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Document Name: **Post Approval Study of the remedē® System Clinical Investigational Plan**

Prospective, single arm cohort study to evaluate the long-term safety, long-term effectiveness, and survival rate in subjects implanted with the **rem**edē System

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Revision History

Rev	Description of Change	Approval Date
A	Initial Release	02-May-2017
B	Clarified definitions of study objectives, added PSG requirement at 60-month follow-up visit.	27-Oct-2017
C	Updates to determine visits based on a 30 day month and updates to data to be collected.	09 Jan 2018

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Post Approval Study of the remedē® System

Clinical Investigational Plan

Prospective, single arm cohort study to evaluate the long-term safety, long-term effectiveness, and survival rate in subjects implanted with the **rem**edē System

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Respicardia

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1 PROTOCOL SYNOPSIS

This Post Approval Study is a multi-center, prospective, open label, single arm cohort study to evaluate the long-term safety, long-term effectiveness, and survival rate in subjects implanted with the **rem**edē System from the **rem**edē System Pivotal Trial. Up to 94 subjects will be enrolled at up to 21 sites in the United States (US) and five (5) sites in the European Union (EU).

Only subjects who were implanted and actively being followed as part of the **rem**edē System Pivotal Trial are eligible for this trial.

An individual subject's participation is expected to continue to five years post **rem**edē System implant. Subjects will start follow-up at the appropriate follow-up visit based on their initial **rem**edē System implant date. Subjects will be seen for an in-office visit at 36, 48, and 60 months post implant for a **rem**edē System assessment, an assessment of medical stability, sleep study (polygram [PG] at 36- and 48-month visits and polysomnogram [PSG] at the 60-month visit), Epworth Sleepiness Scale (ESS) completion, and adverse event monitoring. Subjects will be contacted by phone at 30, 42, and 54 months post implant for survival and adverse event monitoring.

Data analyses will include an evaluation of long-term safety, long-term effectiveness, and survival rate.

2 STUDY PURPOSE AND JUSTIFICATION

This extended follow-up study is a Food and Drug Administration (FDA) condition of approval of the **rem**edē System in adult patients with moderate to severe central sleep apnea (CSA). The primary purpose of this prospective, multicenter, single arm cohort study is to evaluate the long-term safety, long-term effectiveness, and survival rate in subjects implanted with the **rem**edē System in the **rem**edē System Pivotal Trial.

3 STUDY MILESTONES AND TIMELINE

Following FDA approval of the protocol, **rem**edē System Pivotal Trial sites with active subjects will be invited to participate in this study. Activation of sites should be complete within six months following FDA approval of the protocol. Enrollment of subjects, defined as signing the informed consent, should be complete within six months following site activation.

Follow-up is planned for five years from the date of implant. Since all subjects have already completed 24 months of follow-up, total study duration is estimated to be three years.

4 BACKGROUND

4.1 Regulatory History

The **rem**edē System Pivotal Trial demonstrated that **rem**edē System therapy effectively treats CSA and delivers statistically significant and clinically meaningful improvements in sleep, respiratory, and patient-centered metrics. The primary effectiveness endpoint of the **rem**edē System Pivotal Trial was met: a significantly higher proportion of subjects in the treatment group (35 of 68, 51%) had a 50% or higher reduction in Apnea-Hypopnea Index (AHI) from baseline to 6 months of follow-up than in the control group (8 of 73, 11%). The difference between groups was 41% ($p \leq .0001$). This significant difference demonstrated the superiority of **rem**edē System therapy compared to no therapy. In the per protocol population, 60% of the Treatment subjects achieved a ≥50% reduction in AHI versus 11% in the Control group. The benefits experienced by the Treatment group continued throughout the course of the study, demonstrating durability of effect, and were confirmed by the results of the Control group after 6 months of active therapy. In addition to the benefits conferred by meeting the primary effectiveness endpoint, all of the hierarchically tested secondary endpoints (Central Apnea Index [CAI], AHI, Oxygen Desaturation Index 4% [ODI4], percent sleep time in Rapid Eye Movement [REM], Patient Global Assessment [PGA], Arousal Index [ArI], and ESS) were met. The therapy was well tolerated, and 91% of subjects were free from serious adverse events (SAEs) related to the implant procedure, **rem**edē System, or delivered therapy through 12 months indicating both procedural and chronic safety of the **rem**edē System.

The **rem**edē System received CE Mark approval on August 13, 2010.

The **rem**edē System was approved for marketing in the US by the FDA on October 6, 2017. As a condition of approval, the Post Approval Study will continue to gather clinical evidence regarding the safety and effectiveness for the **rem**edē System in adult subjects with moderate to severe CSA.

5 DEVICE NAME, INTENDED USE, AND SYSTEM DESCRIPTION

5.1 Device Name

The **rem**edē® System

5.2 Indications for Use

The **rem**edē System is an implantable phrenic nerve stimulator indicated for the treatment of moderate to severe CSA in adult patients.

5.3 System Overview

The system consists of an implantable pulse generator (IPG), one transvenous lead to stimulate the phrenic nerve, and one transvenous sensing lead to sense respiration via

transthoracic impedance. External, non-implanted devices and accessories of the **rem**edē System include the **rem**edē System programmer, external IPG, and programming wand. A detailed description of the **rem**edē System can be found in the **rem**edē System Implant and Clinician Use Manual found in **Appendix F**.

6 STUDY DESIGN AND SCOPE

This is a multi-center, prospective, open label, single cohort study to evaluate the long-term safety, long-term effectiveness, and survival rate in subjects implanted with the **rem**edē System in the **rem**edē System Pivotal Trial. Up to 94 subjects will be enrolled at up to 21 US sites and 5 EU sites.

Only subjects who were implanted and actively being followed as part of the **rem**edē System Pivotal Trial are eligible for this trial.

An individual subject's participation is expected to continue through five years post **rem**edē System implant. Subjects will be seen for an in-office visit at 36, 48, and 60 months post implant for a **rem**edē System assessment, an assessment of medical stability, sleep study (polygram [PG] at 36- and 48-month visits and polysomnogram [PSG] at the 60-month visit), Epworth Sleepiness Scale (ESS) completion, and adverse event monitoring. Subjects will be contacted by phone at 30, 42, and 54 months post implant for survival and adverse event monitoring. See **Table 1** Follow-up Schedule.

7 STUDY OBJECTIVES

1. Evaluate the survival rate

   This endpoint is an assessment of survival in subjects with moderate to severe CSA being treated with the **rem**edē System. Survival will be compared to historical controls or newly published results at three and five years post implant. No formal statistical hypothesis will be tested.

2. Evaluate long-term three and five-year device-related Serious Adverse Events (SAEs)

   This endpoint is an assessment of long-term safety via summary of anticipated or unanticipated device-related SAEs. Events must meet the definition of serious as defined in **Section 10.8**. Device-related SAEs include device explants due to device-related infection and events such as: device malfunction, lead fracture, lead component failure, lead dislodgment, lead displacement, pocket perforation, or extra-respiratory sensation requiring lead revision. **rem**edē System IPG replacement for battery depletion will not be considered a device-related SAE unless it is earlier than anticipated. The number of events and subjects with an

event will be summarized through each time point. No formal statistical hypothesis will be tested.

3. Evaluate long-term three and five-year therapy-related SAEs

   This endpoint assesses the safety of the **rem**edē System by evaluating anticipated or unanticipated therapy-related SAEs. Therapy-related SAEs must meet the definition of a SAE as defined in **Section 10.8** and include events such as diaphragmatic stimulation discomfort, extra-respiratory stimulation, or concomitant device interaction. The number of events and subjects with an event will be summarized through each time point. No formal statistical hypothesis will be tested.

4. Evaluate the AHI, CAI, and obstructive apnea index (OAI) at three years using in-home polygram (PG) and at five years using in-lab polysomnogram (PSG)

   This effectiveness endpoint will be assessed by summarizing the AHI, CAI, and OAI at three and five years, as well as change from baseline at five years. No formal statistical hypothesis will be tested.

