.

There are potential risks or side effects associated with the use of the Investigational Software Application and Research Sensor Holter Mode feature with the Crome and Cobalt ICD and CRT-Ds. The Investigational Software Application (ISA) was developed solely for the purposes of this study and both the ISA and the Sensor Research Holter Mode feature have not been used in any previous clinical studies or investigations. Table 4 below describes the foreseeable, potential adverse events that could occur as a result of the use of the study research system or participation in the study. The risks associated with the use of the market-approved products are included in their commercially available product information. There may be additional discomforts or risks associated with participation in this study that are not foreseen at this time.

10.2 Risk Minimization

The potential risks associated with the Investigational Software Application and Sensor Research Holter Mode feature were identified, assessed, evaluated and effectively controlled. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the Clinical Investigation Plan.

Medtronic has further minimized the possibility of risks by: performing required laboratory and pre-clinical testing prior to the clinical study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 48 of 82



Table 4: Potential Risks and Risk Minimization

Potential Hazardous Situation	Harm (Potential AE)	Potential Risk During Clinical Study	Mitigation
Investigational Software Application-Related			
Patient is sent home with SRHM feature unknowingly active due to a user error resulting in: • An earlier than expected device replacement • BioZ (Bio-impedance) is enabled and BioZ waveform causes cardiac stimulation during vulnerable period leading to arrhythmia induction	• Complications associated with the surgical procedure • Cardiac Arrest • Dizziness • Lethargy • Palpitations • Syncope • Tachyarrhythmia	Remote (<1%)	• ISA allows user to read the current SRHM operating status and sensor configuration • ISA indicates success or failure of each programming request • The system is operated by trained Medtronic personnel only • ISA displays timestamp of when first SRHM is enabled and most recent time SRHM is disabled • User Manual includes instructions to disable and confirm disabled status of SRHM feature at completion of In-clinic Testing Visit • BioZ signal will include stimulation current of 10uA, a sampling frequency of 4kHz, and all BioZ vectors stimulate from the ring electrode
ISA becomes unstable, corrupt and/or reset while BioZ is enabled and user is unable to disable SRHM feature for an extended period of time. BioZ waveform causes cardiac stimulation during vulnerable	• Cardiac Arrest • Dizziness • Lethargy • Palpitations • Syncope • Tachyarrhythmia	Remote (<1%)	• ISA allows user to read current SRHM operating status and sensor configuration • ISA indicates success or failure of each programming request • The system is operated by trained Medtronic personnel only • ISA displays timestamp of when first SRHM is enabled

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 49 of 82



period leading to arrhythmia induction			and most recent time SRHM is disabled • BioZ signal will include stimulation current of 10uA, a sampling frequency of 4kHz, and all BioZ vectors stimulate from the ring electrode
Sensor Research Holter Mode Feature-Related			
The loss of the device functions lead to insufficient cardiac output and cardiac arrest, resulting in insufficient pacing support.	• Cardiac Arrest • Discomfort • Dizziness • Dyspnea • Heart Block • Heart Failure Decompensation (hospitalization) • Impaired Cardiac Function (due to device) • Inability to Deliver Therapy • Lethargy • Loss of Pacing • Mental Anguish • Oversensing • Pacemaker Syndrome • Return of Cardiac Symptoms • Syncope • Undersensing	Remote (<1%)	• Laptop is Medtronic managed system with password protection • Laptop is operated by trained Medtronic personnel only • The modified device programming that is executed by the application will apply while in-clinic under medical supervision only • The SmartSync Programmer will be present and used periodically during the in-clinic portion of the study • The application will be constrained to allow only device parameter changes needed for the study – Restrict Programmability: ISA is capable of programming only device parameters associated with the SRHM feature • An interaction analysis to demonstrate the programming is executed correctly with no unintended side-effects and that no other device parameters are affected
The loss of the device functions lead to insufficient cardiac output and	• Dizziness • Dyspnea • Short of breath	Remote (<1%)	• Laptop is Medtronic managed system with password protection

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 50 of 82



cardiac arrest, resulting in inadequate CRT therapy.	• Heart failure decompensation (hospitalization) • Hemodynamic compromise • Impaired cardiac function (due to device) • Lethargy • Palpitations • Return of cardiac symptoms		• Laptop is operated by trained Medtronic personnel only • The modified device programming that is executed by the application will apply while in-clinic under medical supervision only • The SmartSync Programmer will be present and used periodically during the in-clinic portion of the study • The application will be constrained to allow only device parameter changes needed for the study – Restrict Programmability: ISA is capable of programming only device parameters associated with the SRHM feature • An interaction analysis to demonstrate the programming is executed correctly with no unintended side-effects and that no other device parameters are affected
The loss of the device functions lead to insufficient cardiac output and cardiac arrest, resulting in inadequate tachyarrhythmia therapy.	• Cardiac arrest • Dizziness • Lethargy • Return of cardiac symptoms • Syncope	Remote (<1%)	• Laptop is Medtronic managed system with password protection • Laptop is operated by trained Medtronic personnel only • The modified device programming that is executed by the application will apply while in-clinic under medical supervision only • The SmartSync Programmer will be present and used periodically during the in-clinic portion of the study