5. Evaluate the change in quality of life from baseline to three and five years using the ESS

   The ESS is a validated instrument that assesses a subject's daytime sleepiness. The objective is to demonstrate a reduction in the ESS score from baseline at three and five years. No formal statistical hypothesis will be tested.

8 SUBJECT SELECTION

8.1 Inclusion Criteria

1. Subjects who were previously implanted with the **rem**edē System and participated in the **rem**edē System Pivotal Trial
2. In the investigator's opinion, willing and able to comply with all study requirements
3. Signed Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approved informed consent (including Health Insurance Portability and Accountability Act [HIPAA] authorization in the US)

8.2 Exclusion Criteria

There are no criteria by which a subject would be excluded.

9 INVESTIGATIVE SITE INFORMATION

9.1 Investigative Site Selection

Sites will be selected for participation based on the following criteria:

- Previous participation in the **rem**edē System Pivotal Trial with currently active subjects
- Sufficient resources within site to conduct follow-up requirements of all subjects
- Willingness and interest in conducting the study

At each of the participating sites, it is expected that there will be coordination among the cardiac physician, interventional cardiologist / electrophysiologist, and the sleep medicine physician. The Principal Investigator (PI) is responsible for the overall conduct of the study. The PI may train and designate person(s) to conduct study-related activities but must retain overall responsibility for the trial. All training and delegation of tasks will be documented.

9.2 Ethical Considerations

The study will be conducted according to the Declaration of Helsinki, Protection of Human Subjects (21 Code of Federal Regulations [CFR] 50), IRBs (21 CFR 56), Financial Disclosure by Clinical Investigators (21 CFR Part 54), Electronic Records and Electronic Signatures (21 CFR Part 11), Obligations of Clinical Investigators (21 CFR 312), The International Standard for Standardization (ISO) 14155:2011, and in accordance with local laws and regulations in each of the countries participating.

9.3 Activation Requirements

This protocol and any amendments will be submitted to the FDA, appropriate regulatory bodies and IRB/IEC for approval to conduct the study prior to initiation.

The study will not commence at a participating institution until all investigational site activation requirements are completed. These include:

- Clinical Trial Agreement (signed)
- IRB/IEC approval letter (and national regulatory approval if required)
- Respicardia, Inc. and IRB/IEC-approved informed consent form (ICF) (and national regulatory approval if required)
- Completed Delegation of Authority Form/Delegation of Responsibilities Form
- Training Documentation Form(s) completed for PI, study coordinator, and any other study site personnel completing trial-related activities at the time of activation.
- PI Curriculum Vitae (CV) and sub-investigators' CVs participating at the time of activation
- Clinical Investigational Plan (CIP) signed by the PI
- IRB/IEC membership list/roster or Assurance Document

- Financial disclosure from the PI and sub-investigators participating at the time of activation

9.4 Informed Consent

Consent forms will be submitted with the protocol for review and approval by the IRB/IEC by the study site.

All subjects for this study will be provided an IRB/IEC-approved consent form describing this study and will be provided sufficient information to make an informed decision about their participation in this study.

The formal consent of a subject, will be obtained before that subject is submitted to any study procedure that is not standard of care. Consent forms must be signed by the subject or legal representative, and the investigator-designated research professional obtaining the consent. Respicardia, Inc. and the IRB/IEC must approve alternative informed consent materials prior to use. Where applicable, a local language informed consent will be provided.

9.5 Study Training

Protocol-specific training and education customized to the specific roles of all investigational site personnel will take place prior to site personnel participating in the study and throughout the study as needed. In particular, all physicians delegated to implant the **rem**edē System will be trained on standardized procedures for system implantation prior to being authorized to perform **rem**edē System modifications or have training documents on file from the **rem**edē System Pivotal Trial. All training will be documented and filed in the regulatory binder at the respective investigational site as well as at Respicardia, Inc. All study personnel, including new study personnel added during the course of the study, must be trained and delegated prior to performing any study-related activities considered non-standard of care.

9.6 Study Suspension or Termination

A study suspension is a temporary postponement of some or all of the study activities whereas termination of the study indicates study closure. Study suspension or termination of the study may occur at a single investigational site or for the study as a whole. Possible reasons for considering suspension or early termination include, but are not limited to, the following:

- **Study Suspension or Early Termination**
  - Adverse events associated with the **rem**edē System may endanger the safety or welfare of the study subjects
  - Observed and / or suspected performance of the **rem**edē System that is different from the product's design intent or specifications in a manner deemed unacceptable

- **Early Individual Investigational Site Termination or Suspension:**
  - Investigational site's noncompliance to the CIP or failure to comply with the country or local regulations
  - Failure to submit data in a timely manner
  - Failure to follow-up on monitoring findings
  - IRB/IEC approval expiration or withdrawal
  - Lack of PI oversight
  - All subjects at the site have completed participation in the trial
  - Fraud or fraudulent misconduct is discovered (as defined by local laws and regulations)

If a study suspension occurs, study subjects who are enrolled and implanted will continue to be followed for safety evaluation and/or per regulatory requirements.

10 STUDY PROCEDURES

Scheduled assessments at each visit are listed below and in **Table 1**. Subjects will start follow-up at the appropriate follow-up visit based on their initial **rem**edē System implant date. Subjects are required to complete the informed consent process prior to participation in the study.

Table 1 Follow-up Schedule

		Months[1] Post Implant								
Assessment **Follow-up window (days)**	**Prior to first visit**	**30 (phone) ±60 days**	**36 (office) ±60 days**	**42 (phone) ±60 days**	**48 (office) ±60 days**	**54 (phone) ±60 days**	**60 (Office) ±60 days**	**Interim Device Management**	**System Modification**	**Study Exit**
Informed Consent	X									
remedē System assessment			X		X		X	O		
Subject status		X	X	X	X	X	X			X
Adverse event review and reporting		X	X	X	X	X	X	X	X	X
Medical stability[2]			X		X		X			
In-home PG			X		X			O		
In-lab PSG							X	O		
ESS			X		X		X			
Concomitant device interaction testing, if applicable								O[3]	X	

X=Required at visit, O=Collected/performed as needed

[1] A month is defined as 30 days for visit target date determinations

[2] Perform medical stability assessment prior to PG/PSG

[3] Concomitant device interaction testing should be repeated prior to therapy initiation and anytime the **rem**edē System or the cardiac device system is modified if applicable

10.1 30, 42, and 54 Month Follow-up

The following assessments will be performed via telephone call:

- Survival
- Adverse event review and reporting
    - Review events with subject and review medical records since last visit

10.2 36 and 48 Month Follow-up

The following assessments will be performed at a clinic office visit:

- Date of visit
- **rem**edē System assessment including
    - stimulation lead impedance and capture levels on final programmed electrode pair
    - unipolar stimulation lead impedance measurements
    - interrogation including pre and post device settings parameter printouts
- Medical stability assessment prior to PG (defined as no hospitalizations in the previous 2 weeks)
    - The PG should not be performed until the subject is medically stable for at least 2 weeks
- In-home PG
    - PG is set up in the office and subject is instructed on proper use
    - Must include a minimum of four hours of high quality recording time
- ESS
- Adverse event review and reporting
    - Review events with subject and review medical records since last visit

10.3 60 Month Follow-up

The following assessments will be performed at a clinic office visit:

- Date of visit
- **rem**edē System assessment including
    - stimulation lead impedance and capture levels on final programmed electrode pair
    - unipolar stimulation lead impedance measurements
    - interrogation including pre and post device settings parameter printouts
- Medical stability assessment prior to PSG (defined as no hospitalizations in the previous 2 weeks)
    - The PSG should not be performed until the subject is medically stable for at least 2 weeks

- PSG in sleep laboratory
    - Must include a minimum of four hours of high quality recording time including a minimum of 2 hours of sleep
- ESS
- Adverse event review and reporting
    - Review events with subject and review medical records since last visit
- Exit the subject from the trial following completion of the visit

10.4 Interim Device Management

The investigator may evaluate the **rem**edē System at any point during the study via office visit, in-home PG, or in-lab PSG. The **rem**edē System Implant and Clinician Use Manual should be used by the Investigator or designee to guide the programming options and **rem**edē System set up. Respicardia, Inc. personnel may also be available for technical and programming support.

The following assessments should be performed and recorded at an interim device management visit:

- Adverse Event review and reporting
    - Review events with subject and review medical records since last visit
- **rem**edē System assessment (optional)
    - stimulation lead impedance and capture levels on final programmed electrode pair
    - interrogation including pre and post device settings parameter printouts

If applicable, concomitant device interaction testing should be repeated prior to therapy initiation and anytime the **rem**edē System or the cardiac device system is modified as described in the **rem**edē System Implant and Clinician Use Manual.

10.5 System Modifications

In the event the **rem**edē System requires modification (i.e., lead repositioning or replacement, system explant, or IPG replacement) the following assessments should be performed:

- Adverse Event review and reporting
    - Review events with subject and review medical records since last visit
- Concomitant device interaction testing, if applicable

In addition, system modifications occurring after exit from the pivotal trial and prior to signing ICF in this trial will be collected.

10.6 Study Exit

If the study exit occurs prior to the 60 Month follow-up visit, the following assessments will be performed:

- Adverse event review and reporting
    - Review events with subject and review medical records since last visit

In addition to subject's exit at study closure or completion of protocol requirements, subjects may be exited from the study for the following reasons and their exit documented on a Study Exit Case Report Form (CRF):

- Subject lost to follow-up
- Subject-initiated withdrawal
- Physician-initiated withdrawal
- Subject death

10.6.1 Subject Lost to Follow Up

In the event the ICF is signed and the subject is lost to follow-up, the study site must make a minimum of two attempts (one certified letter and one documented phone call or two certified letters) to contact the subject. Each attempt to contact a lost to follow-up subject and the method used will be documented in the subject's medical record.

10.6.2 Subject-Initiated Withdrawal

A subject may withdraw from the study at any time by notifying their physician. If a subject withdraws participation in the study at any time, there will be no penalty or loss of future medical care.

10.6.3 Physician-Initiated Withdrawal

The PI may withdraw the subject from the study without the subject's consent at any time if medically justified or for other documented reasons.

10.6.4 Subject Death

Subject deaths must be reported to Respicardia or designee within 24 hours of investigator knowledge, and the site must also complete an Adverse Event CRF.

If a subject death occurs while the subject is in the hospital, submit a copy of the hospital discharge note(s) and/or progress note(s) related to the death and/or death summary to Respicardia, Inc. If an autopsy is performed, submit a copy of the autopsy report and once the death certificate becomes available, send a copy to the Sponsor within 10 days. If a subject death occurs at a site remote from the investigational site, it is the investigative site's responsibility to make an attempt to retrieve all pertinent information related to the subject's death and submit the PI's summary of the known events surrounding the death. In all cases

following subject death, the investigator should request that the **rem**edē System be explanted and returned to Respicardia, Inc.

10.7 Protocol Deviations

A protocol deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP, including the Investigator Agreement, IRB/IEC, or local regulatory requirements.

The PI must maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol. Protocol deviations must be reported to Respicardia, Inc. regardless of whether or not medically justifiable. In the event the deviation involved 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 Respicardia, Inc. and the IRB/IEC within 5 working days of the deviation occurring. All other deviation reporting to IRB/IEC must comply with local IRB/IEC and local regulatory requirements.

Respicardia, Inc. will be responsible for analyzing, assessing and trending deviations to determine if corrective or preventive action is required. All deviations will be reported in the progress and final study reports.

10.8 Adverse Events

All adverse events (AEs) that occur between the subject signing the ICF and study exit will be documented in a timely manner and reported to the Sponsor. The investigator at the site should follow AEs until they have resolved, the condition has stabilized, or the subject exits the trial and report such follow-up information to the sponsor. AEs will be recorded in detail on the AE CRF.

In addition, serious AEs, implant-related AEs, therapy-related AEs, and device-related AEs occurring after exit from the pivotal trial and prior to signing ICF in this trial will be collected.

An independent Clinical Events Committee (CEC) will adjudicate, at minimum, all serious adverse events, including deaths, and therapy-, device- or implant-related adverse events.

CEC membership will include at least one physician from each of the following specialties: sleep, cardiology (preferably heart failure), and electrophysiology (familiarity with device implant procedures).

Definitions and Classifications

Adverse event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects, users or other

persons, or resulting in abandonment of **rem**edē System therapy, whether or not related to the **rem**edē System or study procedures. For users or other persons, this definition is restricted to events related to the **rem**edē System.

Procedure-related: An adverse event (whether serious or not) that occurs due to any procedure required to implant, revise, or explant the **rem**edē System.

Device-related: An adverse event (whether serious or not) that is related to the **rem**edē System and includes device explant due to device-related infection and events such as: device malfunction, lead fracture, lead component failure, lead dislodgment, lead displacement, pocket perforation, or extra-respiratory sensation requiring lead revision.

Battery depletion within an expected timeframe and resulting IPG replacement will be reported as a system modification and not an adverse event, unless the battery depletion occurred earlier than expected in which case it will also be recorded as an AE.

Therapy-related: An adverse event (whether serious or not) that includes events such as diaphragmatic stimulation discomfort, extra-respiratory stimulation, or concomitant device interaction.

Anticipated Adverse Event: An adverse event for which the nature, severity, or degree of incidence is known and identified in the product labeling or CIP.

Possible adverse effects include, but are not limited to, the following:

Implant Procedure-Related

- Adverse contrast dye reaction such as allergic reaction, pulmonary edema, or worsening renal function
- Adverse reaction to radiation exposure
- Thromboembolism
- Air embolism
- Bleeding
- Cardiac perforation including tamponade
- Hematoma, seroma, local bruising or swelling
- Hypotension
- Local wound healing issues at device implant site including wound dehiscence, pocket erosion, extrusion, movement of implanted device, keloid formation
- Pneumothorax
- Hemothorax
- Vascular damage, e.g., venous dissection, perforation

Lead and System-Related

- Adverse biocompatibility reaction to the implanted system
- Infection
- Lead breakage
- Lead dislodgement
- Lead not connected or secured appropriately in device header
- Implantable device malfunction
- Requirement for more energy to stimulate the nerve or ineffective stimulation
- Venous occlusion

Therapy-Related

- Crosstalk with another implanted device
- Disrupted sleep
- Muscle fatigue or discomfort in diaphragm, chest or abdomen from appropriate stimulation
- Nerve dysfunction
- Perturbation of blood gases causing hypoxia, hypercapnea and/or hypocapnea
- Inappropriate sensations
- Worsening heart failure, respiratory status or overall health

Other Procedure, System or Therapy-Related

- Anxiety
- Arrhythmia, including ventricular fibrillation
- Death
- Depression
- Hypotension
- Pain
- Skin irritation or local allergic reaction
- Thrombus or embolism, potentially leading to pulmonary embolism or stroke

Serious Adverse Event (SAE): Any adverse event as defined above (whether anticipated or unanticipated) that:

- led to a death,
- led to a serious deterioration in the health of the subject that
    - resulted in a life-threatening illness or injury,
    - resulted in a permanent impairment of a body structure or a body function,
    - required inpatient hospitalization or prolongation of existing hospitalization,
    - resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function, or
- led to fetal distress, fetal death or a congenital abnormality or birth defect

In addition, the following will be considered an SAE for purposes of this trial:

- A device or therapy related AE that required a system modification (excluding IPG replacement for battery depletion within anticipated timeframe or elective explant)

Unanticipated Adverse Device Effect (UADE): any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device (**rem**edē System), if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the product labeling, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. Investigators must report any suspected UADE to the sponsor as soon as possible but no later than ten (10) working days of knowledge of the event. Respicardia, or designee, will report results of any UADE evaluation to FDA and to all reviewing IRBs/IECs and participating investigators within ten (10) working days after Respicardia first receives notice of the effect.

10.8.1 Safety Endpoint Definitions

Serious device-related: For the purpose of assessing the device-related safety endpoint, a serious device-related adverse event is an event that meets the definition of serious and includes device explant due to device-related infection and events such as: device malfunction, lead fracture, lead component failure, lead dislodgment, lead displacement, pocket perforation, or extra-respiratory sensation requiring lead revision.