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 51 of 82



			• The application will be constrained to allow only device parameter changes needed for the study – Restrict Programmability: ISA is capable of programming only device parameters associated with the SRHM feature • An interaction analysis to demonstrate the programming is executed correctly with no unintended side effects and that no other device parameters are affected
A system revision required, due to negative device interaction, to repair/replace implanted products exposes the patient to risk of harm related to the surgical procedure	Complications associated with the surgical procedure	Remote (<1%)	• Laptop is Medtronic managed system with password protection • Laptop is operated by trained Medtronic personnel only • The modified device programming that is executed by the application will apply while in-clinic under medical supervision only • The SmartSync Programmer will be present and used periodically during the in-clinic portion of the study • The application will be constrained to allow only device parameter changes needed for the study – Restrict Programmability: ISA is capable of programming only device parameters associated with the SRHM feature • An interaction analysis to demonstrate the programming is executed correctly with no

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 52 of 82



			unintended side effects and that no other device parameters are affected
A system revision required, due to premature battery depletion, to repair/replace implanted products exposes the patient to risk of harm related to the surgical procedure	Complications associated with the surgical procedure	Remote (<1%)	• The research feature will be enabled for a limited time while the patient is in-clinic only • Documented current drain analysis • Identifying methods to communicate research features are enabled – ISA allows user to read the current SRHM operating status and sensor configuration • Instructions to set back all device changes to original settings before the patient leaves the clinic
Application of pacing therapy at an excessive rate may cause symptoms such as palpitations, dyspnea and short of breath	• Dizziness • Dyspnea • Short of breath • Heart failure decompensation (hospitalization) • Hemodynamic compromise • Impaired cardiac function (due to device) • Lethargy • Palpitations • Return of cardiac symptoms	Probable (>5% - 10%)	• Pacing rate will not be increased by more than approximately 10 beats per minute and for an expected total duration of approximately 10 minutes over the course of the In-clinic Testing Visit • Ensure pacing parameter is set not to exceed 90 beats per minute • Identifying methods to communicate research features are enabled – ISA allows user to read the current SRHM operating status and sensor configuration • Instruction to set back all device changes to original settings before the patient leaves the clinic • Pacing parameters will be adjusted temporarily while

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 53 of 82

Medtronic

			the subject is in clinic only, with access to health care professionals as needed
Stimuli may fall within the vulnerable period and initiate ventricular fibrillation which may introduce harm	• Cardiac arrest • Dizziness • Lethargy • Return of cardiac symptoms • Syncope • Threshold elevation	Remote (<1%)	• BioZ signal will include stimulation current of 10uA, a sampling frequency of 4kHz, and all BioZ vectors stimulate from the ring electrode • Inherent device backup anti arrhythmia therapy feature to provide treatment to patients
Crome/Cobalt Respiration Study Testing Procedure-related			
Allergic reaction due to medical adhesive/ECG patches	• Skin irritation • Pain/discomfort	Frequent (>10%)	• Medical adhesive/ECG patches will be worn for a short period of time while patient is in clinic
Study protocol requires breathing/exercise activities for an extended period of time	• Shortness of breath • Fatigue • Fall	Frequent (>10%)	• Breathing/exercise activities will be performed while the subject is in clinic only, with access to health care professionals as needed • Rest time between activities allowed, if needed

10.3 Potential Benefits

Participating in this study may offer no direct benefit to subjects. The objective of this study is to collect physiologic data from subjects. Subjects may benefit from temporary capnography monitoring, which could lead to a diagnosis as a result.

Being able to derive respiratory rates from an implantable device could lead to a reliable and automatic technique for measuring respiration and ultimately, allow for the continuous monitoring of patients for various disease states, including heart failure, outside the clinic setting. The information gained from this study could result in the improved management of heart failure symptoms of other patients receiving a Crome or Cobalt ICD or CRT-D system in the future, including respiratory rate remote monitoring and other sensor measures. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

10.4 Risk-Benefit Rationale

The differences between the Crome and Cobalt ICD and CRT-D market-released devices with or without the Sensor Research Holter Mode feature enabled are minimal. The risks introduced by the use of the Sensor Research Holter Mode feature were evaluated and risk control measures are being implemented to reduce the risk to as low as possible to minimize subject harm.

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

The study requirement for an in-office visit carries the potential for incidental findings related to in-clinic monitoring that might not be present if the subject was not enrolled in the study. Lastly, the value of the knowledge to be gained by conducting this clinical study could lead to a reliable and automatic technique for measuring respiration and ultimately, allow for the continuous monitoring of patients for various disease states outside the clinic setting.