Serious therapy-related: For the purpose of assessing the therapy-related safety endpoint, the event must meet the definition of serious and include events such as diaphragmatic stimulation discomfort, extra-respiratory stimulation, or concomitant device interaction.

10.8.2 Serious Adverse Event Reporting

Any SAE must be reported to the Sponsor within 24 hours of investigational site knowledge. If the SAE requires expedited reporting to regulatory bodies (for example, a UADE resulting in death), the Sponsor will complete reporting requirements to FDA and other applicable regulatory bodies, as well as all reviewing IRBs and participating investigators within 10 working days after the Sponsor first receives notice of the event. The Sponsor will submit additional reports as requested from the FDA concerning the reported event.

10.9 Concomitant Cardiac Devices

Any addition of or change to a concomitant cardiac device during this trial or occurring after exit from the pivotal trial and prior to signing ICF for the post approval study will be collected.

10.10 Technical Observations

A technical observation is defined as a deficiency related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it has been released for distribution.

All technical observations that occur between the subject signing the ICF and study exit will be documented in a timely manner and reported to the Sponsor. Technical observations will be recorded on the technical observation CRF.

11 STATISTICAL METHODS

11.1 General Statistical Considerations

Data from this study will be combined with data from the **rem**edē System Pivotal Trial. All subjects will be pooled for analysis regardless of original randomization assignment.

Descriptive statistics will be used to summarize data. Continuous variables will be summarized using means, standard deviations, medians, interquartile ranges, minimums and maximums. Categorical variables will be summarized by calculating the percent of subjects in each category. No imputation for missing data will be performed.

Statistical analyses will be performed using validated software (e.g., SAS).

Copies of databases used to prepare clinical report summaries will be archived to enable any statistical analyses performed to be replicated.

11.2 Analysis Population

Intention-to-Treat (ITT): Subjects who were previously consented and randomized in the **rem**edē System Pivotal Trial. All effectiveness and safety evaluations will be based on the ITT population. Effectiveness analyses will only include subjects with data at the visit of interest.

11.3 Data Analyses

All subjects randomized in the **rem**edē System Pivotal Trial will be included in the safety assessments, unless otherwise noted. All adverse events will be summarized by seriousness, relatedness, and temporal relationship to the procedure and will be analyzed in a descriptive fashion. The number of events and number of subjects experiencing events will be summarized.

The survival distribution will be estimated with a Kaplan-Meier curve and the 95% confidence interval for the three and five year (or other time point of interest) survival rates will be calculated using the standard error determined by the Peto method.[1] The survival rate will be compared to historical controls and/or newly published results.

Subjects with follow-up data at the visit of interest will be included in the effectiveness assessments. Change from baseline analyses will include subjects with baseline and follow-up visit data.

Additional exploratory and/or subgroup analyses may also be performed to characterize study outcomes.

11.4 Sample Size Justification

No sample size calculations were performed.

12 DATA MANAGEMENT

Clinical data will be captured on CRFs and reported to Respicardia, Inc. CRF elements can be found in **Appendix C**. Device and sleep study data will be collected at applicable protocol-required visits in addition to source documentation collected for AE review and adjudication. All data should be entered into the CRFs, reviewed, and approved by the Investigator in a timely manner after the study visit or adverse event occurs.

In order to protect subject confidentiality, subjects will be identified by a subject ID number. The subject ID will be the same ID number that was assigned in the **rem**edē System Pivotal Trial.

All clinical data not collected via CRF (i.e., interrogation including pre and post device settings parameter printouts) should be uploaded to the Sponsor via a secure web portal. Sleep study data from the 36, 48, and 60 month post implant follow-up visits will be submitted directly to the core lab for analysis. Core Lab personnel will review the sleep studies per the 2007 American Academy of Sleep Association Manual (AASM) and provide the data to Respicardia, Inc. A sleep study report will be provided to the respective investigational site. The intent of providing the report is to document study procedure compliance and CRF completion; it is not to assist in patient care. The study site should have the sleep study read locally if needed for timely patient care.

All study documents must be retained by the investigational site for a period of two years after study conclusion and made available for monitoring or auditing by the sponsor's representative or representatives of the FDA and other applicable regulatory agencies. The investigator must ensure the availability of source documents from which the information on the CRFs was derived.

13 MONITORING

Each investigational site will be monitored to ensure compliance with the signed investigator agreement, CIP, IRB/IEC reporting requirements, and the applicable regulatory requirements. Monitoring will be conducted by the Sponsor or designee. The monitor will

verify that the study records are adequately maintained and the data is complete and reported in a timely matter. Monitoring may occur via an on-site visit or remotely.

Additional details regarding the monitoring process will be defined in the Monitoring Plan.

14 RECORD RETENTION AND REPORTS

The investigator is responsible for the preparation (review and signature) and/or retention of the records below. The following records are subject to inspection and must be retained for a period of two years after the date on which the study is terminated or completed. In Europe, records must be retained per local regulations.

- All correspondence that pertains to the investigation
- CV of the principal Principal Investigator and sub-investigators
- Signed and dated Clinical Trial Agreement and compensation records
- Subject's case history records, including: signed/dated subject ICF, all relevant observations of adverse device effects, medical history, exposure to the system under study, and documentation of the dates and rationale for any deviation from the CIP or Investigator Agreement
- The Clinical Investigational Plan
- IRB/IEC approval documents (with documentation that the investigator did not participate in the approval process)
- Monitoring Log
- Any other records that local regulatory agencies require to be maintained

Table 2 summarizes the minimum reporting requirements for the investigator. The investigator is responsible for the preparation (review and signature) and submission to Respicardia, Inc. of all CRFs, reportable AEs, deaths, and deviations from the CIP. If any action is taken by an IRB/IEC with respect to the investigation, the information must be forwarded to Respicardia, Inc. Reports are subject to inspection and to the retention requirements as described above for investigator records. The investigator shall prepare and submit all required reports in a complete, accurate and timely manner.

Table 2 Investigator Reporting Requirements

Report	Investigator Prepares Report For	Reporting Requirements and Timeframe
Unanticipated Adverse Device Effects (UADEs)	Sponsor and IRB/IEC	Notification to Respicardia or designee, as soon as possible but no later than 10 working days after investigators are first aware of the effect.
Medical Device Report (MDR)	FDA and Sponsor	Investigators may report to the FDA when they learn that any of their devices may have caused or contributed to a death or serious injury. Investigator may also report to the FDA when they become aware that their device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.
Vigilance Reporting (EU only)	Sponsor	Notification to Sponsor of an Incident as soon as possible. An Incident is defined as: "Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or USER or of other persons or to a serious deterioration in their state of health."
Serious Adverse Events	Sponsor and IRB/IEC and applicable regulatory authorities	Notification to Sponsor and IRB/IEC within 24 hours after investigators are first aware of the event.
Withdrawal of IRB/IEC approval or other action on part of the IRB that impacts study	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
Lack of informed consent	Sponsor and IRB/IEC	If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
Deviations from Investigational Plan	Sponsor and IRB/IEC	An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB approval in accordance with 812.35(a) also is required.
Progress Reports	Sponsor and IRB/IEC	An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

Table 2 Investigator Reporting Requirements

Report	Investigator Prepares Report For	Reporting Requirements and Timeframe
Final Report	Sponsor and IRB/IEC	The investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the Sponsor and the reviewing IRB/IEC and/or appropriate national regulatory authorities.

Table 3 summarizes Respicardia's reporting requirements relative to study findings and progress.

Table 3 Sponsor Reporting Requirements

Report	Sponsor Prepares Report For	Reporting Requirements and Timeframe
Unanticipated Adverse Device Effects	Investigators, IRBs/IECs and FDA	Within 10 working days from the time the Sponsor first learns of the effect.
Serious Adverse Events requiring expedited reporting	Investigators, IRBs/IECs and FDA	Within 10 working days from the time the Sponsor first learns of the event.
Withdrawal of IRB/IEC approval or other action on part of the IRB that impacts study	Investigators, FDA, and European Competent Authorities (CAs)	Within 5 working days after receipt of the withdrawal of approval.
Medical Device Report (MDR)	Sponsor	Manufacturers are required to report to the FDA when they learn that any of their devices may have caused or contributed to a death or serious injury. Manufacturers must also report to the FDA when they become aware that their device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.
Vigilance Reporting (EU only)	Local CA and Notified Body	Notification to Sponsor of an Incident as soon as possible. An Incident is defined as: "Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or USER or of other persons or to a serious deterioration in their state of health."
Lack of informed consent	FDA and European CAs where applicable	Investigator's report submitted within 5 working days of notification.
Progress Reports	Investigators, FDA, and European CAs where applicable	Every 6 months for the first two years of the study and annually, thereafter.
Final Report	Investigators, FDA, and IRBs/IECs	Within 6 months of study closure.

Table 3 Sponsor Reporting Requirements

Report	Sponsor Prepares Report For	Reporting Requirements and Timeframe
Withdrawal of FDA approval	Investigators and FDA	Within 5 working days after receipt of notice of the withdrawal of approval.
Recall and device disposition	FDA,IRBs/IECs, European CAs, and Notified Body	Any request that an investigator return, repair, or otherwise dispose of any units of a device within 30 working days after request and stating why the request was made.

15 INSURANCE

Respicardia, Inc. has obtained local insurance within and outside of the US as required by law for the purpose of conducting this trial.

APPENDIX A: SAMPLE INFORMED CONSENT

Respicardia

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	Post Approval Study of the **rem**edē® System
PROTOCOL NO.:	Respicardia CR1079
SPONSOR:	Respicardia, Inc. Minnetonka, Minnesota United States
INVESTIGATOR:	[Name] [Address] [City, State, Zip Code] [Country]
STUDY-RELATED PHONE NUMBER(S):	[Name] [Phone Number(s)]

A person who takes part in a research study is called a research or study subject. In this consent form "you" always refers to the research subject. If you are a legally authorized representative, please remember that "you" means the research (study) subject.

SUMMARY

You are being asked to be in a research study. The purpose of this consent form is to help you decide if you want to be in a research study.

You should not sign this consent form until all of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- The decision to join or not to join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.

- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study.

PURPOSE AND BACKGROUND

The purpose of this study is to assess the continued safety and effectiveness of this approved device.

The **rem**edē System Pivotal Trial showed that **rem**edē System benefits patients with central sleep apnea. Based on these results, the FDA approved the **rem**edē System for sale in the United States (US). As part of the approval, the FDA is requiring the sponsor to conduct this post-approval study.

There are no experimental (investigational) procedures or devices involved in this study.

STUDY PROCEDURES

If you agree to take part in this study, the study doctor and study staff will collect information about you. They may ask you questions, and they may review your medical records to obtain health information.

Your participation in this study may last up to 36 months. Up to 94 subjects will take part in this study, which is being conducted at up to 26 sites worldwide.

You will be asked about serious health problems, problems related to the **rem**edē System, and any new or changes to your cardiac device (if you have one) that you have experienced since you exited the **rem**edē System Pivotal Trial.

This study requires annual office visits at 36, 48, and 60 months after your **rem**edē System was implanted. It is possible that you have already completed some of these visits while enrolled in the **rem**edē System Pivotal Trial. If you consent to be in this study, your first visit will be calculated based on the date of your original implant of the **rem**edē System. For example, if you were implanted in January of 2014 and sign consent in January of 2018, your first visit would be considered your 48 month visit or 54 month visit depending on the visits you completed in the **rem**edē System Pivotal Trial. Your final visit will be at 60 months post **rem**edē System implant.

During the 36 and 48 month office visits, you will have the following assessments:

- a **rem**edē System device evaluation (a wand is placed over the skin where the device is located and it reports its condition electronically)
- an in home, overnight sleep study
- a quality of life questionnaire asking how sleepy you are during the daytime
- review of new or worsening health problems, hospitalizations, illness or injury, or outpatient procedures that you have experienced

During the 60 month office visit, which is your last visit, you will have the following assessments:

- a **rem**edē System device evaluation (a wand is placed over the skin where the device is located and it reports its condition electronically)
- an overnight sleep study done in a sleep laboratory
- a quality of life questionnaire asking how sleepy you are during the daytime
- review of new or worsening health problems, hospitalizations, illness or injury, or outpatient procedures that you have experienced

At the time of these annual visits, if you were hospitalized within the two weeks prior to the visit, you will be asked to delay the sleep study until it has been at least two weeks since your hospitalization or your doctor determines you are stable enough to perform the sleep study.

Telephone visits will be conducted in between the annual office visits at 30, 42, and 54 months. During these calls, your health status will be determined by review of new or worsening health problems, hospitalizations, illness or injury, or outpatient procedures that you have experienced since your last office visit.

If you have other stimulation devices implanted or modified during the study, contact your study doctor as special testing will be needed to ensure the devices are not interacting.

If you die when you are in the study, your emergency contact or next of kin may be contacted to inquire about the cause of your death. An attempt may be made to collect the **rem**edē System if it is explanted.

ROLE OF SPONSOR REPRESENTATIVE

Respicardia, Inc. personnel may be present at office visits for technical and programming support.

RISKS AND DISCOMFORTS

There are no research-related risks to you by allowing your study doctor to continue to collect information about you and the **rem**edē System.

NEW INFORMATION

You will be told about any new information that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS

Your central sleep apnea may improve while you are in this study. The results of this study may help people with central sleep apnea in the future.

COSTS

Now that the FDA has approved the **rem**edē System, follow-up care will be considered standard of care. Respicardia, Inc. (Sponsor) will no longer be paying for procedures related to the **rem**edē System such as lead revisions, replacement of the battery, explant (removal) of the **rem**edē System, or routine follow-up visits. The reason the Sponsor is no longer paying for these procedures is that they are now considered standard of care and will be billed to appropriate third party payors, such as your insurance carrier or Medicare. The usual costs connected with the device procedures will normally be covered by your health insurance. You will be responsible for any co-pays, co-insurance or deductibles you would normally pay. If you have any questions about your health insurance, or possible expenses, please talk with the study doctor and your health insurer or Medicare.

PAYMENT FOR PARTICIPATION

You will not be paid for being in this study.

ALTERNATIVE TREATMENT

This is not a treatment study. Your alternative is not to be in this study.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

[Use the following authorization format if the site is collecting health information, is a covered entity under HIPAA and is not using a separate HIPAA authorization form.

If the site is not collecting health information, is not a covered entity under HIPAA or is using a separate HIPAA authorization form, use the "Confidentiality" text that follows, rather than the authorization text below.

California sites: This entire HIPAA section plus authorization statement should be placed at the end of the consent form following a page break and must include its own set of signature lines.]

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits

Who may use and give out information about you?
The study doctor and the study staff.

Who might get this information?
The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor.

Your information may be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- Governmental agencies to whom certain diseases (reportable diseases) must be reported, and
- [IRB Name]

[Add any institutional names above IRB Name.]

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to see if the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
Yes, but this permission will not stop automatically.

[or]
This permission will be good until [date] *[required in CA, DE, IN, IL, WA, and WI]*.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.
*[Use the following confidentiality text if the site is **not** collecting health information, is **not** a covered entity under HIPAA,or is using a separate HIPAA authorization form.]*

Confidentiality
Information from this study will be given to the sponsor. "Sponsor" includes any persons or companies that are contracted by the sponsor to have access to the research information during and after the study.

The information will also be given to the U.S. Food and Drug Administration (FDA). It may be given to governmental agencies in other countries where the study device may be considered for approval. Medical records which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by:

- the sponsor,
- [CRO name], an agent for the sponsor,

and may be looked at and/or copied for research or regulatory purposes by:

- the FDA,
- Department of Health and Human Services (DHHS) agencies,
- governmental agencies in other countries, and
- [IRB Name]
  [Add any institutional names above IRB name]

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations.

If you approve, your personal physician will be informed of your participation in the clinical study.

COMPENSATION FOR INJURY

For this study, we are only collecting information about you and your **rem**edē System. However, if you believe that an injury has occurred, call your study doctor immediately. If you need any medical treatment, it will be provided. Your insurance will be billed for this treatment. No monetary compensation or subsidized medical treatment will be routinely provided to you by any person involved in this study including the study doctors, the hospital, or the study sponsor. If there is a defect in your **rem**edē System, the standard terms and conditions of the product warranty will apply.