10.5 Risk Determination

The Crome/Cobalt Respiration Study is considered a nonsignificant risk study, as it is non-interventional, is not designed to support or sustain life, is not designed to diagnose, cure, mitigate, or treat disease, and does not otherwise present a potential for serious risk to the health, safety, or welfare of subjects.

11. Adverse Events and Device Deficiencies

11.1 Adverse Events

AE definitions are provided in Table 5. All adverse events will be collected throughout the study duration, starting at the time of signing the ICF. Reporting of these events to Medtronic will occur on an AE eCRF. Each event must be reported separately.

Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. For AEs that require immediate reporting (see Table 7), initial reporting may be done by phone, fax, or on the eCRF completing as much information as possible. The completed AE eCRF must be submitted to Medtronic as soon as possible.

Any medication/treatment associated with the treatment of an AE must be reported.

Subject deaths are also required to be reported. Refer to [Section 11.6](#) for Subject Death collection and reporting requirements.

11.2 Device Deficiency

The Device Deficiency (DD) definition is provided in Table 5. DD information will be collected throughout the study and reported to Medtronic. A DD that results in an AE to the subject should be captured as an AE only.

A DD that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) requires immediate reporting (see Table 7).

11.3 Processing Updates and Resolution

For any changes in status of a previously reported AE or DD (i.e., change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD form. It is optimal for AEs to have an outcome of “Resolved” when a subject exits the study, but due to the brief length of participation in this study, an AE might not be fully resolved at study exit.

In the event that a subject would like to discontinue their study participation prior to completing the study, all efforts should be made to wait to exit the subject until all unresolved system or study testing procedure related AEs, as classified by the investigator, are resolved, unresolved with no further actions planned, or 30 days post the In-clinic Testing Visit, whichever occurs first. Additionally, if there are

Medtronic Business Restricted

unresolved system or study testing procedure related AEs at the time of study completion, the subject should not be exited, but should continue to be followed for up to 30 days to assess the ongoing AE. Once the ongoing system or study testing procedure AE(s) is/are resolved, or the subject has been followed for 30 days, whichever occurs first, the subject should be exited. If AEs are still ongoing 30 days post study completion, it should be noted on the AE CRF that the AE is unresolved at time of study exit.

11.4 Definitions/Classifications

All AEs and DDs will be classified using the ISO14155:2020 definitions, as defined in Table 5. Where the definition indicates “device”, it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

Each of the relatedness classifications will be assessed for causality using four different levels of causality. The relationship of an AE will be classified as study testing procedure related or system related as defined in Table 5.

Table 5: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE) (ISO 14155:2020, 3.2)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.
Adverse Device Effect (ADE) (ISO 14155:2020, 3.1)	AE related to the use of an investigational medical device. NOTE 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. NOTE 3: This includes ‘comparator’ if the comparator is a medical device.

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 56 of 82

Medtronic

Device Deficiency (DD) (ISO 14155:2020, 3.19)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. NOTE 1: DDs include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling. NOTE 2: This definition includes DDs related to the investigational medical device or the comparator.
Relatedness	
Crome/Cobalt Respiration Study System Related	An adverse event that results from the presence or performance (intended or otherwise) of any component of the Crome or Cobalt ICD or CRT-D systems, the mHolter Recorder, Capnostream 35 Portable Respiratory Monitor, Smart CapnoLine® Plus, Adult/Intermediate-Oral-Nasal, Nellcor FLEXMAX SpO2 Sensor, CareLink SmartSync™ Device Manager Base, 24967 Patient Connector with attached USB cable, and the Investigational Software Application.
Crome/Cobalt Respiration Study Testing Procedure Related	An adverse event that is directly related to the study testing procedures, which includes application of the mHolter recorder and capnography monitor and completion of the breathing and/or exercise activities.
Not Related	Relationship can be excluded when: • The event has no temporal relationship with the use of the device or procedure; • The event does not follow a known response pattern to the device (if the response pattern is previously known) and is biologically implausible; • The discontinuation of device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact the event; • The event involves a body-site or an organ not expected to be affected by the device or procedure; • The event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 57 of 82

Medtronic

	condition, an effect of another device, drug, treatment or other risk factors); The event does not depend on a false result given by the device used for diagnosis, when applicable. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Causality	
Possible	The relationship is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship seems relevant and/or the event cannot be reasonably explained by another cause.
Causal Relationship	The event is associated beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with device use/application or procedures; - the event involves a body-site or organ that - the device or procedures are applied to; - the device or procedures have an effect on; - the event follows a known response pattern to the device (if the response pattern is previously known); - the discontinuation of device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible); - other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the device used for diagnosis, when applicable.