VOLUNTARY PARTICIPATION/WITHDRAWAL

Your participation is voluntary. You may decide not to participate or may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any reason, including:

- if it is in your best interest
- you do not consent to continue in the study after being told of changes in the research that may affect you
- or for any other reason

If you leave the study before the planned final visit, you may be asked by the study doctor to have some tests or procedures done so that you leave the study safely.

SOURCE OF FUNDING

Funding for this research study will be provided by Respicardia, Inc.

QUESTIONS

Discuss with your study doctor any questions, concerns, or complaints which you may have regarding your participation in this study or if you have experienced a research-related injury. If you have any questions, contact:

NAME	TITLE/POSITION	PHONE
[PI Name]	Study Doctor	
[Coordinator Name]	Study Coordinator	

If you have any questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, you should contact:

[IRB Contact Information]

[IRB name] is a group of people who independently review research.

[IRB name] will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact IRB name] if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

A description of this clinical study will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT

- ✓ I voluntarily agree to participate in this clinical investigation and to follow the investigator's instructions.
- ✓ If I refuse to participate, I will incur no penalties.
- ✓ I may discontinue the study at any time without incurring any penalties.
- ✓ I acknowledge the information provided to me about the study and all of my questions have been answered.
- ✓ I agree, or my legally authorized representative agrees, to the use of my personal data for purposes of the study.
- ✓ I agree, or my legally authorized representative agrees, that the sponsor's representatives, regulatory authorities, Ethics Committees or Internal Review Boards representatives may be granted direct access to my medical records.
- ✓ I understand that I will receive a copy of this form.

_____

Printed Name of Subject

_____ _____

Signature of Subject or of Subject's Legally Authorized Representative Date

_____

Printed Name of Subject's Legally Authorized Representative (if applicable)

I have explained the Post Approval Study to the study subject, and I have answered all questions about this research to the best of my ability. A signed copy of this consent form has been provided to the study subject.

_____

Printed Name of Person Conducting Informed Consent Discussion

_____ _____

Signature of Person Conducting Informed Consent Discussion Date

APPENDIX B: QUALITY OF LIFE QUESTIONNAIRE

The following standardized, validated tool will be used to assess Quality of Life.

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life recently.

Even if you haven't done some of these things recently, try to figure out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = **no chance** of dozing
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each item as best as you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g., a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	

THANK YOU FOR YOUR COOPERATION

ESS - USA/English - Final version - 21 Nov 07 - Mapi Research Institute.
ID 4193

APPENDIX C: PLANNED DATA COLLECTION LIST OF DATA VARIABLES ON CASE REPORT FORMS (CRFs)

- Enrollment CRF
  - Date of consent
  - Protocol Version active at the time of consent If subject is currently receiving therapy from the **rem**edē System
  - Original implant date
- Visit CRF
  - Did subject complete visit?
    - If yes, type of visit
      - office or phone call
      - Date of visit or phone call
    - If no
      - Date of last contact
- **rem**edē System assessment CRF
  - Was capture threshold successfully obtained?
  - If no, select reason
  - If yes,
    - Date tested
    - Final programmed pair
      - Lead
        - Left
        - Right
      - Anode
      - Cathode
      - Lead Impedance
      - Current weak
      - Current strong
      - Pulse width
      - Frequency
    - Unipolar Stimulation Lead Impedance Measurements
      - 1-Can
      - 2-Can
      - 3-Can
      - 4-Can
      - 5-Can (if applicable)
      - 6-Can (if applicable)
    - Therapy mode at end of visit
- Interim Device Management CRF

    - Same information as **rem**edē System assessment, if testing is performed
- Adverse Event CRF
    - Onset date
    - Event type
        - New event
        - Update to event reported in Pivotal Trial
    - Event number
    - Diagnosis of event or symptoms if no diagnosis
    - Event description
    - Sponsor Event code
    - Relation to device
        - Definitely
        - Probably
        - Possibly
        - None
            - If related to device or therapy, which component
                - Therapy delivered by **rem**edē System
                - Stimulation Lead
                - Sensing lead
                - IPG (excludes early battery depletion)
                - Early battery depletion
                - Other, specify:_____
    - Relation to procedure
        - Definitely
        - Probably
        - Possibly
        - None
    - Treatment provided
        - Medication administered
        - Surgical procedure
            - If yes, specify: _____
        - **rem**edē System programming
        - Concomitant device programming
        - Other, specify
    - Serious adverse event (Yes/No). If yes:
        - Led to Death
        - Resulted in a life-threatening illness or injury
        - Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function

        - Required inpatient hospitalization or prolongation of existing hospitalization
            - Date of admission
            - Date of discharge
        - Resulted in permanent impairment of a body structure or a body function
        - Led to fetal distress, fetal death or a congenital abnormality or birth defect
        - A device or therapy related AE that required a system modification (excluding IPG replacement for battery depletion within anticipated timeframe or elective explant)
    - Unanticipated adverse device effect
    - Adverse event status
        - Resolved
            - Date of Resolution
        - Ongoing, expect eventual resolution
        - Ongoing, stable or chronic condition
        - Death
        - Unknown
- Technical Observation CRF
    - Date of observation
    - Product
        - Physician Programmer
            -
        - Programming wand
        - IPG
        - External IPG
        - Stimulation Lead
        - Therapy delivered by **rem**edē System
        - **respi**guide™
        - Other
    - Model (if applicable)
    - Serial number (if applicable)
    - Comments
- Sleep Study CRF
    - Date
    - Was the subject medically stable?
    - Type of Sleep Study
        - PG
        - PSG

  - Total recording time
  - AHI
  - CAI
  - OAI
  - MAI
  - HI
  - Was the subject receiving **rem**edē System therapy?
  - Was the subject using concomitant sleep disordered breathing therapy?
    - If yes, select all that apply
      - CPAP
      - Oxygen
      - ASV
      - Bi-PAP
      - Dental appliance
      - Other, specify:_____
- Epworth Sleepiness Scale (ESS) CRF
  - Was ESS completed (Yes,/No). If yes:
    - Date
    - Question responses
- Concomitant Cardiac Device CRF
  - Reason for procedure
    - New device
    - Upgrade to new device type
    - Replacement of device
    - Other, specify
  - Date or procedure
  - Type of device
  - Manufacturer and model number
  - Location of device
  - Was interaction testing performed?
    - Date of testing
- System Modification CRF
  - Date
  - Primary reason for system modification
  - Modifications to **rem**edē System
    - IPG
      - Not modified
      - Repositioned
      - Replaced
        - Manufacturer, Model, Serial Number

        - Explanted (without replacement)
    - Stimulation Lead
        - Not modified
        - Repositioned
        - Replaced
            - Manufacturer, Model, Serial Number
        - Capped with replacement
            - Manufacturer, Model, Serial Number
        - Capped without replacement
        - Explanted (without replacement)
    - Sensing Lead
        - Not applicable
        - Not modified
        - Repositioned
        - Replaced
            - Manufacturer, Model, Serial Number
        - Capped with replacement
            - Manufacturer, Model, Serial Number
        - Capped without replacement
        - Explanted (without replacement)
- Was system functional following procedure?
    - If no, Reason
    - If yes, Therapy mode
    - If yes, Was interaction testing performed

- Protocol Deviation CRF
    - Date of deviation
    - Visit deviation applies to
    - Type of deviation
        - Visit not performed
        - Visit out of window
        - Assessment out of window
        - Required assessment(s) not done
            - Specify:_____
        - Assessment by untrained / not delegated staff
        - Informed Consent
        - Other, specify:_____
    - Describe the deviation:_____
    - Reason for deviation
- Study Exit CRF
    - Date of study exit

- Reason for study exit
  - Subject completed study follow-up requirements
  - Subject Lost to Follow-up
  - Subject-Initiated Withdrawal
  - Physician-Initiated Withdrawal
  - Subject Death
  - Early termination of site or study
- If lost to follow-up, subject or physician initiated withdrawal or early termination: Date of last contact

APPENDIX D: ACRONYMS/ABBREVIATIONS/GLOSSARY

AE	Adverse Event
AHI	Apnea Hypopnea Index
ArI	Arousal Index
CA	Competent Authority
CAI	Central Apnea Index
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CIP	Clinical Investigational Plan
CRF	Case Report Form
CSA	Central Sleep Apnea
CV	Curriculum Vitae
CVA	Cerebrovascular Accident
EC	Ethics Committee
ESS	Epworth Sleepiness Scale
EU	European Union
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention-to-Treat
IEC	Independent Ethics Committee
OAI	Obstructive Apnea Index
ODI4	Oxygen Desaturation Index 4%
PGA	Patient Global Assessment
PI	Primary Investigator
PSG	Polysomnogram
PG	Polygram
REM	Rapid Eye Movements
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
US	United States

APPENDIX E: BIBLIOGRAPHY

1. **Survivorship analysis for clinical studies**. Eugene K. Harris and Adelin Albert, Marcel Dekker, New York, 1991.

APPENDIX F: remedē **System Implant and Clinician Use Manual**

remedē® System

System Implant and Clinician Use Manual

remedē® Implantable Pulse Generator Model 1001

remedē® System Programmer Model 1002A

remedē® System Programming Wand Models 1004A, 1004A–F

remedē® External IPG Model 1006

respi**stim**® L Stimulation Lead Models 2001, 2002, 2003, 2004

respi**stim**® LQ Stimulation Lead Models 5045, 5055, 5065, 5085

respi**stim**® LQS Stimulation Lead Models 4045, 4055, 4065, 4085

respi**stim**® R Stimulation Lead Models 3101, 3102, 3103, 3104, 3105, 3106, 3201, 3202, 3203, 3204, 3205, 3206

RxOnly

CE 0086

Issued 2010

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1.1 Symbols Used on Product or Package Labeling

Refer to individual product for applicable symbols.

	Applies to U.S. audiences only
	Catalog or Reference Number
	Lot Number
	Sterilized using ethylene-oxide gas
	Sterile Lot Number
	Do Not Reuse/Single Use Only
	Do Not Resterilize
	Temperature Limitation/Temperature Range
	Caution
	MR Unsafe
	Use by/Expiration date
	Date of Manufacture

Manufacturer

Quantity in Package

Inside Diameter

Outside Diameter

Length

Consult Instructions for Use

Keep away from heat and keep dry

Type B Applied Part – No electrical connection to patient and may be grounded

Type BF Applied Part – Electrically connected to patient but not directly to the heart

Type CF Applied Part – Electrically connected to the heart of the patient

Non-ionizing electromagnetic radiation

Federal Communications Commission notice (USA)

Conformité Européne (European Conformity). This system fully complies with the European Union Council Directive 90/385/EEC

RxOnly

Use by prescription only

1.2 Introduction

This manual is intended to provide clinicians with information regarding the implant and use of the **rem**edē® System. Included in this manual are descriptions of the **rem**edē System as well as instructions for handling, storing and surgical placement of the **rem**edē System. This manual also includes an overview of the **rem**edē System therapy and instruction for clinical use and follow-up care of patients using the **rem**edē System Programmer.

1.3 Indications for Use

The **rem**edē® System is an implantable phrenic nerve stimulator indicated for the treatment of moderate to severe central sleep apnea (CSA) in adult patients.

1.4 System Overview

The system consists of an implantable pulse generator (IPG), one transvenous lead to stimulate the phrenic nerve, and one transvenous sensing lead to sense respiration via transthoracic impedance. External, non-implanted devices and accessories of the **rem**edē System include the **rem**edē System Programmer, external IPG, and programming wand.

1.5 Description of System Components

All implanted components of the **rem**edē System are intended for single use only.

1.5.1 remedē® IPG

The **rem**edē IPG (Model 1001, Figure 1) is an implantable, multi-programmable stimulator designed for unilateral, transvenous phrenic nerve stimulation. The device monitors the patient's respiratory signals and provides electrical stimulation to the left or right phrenic nerve to restore patients to a normal breathing pattern during sleep. The **rem**edē IPG contains electronic circuitry components and a battery, which are hermetically sealed in a titanium case. Therapy settings are determined by the physician and configured using an external programmer via telemetry.

The **rem**edē IPG has four 3.2 mm connector ports (Figure 2) that are compatible with IS-1 connectors. The IS-1 lead connectors in each 3.2 mm connector port are secured by two set screws.

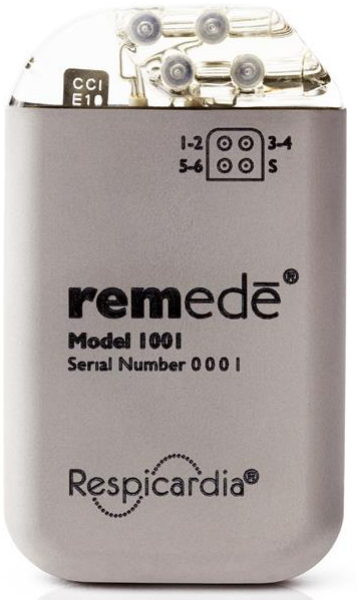

Figure 1 The remedē® System IPG **Figure 2 The remedē® IPG Connector Ports**

1.5.2 respi**stim®** Stimulation Leads

Respicardia, Inc. has developed a respi**stim** L (left) family of leads and a respi**stim** R (right) family of leads for phrenic nerve stimulation to treat CSA. The respi**stim** family of stimulation leads is comprised of four unique transvenous leads designed for chronic stimulation and sensing when placed in a thoracic vein and connected with a compatible pulse generator.

*1.5.2.1 respi**stim®** L Stimulation Lead*

The respi**stim** L stimulation lead (Models 2001, 2002, 2003, and 2004) is a bipolar, transvenous, over-the-wire lead. The proximal end of the lead contains one IS-1 terminal pin/connector and the distal end is comprised of two ring electrodes. The lumen of the lead is continuous, permitting the passage of a 0.014” guide wire for delivery into the desired target vein.

*1.5.2.2 respi**stim®** LQ Stimulation Lead*

The respi**stim** LQ stimulation lead (Models 5045, 5055, 5065, and 5085) is a quadripolar, transvenous, over-the-wire lead. The proximal end of the lead has two IS-1 terminal pins/connectors and the distal end is comprised of four ring electrodes. The lumen of the lead is continuous, permitting the passage of a 0.014” guide wire for delivery into the desired target vein.

1.5.2.3 respistim® LQS Stimulation Lead

The respi**stim** LQS stimulation lead (Models 4045, 4055, 4065, and 4085) is a quadripolar, transvenous, over-the-wire lead. The proximal end of the lead has two IS-1 terminal pins/connectors and the distal end is comprised of four ring electrodes having an S-shape bias. The lumen of the lead is continuous, permitting the passage of a 0.014" guide wire for delivery into the desired target vein.

1.5.2.4 respistim® R Stimulation Lead

The respi**stim** R stimulation lead (Models 3101, 3102, 3103, 3104, 3105, 3106 and 3201, 3202, 3203, 3204, 3205, 3206) is a hexapolar, transvenous, stylet delivered lead. The proximal end of the lead has three IS-1 terminal pins/connectors and the distal end of the lead is comprised of six ring electrodes and a non-electrically active tip having a helical shape bias. The lead is designed for use with a stylet to remove the distal bias and permit delivery of the lead into the desired target vein.

1.5.3 Respiratory Sensing Lead

The **rem**edē System is designed to monitor respiration by sensing changes in transthoracic impedance. The system is capable of sensing respiration signals through either an implanted respi**stim** stimulation lead or through a commercially available IS-1 compatible bipolar lead.

1.5.4 remedē® System Programmer

The **rem**edē System Programmer (Model 1002A, Figure 3) is a touch screen tablet computer used to communicate with the **rem**edē implantable pulse generator (IPG) via inductive telemetry and allows for configuration of programmable settings, initiation of system testing and review of collected diagnostic data. Communication with the implanted device is achieved using the **rem**edē programming software and an external programming wand (Model 1004A or 1004A-F) connected to the programmer via USB cable.