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 58 of 82

Medtronic

	In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Seriousness	
Serious Adverse Event (SAE) (ISO 14155:2020, 3.45)	AE that led to any of the following: a) death, b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function including chronic diseases, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function, c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE.
Serious Adverse Device Effect (SADE) (ISO 14155:2020, 3.44)	Adverse device effect that has resulted in any of the consequences characteristic of a SAE.
Unanticipated Adverse Device Effect (UADE) (21 CFR 812.3 (s))	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Unanticipated Serious Adverse Device Effect (USADE) (ISO 14155:2020, 3.51)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
Serious Health Threat (ISO 14155:2020, 3.46)	Signal from any AE or DD that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

11.5 Reporting of Adverse Events and Device Deficiencies

11.5.1 Adverse Event and Device Deficiency Classification

All adverse events and device deficiencies will be collected throughout the study duration, beginning from the time of signing of the informed consent.

Reporting of AEs to Medtronic will occur on an AE eCRF, including date of event, primary diagnosis, event description, diagnostics tests and procedures, actions taken (i.e., healthcare utilization, medication changes, etc.), event relatedness, seriousness and outcome. Each AE must be recorded on a separate AE eCRF. If a subject death occurs, the AE that led to the cause of death should be reported with an outcome of “fatal”.

All AEs and DDs will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided. Upon receipt of an AE/DD at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary, will request clarification and/or additional information from the Investigator.

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Refer to Table 7 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of both to abide by any additional AE reporting requirements stipulated by the IRB responsible for oversight of the study.

For AEs that require immediate reporting (see Table 7), initial reporting may be done by contacting the study sponsor per the sponsor contact information. The original completed AE eCRF must be submitted to Medtronic as soon as possible.

All AEs are required to be collected throughout the duration of the study. Please refer to [Section 10](#) for potential risks and foreseeable adverse events that subjects could experience while participating in the study and risk minimization strategies.

Medtronic Business Restricted

AEs and Deaths will be classified according to the standard definitions as outlined below:

Table 6: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Relationship assessment applies to Crome/Cobalt Respiration Study System and Crome/Cobalt Respiration Study Testing Procedures.
	Sponsor	Relationship assessment applies to Crome/Cobalt Respiration Study System and Crome/Cobalt Respiration Study Testing Procedures.
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, UADE/USADE (for all system or study testing procedure related adverse events), DD with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

11.5.2 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and DDs will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator and the sponsor to abide by the AE reporting requirements stipulated by local law and the study site's IRB. Table 7 below outlines the reporting requirements the investigator and/or sponsor shall submit to.

Table 7: Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator shall submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Sponsor shall submit to:	
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Adverse Device Effects (ADEs)	

Medtronic Business Restricted

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 61 of 82

Medtronic

Investigator shall submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the effect.
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Sponsor shall submit to:	
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Serious Adverse Device Effects (SADEs)	
Investigator shall submit to:	
Medtronic	Immediately after the investigator learns of the event or of new information in relation to an already reported event.
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Sponsor shall submit to:	
FDA	Submit to FDA per local reporting requirement.
Investigators	Submit per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Unanticipated Adverse Device Effects (UADEs) and Unanticipated Serious Adverse Device Effects (USADEs)	
Investigator shall submit to:	
Medtronic	As soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. (21 CFR 812.150(a))
IRB	As soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. (21 CFR 812.150(a))
FDA	Submit to FDA per local reporting requirement.
Sponsor shall submit to:	

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 62 of 82

Medtronic

FDA	As soon as possible, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b))
Investigators	As soon as possible, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b))
IRB	Submit to IRB per local reporting requirement.
Device Deficiencies (DDs) with SADE potential	
Investigator shall submit to:	
Medtronic	Submit or report as required per local reporting requirements.
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
Sponsor shall submit to:	
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.
All other reportable AEs and DDs	
Investigator shall submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event or deficiency.
FDA	Submit to FDA per local reporting requirement.
IRB	Submit to IRB per local reporting requirement.

11.6 Subject Death

All subject deaths must be reported by the investigator to Medtronic on an AE eCRF (AE with outcome of fatal) as soon as possible after the investigator first learns of the death. In case of death, there should be one SAE with the outcome of fatal.

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to Medtronic for analysis whenever possible per local process. Local laws and procedures must be followed where applicable. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

A de-identified copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records, if requested and available, should be sent to the Medtronic clinical study team. If an autopsy is conducted, a copy of the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When the death occurs at a

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

remote study site, it is the investigative study site's responsibility to attempt retrieval of information about the death.

In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- Device interrogation information/reports and Save-to-Media information/reports (if available)
- Device disposition information
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

11.6.1 Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.

Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, Sudden Cardiac Death will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.

Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

Non-cardiac Death: A death not classified as a cardiac death.

Unknown Death Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

11.7 Product Complaint Reporting

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a medical device that has been placed on the market. It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless of whether they are related to intended use, misuse, or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints is not part of the study and should be done in addition to the AE reporting requirements. Refer to local regulations for reporting requirements.

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the Regulatory Authorities (e.g., FDA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
 - Life-threatening illness or injury
 - Permanent impairment of a body function or permanent damage to a body structure
 - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

12. Data Review Committees

12.1 Core Lab

This study will use one Core Lab, which will determine each subject's breath count based on waveform data collection using capnography. This information may be subject to change during the course of the study. Periodic updates to study contact information will be sent to study sites as needed.

Table 8: Core Laboratory Information

Contact Information	Role
Clinimark, LLC 80 Health Park Drive, Suite 20 Louisville, CO 80027 Phone: (303) 926-5432	• Visual scoring of exhaled carbon dioxide waveform to determine respiratory rate • Adjudication of waveforms

12.2 Data Monitoring Committee

A Data Monitoring Committee is not needed for this study. The study is low risk for subjects, and the relatively short projected timeframe for enrollment and completion of the study make a DMC review that could stop the study early impractical.

13. Statistical Design and Methods

This section presents statistical considerations for the study design and provides a high-level description of planned analysis and reporting. More details will be given in a separate Statistical Analysis Plan (SAP) that will be approved before data freeze or lock. Any deviation to the pre-specified statistical analyses will be noted in the study report.

13.1 General Aspects of Analysis

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 subgroup of most interest is heart failure / non-heart failure. Missing data should be minimal, and as such, will not be imputed.

The Crome/Cobalt Respiration Study will be considered successful if the 95%-80% tolerance interval for the difference in daily respiration rates (RRs) between device-derived RR and capnography RR is within ± 3 breaths per minute.

The first 15 subjects' data will be used to refine the algorithm that converts EGM data to respiration rate to create a final algorithm. The final algorithm will be applied to the final (~45) subjects' EGM's. Because they contributed to algorithm enhancement, the first 15 subjects will be excluded from the primary and ancillary objectives.

13.2 Analysis Execution

There are no plans to analyze the study data prior to completion of all study follow-ups by all subjects. However, since this is a feasibility study and there are no hypothesis tests planned, accumulating study data may be analyzed.

Once all data is collected, a final report will be produced.

13.3 Interim Analysis

No interim analysis is planned.

13.4 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.

Endpoint definition and derivation

The endpoint is the difference in daily RRs between EGM-derived RR and capnography RR.

In practice, it is planned that the EGM-derived daily RR will be calculated as follows:

- Record EGM during a 1-minute window every hour from 11pm – 6am
 - record only if accelerometer is 'quiet'
- Combine all 'quiet' measurements into a median respiration rate – the daily RR

To simulate a daily RR, 8 paired (device-derived and capnography) RR measurements will be used. Based on these 8 readings, a "daily" RR for each method will be calculated using the median of the

Medtronic Business Restricted

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 66 of 82

Medtronic

measures. The capnography RR represents the true RR. Further calculation details will be provided in the statistical analysis plan prior to analysis.

Performance Requirements:

The study will be successful if it demonstrates, with 95% confidence, that at least 80% of daily EGM Derived RRs are within ± 3 breaths per minute of daily capnography RRs.

Rationale for Performance Criteria

The accuracy performance requirement was determined by surveying the reported accuracy of Medtronic commercially released monitors, in order to achieve similar performance. Figure 10 provides details of Medtronic's devices. An RR accuracy of 3 breaths per minute is similar to the Zephyr device for low activity, and the pulse oximeter probe used in hospital patients. Since the algorithm proposed for the Cobalt/Crome devices uses EGM, it cannot match the higher accuracy of a bedside sensor directly placed in the airway (± 1 breaths per minute, Medtronic Capnostream with oral/nasal sensors).

Device	Company	Cable Wearable Non-contact	Underlying tech	Hosp / Home	RR MIN	RR MAX	RR Accuracy	Failure Criteria if Specified	Reusable/ disposable	Tidal and/or minute volume	Adult children neonates
Nellcor Respiration rate sensor	Medtronic	Pulse Oximeter Probe	Pulse Oximetry	Hosp	4	40		motion	disposable	No	
Capnostream	Medtronic	Nasal Cannula (intubated/ nasal/ oral-nasal.)	Capnography	Hosp	0	150		extreme moisture	disposable	flow rate	adults/children/neonates
Zephyr	Medtronic	Chest strap	Accelerometry and GPS	Sports	3	70	► Lab-breathing ► Low activity ► High activity (run): ± 5 ► Talking & breathing rate in range ± 5	excessive motion	reusable	No	weight > 10kg

Figure 10. Respiration Rate Accuracy Determination

Analysis Methods:

Using the difference in daily RRs (one per subject), 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.

Determination of Subjects/Data for Analysis

All subjects, other than the first 15 that complete the protocol, with paired device-detected and capnography daily RR's will be included.

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

13.5 Ancillary Objective(s)

The ancillary objectives will be analyzed with descriptive statistics. No formal statistical test procedures are planned.

13.5.1 Ancillary Objective #1

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

Endpoint definition and derivation

Subjects will be monitored in various states (e.g., lying down, sitting, standing, pacing rate increase, and walking) and their RR will be recorded based on capnography and EGM. The endpoint for this objective is the difference between the capnography waveform-derived RR and the EGM-derived RR.

Analysis Methods:

The analysis methods will be detailed in the statistical analysis plan. Generally, summary statistics for each testing state will be calculated, along with confidence intervals.

Determination of Subjects/Data for Analysis

All subjects, other than the first 15 that complete the protocol, with paired device-derived and capnography waveform-derived daily RR's will be included.

13.5.2 Ancillary Objective #2

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

Analysis Methods

This data is being collected for future research work. It will not be summarized in the Crome/Cobalt Respiration Study Final Report.

13.5.3 Ancillary Objective #3

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

Analysis Methods

This data is being collected for potential future algorithm development. It will not be summarized in the Crome/Cobalt Respiration Study Final Report.

13.6 Sample Size Determination

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 9 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 9: 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

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056-F275 Rev E Clinical Investigation Plan Template

13.7 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.

14. Ethics

14.1 Statement(s) of Compliance

This study will be conducted in compliance with the Declaration of Helsinki (DoH), the Clinical Investigation Plan, Good Clinical Practice (GCP) and in accordance to the national and local laws, regulations, standards, and requirements of the country in which the study is conducted. GCP includes review and approval by an independent IRB before initiating a study, continuing review of an ongoing study by an IRB, and obtaining and documenting the freely given informed consent of a subject before initiating the study. The principles of the DoH have been implemented through the informed consent process, IRB approval, study training, clinical trial registration, and risk-benefit assessment.

The clinical investigation shall not begin until all required approvals and documents from the IRB and regulatory authorities, if needed, have been received. Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate.

The Crome/Cobalt Respiration Study was designed to reflect the GCP principles outlined in ISO 14155:2020 and other clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155:2020, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. Adverse Event and Device Deficiency handling in the Crome/Cobalt Respiration Study is ISO 14155:2020 compliant for all participating study sites.

Ultimately, all study sites in the United States will follow and comply with:

Medtronic Business Restricted

- Principles of Declaration of Helsinki
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- 21 CFR Part 50 (Protection of Human Subjects)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- 21 CFR Part 56 (Institutional Review Boards)
- 21 CFR Part 812 (Investigational Device Exemptions)
- The Clinical Trial Agreement
- The procedures described within this CIP
- Local IRB Requirements
- ISO 14155:2020 (with noted exceptions outlined throughout the CIP)

The study will be publicly registered in accordance with the 2007 FDAAA and Declaration of Helsinki on <http://clinicaltrials.gov> (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.

Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (where required by local law/regulations)
- Geography-specific regulatory authorities (if regulatory approval is required)
- Institutional Review Board

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above-mentioned groups prior to implementation of the revised CIP at the study site.

15. Study Administration

15.1 Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the CTA, and the applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the ICF, Research Authorization (where applicable) and CTA. The principal investigator should also be available during monitoring visits.

15.1.1 Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, study compliance, number of adverse events, number of deviations, observations from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents will be reviewed at each study

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site. Monitoring for the study, including interim monitoring visits and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess study site progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs in accordance to the study-specific monitoring plan. Monitors review study site regulatory and study compliance by identifying observations of non-compliance and communicating those observations along with recommendations for preventative/corrective actions to study site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular study site.

15.2 Data Management

Data will be collected using an electronic data management system for studies. eCRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained by Medtronic in accordance with applicable regulations.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to pseudonymize, for instance, where the subject's name cannot be removed from the data carrier.

Procedures in the CIP require source documentation. Source documentation will be maintained at the study site. Source documents, which may include worksheets, subject medical records, programmer printouts, and interrogation files, must be created and maintained by the investigational study site team.

The investigator must clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. See [Section 9.13](#) for eCRFs and data collection elements that may be considered source.

Device data collected at office visits will be provided to Medtronic. Upon receipt, device data will be maintained with databases and retrieved for analysis and reporting.

15.3 Direct Access to Source Data/Documents

Medtronic may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly involved in the study. RAs, such as the FDA, may also perform inspections at participating study sites. The investigator and/or institution shall permit Medtronic, IRBs and RAs direct access to source data and documents during monitoring, audits and regulatory inspections.

15.4 Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique Subject Identification (SID) number to each subject. Records of the subject/SID number relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of their information shall be preserved in reports and when publishing any data. In the US, "Protected Health Information" (PHI) will be maintained in compliance with the HIPAA of 1996. To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study document other than the ICF. This scenario will be covered in the ICF. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

15.5 Liability/Warranty/Insurance Information

Warranty information is provided in the product packaging for the commercially released Crome and Cobalt ICD and CRT-D MRI SureScan™ Systems and additional copies are available upon request.

15.6 CIP Amendments

Approval of CIP amendments is required from the following groups prior to any study procedures occurring at a study center:

- Medtronic
- Principal Investigators (where required by local law)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent Institutional Review Board (IRB)

If a CIP amendment occurs, site personnel will need to be re-trained as necessary, and will need to submit any changes to their IRB as required.

15.7 Record Retention

Per Federal regulations (CFR 812.140), an investigator must maintain clinical study records for a period of at least 2 years after study closure (e.g., date of Medtronic final report) or longer as per local law or hospital administration requires. No study document or image will be destroyed without prior written agreement between Medtronic and the investigator. The investigator should take measures to prevent accidental or premature destruction of documents. Medtronic will inform the investigator/study site when these documents are no longer required to be retained.

Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

Medtronic will retain the study records according to Medtronic corporate policy and record retention schedule.

Medtronic Business Restricted

15.7.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (ISF) (e.g., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the date of study closure (e.g., date of Medtronic final report).

- All correspondence between the IRB, sponsor, monitor, regulatory authority and the investigator that pertains to the investigation, including required reports
- Subject's case history records, including:
 - Signed and dated Informed Consent Form
 - Observations of AEs/ADEs/DDs
 - Medical history
 - Follow-up data
 - Documentation of the dates and rationale for any deviation from the protocol
- Financial Disclosures and Investigator Statements of investigators
- Subject Screening & Identification and Enrollment log
- Electronically signed and dated eCRFs
- Device Disposition Logs containing Model and serial numbers of devices delivered to the study site, received dates of devices, returned-to-sponsor dates and reasons, initials of all persons who received or returned each device, and method of return
- All approved versions of the CIP and ICF
- Signed and dated Clinical Trial Agreement
- CV of principal investigators and key members of investigation study site team, signed and dated
- Documentation of delegated tasks
- IRB approval documentation, including written information that the investigator or other study staff, when member of the IRB, did not participate in the approval process; approval documentation must include the IRB's composition
- Regulatory authority notification, correspondence and approval, where required per local law
- Study training records for study site staff
- Any other records that local regulatory agencies require to be maintained
- Final Study Report including the statistical analysis

15.7.2 Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

Medtronic Business Restricted

- All correspondence which pertains to the investigation
- Product traceability records
- Sample of label attached/affixed to the Medtronic-owned laptop with the investigational ISA installed
- Signed Clinical Trial Agreements
- Financial Disclosures and Investigator Statements of investigators
- CV of principal investigator and key members of the investigation study site team, signed and dated
- Documentation of delegated tasks for all participating sites
- All approved ICF templates, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB approval letters and relevant IRB correspondence and IRB voting list/roster/letter of assurance, if applicable
- Names of the institutions in which the clinical study will be conducted
- Electronically signed and dated eCRFs
- Regulatory authority correspondence, notification and approval as required by national legislation
- Names/contact addresses of monitors
- Monitoring visit reports
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The CIP and study related reports, and revisions
- Study training records for study site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in secured file cabinets at Medtronic during the course of this study.

After closure of the study Medtronic will archive records and reports according to Medtronic corporate policy and record retention schedule.

15.8 Reporting Requirements

15.8.1 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the clinical investigation

Medtronic Business Restricted

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 75 of 82

Medtronic

plan. If any action is taken by an IRB with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in [Section 11.5.2](#). The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 10: Investigator Reports Applicable per Medtronic Requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days. (21 CFR 812.150(a)(2))
Study Deviations	Sponsor and IRB	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. (21 CFR 812.150(a)(4))
Progress report	Sponsor and IRB	The investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly intervals. (21 CFR 812.150 (a)(3)).
Failure to obtain IC prior to investigational device use	Sponsor and IRB	If an investigator uses a device without obtaining IC, the investigator shall report such use within 5 working days after device use. (21 CFR 812.150(a)(5))
Final Report	IRBs and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or completion or termination of the investigator's part of the investigation. (21 CFR 812.150(a)(6))
Other	IRB and Relevant Authorities	An investigator shall, upon request by a reviewing IRB or any other relevant Regulatory Authority, provide accurate, complete and current information about any aspect of the investigation. (21 CFR 812.150(a)(7))

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

15.8.2 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of the reviewing IRB, regulatory authority or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in [Section 11.5.2](#).

Table 11: Sponsor Reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of IRB approval	Investigators, IRB, and relevant authorities	Sponsor shall notify of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within five working days after receipt of the withdrawal of approval. (21 CFR 812.150(b)(2))
Progress Reports	IRB	Sponsor shall submit progress reports to all reviewing IRBs at least annually. (21 CFR 812.150(b)(5))
Recall and device disposition	Investigators, Head of Institution, IRB, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. (21 CFR 812.150(b)(6))

Crome/Cobalt Respiration Study Clinical Investigation Plan

MDT22030

Version 2.0

Page 77 of 82

Medtronic

Report	Submit to	Description/Constraints
Final report	Investigators, IRB, RAs upon request	Sponsor will notify IRB within 30 working days of the completion or termination of the investigation. A final report will be submitted to the investigators and all reviewing IRBs within six months after completion or termination of this clinical study. (21 CFR 812.150(b)(7)) In addition, the following requirements will be followed in accordance with ISO 14155:2020: • The investigator shall have the opportunity to review and comment on the final report • If a clinical investigator does not agree with the final report, their comments shall be communicated to the other investigator(s) • The coordinating investigator shall sign the report. If no coordinating investigator is appointed, then the signature of the principal investigator in each study site should be obtained.
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. Study site specific study deviations will be submitted to investigators periodically.
Other	IRB	Sponsor shall, upon request by a reviewing IRB, provide accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(b)(10))
Premature termination or suspension of clinical study	IRB, Investigators, and regulatory authorities, where applicable	Sponsor will provide prompt notification of termination or suspension and reason(s) to investigator and where required to IRB and RAs, where applicable.

15.9 Publication and Use of Information

Publications from the Crome/Cobalt Respiration Study will be handled according to Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Medtronic Business Restricted

CONFIDENTIAL

056-F275 Rev E Clinical Investigation Plan Template

15.9.1 Publication Committee

Medtronic may form the Crome/Cobalt Respiration Publication Committee from study investigators. Medtronic personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to: 1) manage elements addressed in the publication plan as outlined in this appendix, 2) develop the final Publication Plan under separate cover, 3) execute the Publication Plan, 4) oversee the publication of primary, secondary and ancillary study results, 5) review and prioritize publication proposals, 6) provide input on publication content, and 7) determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan.

Membership in the Publication Committee does not guarantee authorship. If formed, the committee will meet as needed.

15.9.2 Management of Primary, Secondary, and Ancillary Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the CIP.

An ancillary publication is any publication that does not address the study objectives identified in the CIP. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this study, and clinicians not participating in this study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual study site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

15.9.3 Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contributions to conception and design of the work, or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Medtronic Business Restricted

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the “Medtronic Crome/Cobalt Respiration Study Investigators” and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

15.9.4 Transparency

Transparency of clinical study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, IRBs and RAs, when required by local law
- Registering and posting the study results on a publicly accessible database, e.g., ClinicalTrials.gov based on the posting rules stipulated
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual study site’s study data accessible to the corresponding investigator after the completion of the study, if requested

15.10 Suspension or Early Termination

15.10.1 Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a study that occurs when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB oversight is required until the overall study closure process is complete. Refer to [Section 9.15](#) for additional information regarding study exit procedures. Upon study closure, subjects should be managed and followed per physician discretion.

15.10.2 Early Termination or Suspension

Early Termination is the closure of a study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single study site. Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single study site.

15.10.2.1 Study-wide termination or suspension

Possible reasons for considering study-wide suspension or termination of the study include but are not limited to:

- AEs associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product’s design intent

Medtronic Business Restricted

- Decision by Medtronic or regulatory authority (where the study is operating under regulatory authority)
- Technical issues during the manufacturing process

15.10.2.2 Investigator/study site termination or suspension

Possible reasons for investigator or study site termination or suspension include but are not limited to:

- Failure to obtain initial IRB approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g., failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g., failure to submit data in a timely manner, failure to follow-up on data queries and monitoring observations in a timely manner, etc.)
- IRB suspension of the study site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g., no longer able to support the study)

15.10.3 Procedures for Termination or Suspension

15.10.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) where required
- In the case of study termination or suspension for reasons other than a temporary IRB approval lapse, the investigator will promptly inform the IRB
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

15.10.3.2 Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the IRB and regulatory authorities and provide detailed explanation of termination/suspension

Medtronic Business Restricted

- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

15.10.3.3 Institutional Review Board-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects, or legally authorized designees or guardians and/or the personal physician of the subjects, with the rationale for the study termination or suspension
- The investigator will promptly inform the regulatory authorities, where applicable

16. References

[1] HeartLogic Algorithm Development and Validation, MultiSENSE Study Summary. Boston Scientific, 92029732-002 HL Performance Evaluation US_S

[2] Medtronic internal data. Erickson, Mark. Pressure Derived Respiration (PDR) Study. May 9th, 2011. MDT1892840

17. Appendices

17.1 Participating Investigator and Institutions

A complete list of participating investigators and institutions will be provided under separate cover.

17.2 Institutional Review Board (IRB) List

A complete list of participating IRBs will be provided under separate cover. This information will be updated throughout the course of the study and the updated list will be maintained at Medtronic and will be available upon request.

18. Version History

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
1.0	Not Applicable, New Document	N/A	N/A	N/A	Alyssa Pieper, Sr. Clinical Research Specialist Mike Eggen, Sr. Research Manager Jeff Cerkenik, Distinguished Statistician
2.0	- Table 4 in Section 10.2 was updated - Section 1. Glossary was updated - Table 11 in Section 15.8.2 was updated	- Table 4 was modified to align with updated Risk Management documents. - Additional abbreviations/ acronyms identified were added - ISO requirements were added for Final Report	N/A	N/A	Alyssa Pieper, Sr. Clinical Research Specialist Mike Eggen, Sr. Research Manager Jeff Cerkenik, Distinguished Statistician