Figure 3 The remedē **System Programmer**

1.5.5 remedē® Programming Wand

The **rem**edē System programming wands (Models 1004A, Figure 4 and 1004A-F) connect to the System Programmer via USB and provide a magnetic inductive communication link to the implanted device. The Model 1004A programming wand requires placement of the wand directly over the implanted device for telemetry communication. The optional Model 1004A-F provides an extended flexible antenna disc that must be placed directly over the implanted device and is intended to allow for real-time monitoring during a polysomnogram (PSG).

Figure 4 The remedē Programming Wand (Model 1004A)

1.5.6 remedē® External IPG

The **rem**edē external IPG (Model 1006, Figure 5) is used for evaluation of stimulation lead placement during implant of the **rem**edē System. The external IPG (eIPG) delivers the same stimulation pulse as the **rem**edē IPG and provides one set of anode and cathode connection ports for use with a sterile cable.

Figure 5 The remedē External IPG

1.6 Contraindications

The **rem**edē System is contraindicated for the following:

- Patients with an active infection
- Patients known to require magnetic resonance imaging (MRI)

1.7 Warnings and Precautions

Carefully read all warnings, precautions, and instructions before use. Follow all operating, maintenance, and installation procedures as described in this manual. Failure to do so may result in patient harm.

1.7.1 Warnings

1.7.1.1 Modified Components

The use of modified components with the **rem**edē® System is not allowed and may result in damaged components, unintended operation, or increased risks to the patient.

1.7.1.2 Magnetic Resonance Imaging (MRI or NMRI)

Do not use magnetic resonance imaging (MRI or NMRI) on patients who have been implanted with the **rem**edē System. Energy produced by MRI equipment may result in permanent tissue damage or damage to the **rem**edē System. Alternative imaging options should be considered.

1.7.1.3 Diathermy

Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (collectively referred to as diathermy) on patients implanted with the **rem**edē System. Energy produced by diathermy equipment may be transferred through the implanted system and can cause permanent tissue damage at the location of the implanted electrodes, resulting in severe injury or death.

Diathermy can also damage the **rem**edē System, resulting in loss of therapy and requiring additional surgery for system explantation and replacement. Advise the patient to inform their health care professionals that diathermy exposure should be avoided.

1.7.1.4 Electric Shock

When operating under AC power, the **rem**edē System Programmer must be connected to a grounded power source to avoid risk of electric shock.

1.7.1.5 Concomitant Active Implantable Devices

Use **rem**edē System with caution in patients with an active implantable device that may be susceptible to unintended interaction with the **rem**edē system. Consult Respicardia to assess the possibility of interaction.

1.7.1.6 Patients with Evidence of Phrenic Nerve Palsy

Therapy with the **rem**edē System may be ineffective in patients who have evidence of phrenic nerve palsy.

1.7.1.7 Pediatric Use

The safety and effectiveness of the **rem**edē® System has not been established for pediatric use.

1.7.1.8 Electromagnetic Compatibility and Medical Procedure Precautions

The **rem**edē System is designed to ensure immunity from most common sources of electromagnetic interference (EMI). In most cases, turning off the EMI source, or moving away from the EMI source will return the IPG to normal operation. Extremely strong sources of EMI could interfere with normal IPG operation, causing the IPG to reset and requiring the programmed settings to be reconfigured. For information on MRI and diathermy, see 'Warnings' in sections 1.7.1.2 and 1.7.1.3.

1.7.1.8.1 Electrocautery

Electrocautery may induce failure of the IPG and leads if direct contact is made. Alternatives to electrocautery should be used when available. If electrocautery is necessary, the **rem**edē System should be programmed off and bipolar cautery should be used. Confirm proper function of the **rem**edē System after any procedure where electrocautery is used.

1.7.1.8.2 Radiofrequency or Cryoballoon Ablation

If radiofrequency or cryoballoon ablation must be used in the vicinity of the IPG or leads, the **rem**edē System should be programmed off. Avoid direct contact between the radiofrequency ablation or cryoballoon catheter and the implanted **rem**edē System.

1.7.1.8.3 Therapeutic Radiation

The IPG should not be directly irradiated by therapeutic levels of ionizing radiation (such as that produced by cobalt machines or linear accelerators used for treatment of certain cancers) because of the risk for damage to the **rem**edē System. If such therapy is required, program the **rem**edē System off, shield the device, and confirm proper function of the **rem**edē System after treatment.

1.7.1.8.4 Computed Tomography (CT) Imaging

If a CT scan is required, ensure that the **rem**edē System is off and confirm proper function of the **rem**edē System after the scan is complete.

1.7.1.8.5 Therapeutic Ultrasound

Exposure to high ultrasonic frequencies may result in damage to the **rem**edē System. It is not recommended to use high-output ultrasonic devices, such as an electrohydraulic lithotripter or bone growth simulator on patients implanted with the **rem**edē System. If therapeutic ultrasound must be performed, program the **rem**edē System off and keep the implanted

system a minimum of 2.5 cm (1 in) away from the ultrasonic field. Confirm proper function of the **rem**edē® System after treatment.

1.7.1.8.6 External Defibrillation Energy

The use of external defibrillation may cause damage to the **rem**edē System. The risk of damage may be minimized by positioning the defibrillation patches or paddles a minimum of 15 cm (6 in) and perpendicular to the IPG. Confirm proper function of the **rem**edē System after any use of external defibrillation.

1.7.1.8.7 Patient Monitoring Equipment

remedē System stimulation therapy may be detectable by patient monitoring equipment including automated external defibrillators. Confirm proper function of monitoring equipment if used while **rem**edē stimulation therapy is active.

1.7.1.8.8 Transcutaneous Electrical Nerve Stimulators (TENS)

TENS therapy should be used only if the **rem**edē System is inactive (not providing stimulation therapy). If TENS therapy must be used, place the TENS electrodes as far from the **rem**edē System as possible. TENS electrodes should also be spaced as close together as possible to reduce the generated electrical field. Confirm proper function of the **rem**edē System after use of TENS therapy.

1.7.1.8.9 Electrical Isolation During Implant

Do not allow the patient to have contact with grounded equipment that might produce electrical current leakage during implant. Electrical current leakage may induce arrhythmias that could result in patient death.

1.7.1.8.10 Lead Compatibility

Only use IS-1 lead or lead extension terminals with the **rem**edē System. Use of non IS-1 compatible terminals may result in undersensing of respiratory activity, failure to deliver necessary therapy, or a leaking or intermittent electrical connection.

1.7.1.8.11 Concomitant Active Implantable Cardiac Devices

It is recommended that testing for oversensing of **rem**edē stimulation therapy by the concomitant cardiac device occur at the time of implant and prior to initiating **rem**edē System therapy in patients with a concomitantly implanted cardiac device (testing protocol described on page 36). Programming of the **rem**edē System and/or the concomitant device, when necessary, can prevent oversensing of **rem**edē stimulation therapy.

To avoid telemetry interference, one telemetric programming system should be utilized at a time if the concomitantly implanted device uses magnetic inductive telemetry.

1.7.1.9 Pacemaker Dependence

Use **rem**edē® System therapy with caution in pacemaker dependent patients without a physiologic escape rhythm. Device interaction may lead to over or undersensing resulting in a loss of pacing.

1.7.1.10 Pregnancy

The safety and effectiveness of the **rem**edē System during pregnancy has not been established.

1.7.2 General Precautions

1.7.2.1 Expiration Date

Do not use any **rem**edē System product after its expiration date.

1.7.2.2 Storage Temperature Ranges

It is recommended the **rem**edē System be stored in a dry place according to the temperature ranges below:

remedē® System	Temperature Ranges
remedē IPG	0ºC (32ºF) and 50ºC (122ºF)
respi**stim®** R, L, LQ, LQS Leads	5ºC (41ºF) and 30ºC (86ºF)
remedē System Programmer	-20ºC (-4ºF) and 70ºC (158ºF)
Programming Wand	-20ºC (-4ºF) and 70ºC (158ºF)
eIPG	0ºC (32ºF) and 50ºC (122ºF)

1.7.3 Home or Work Environment Precautions

1.7.3.1 High Powered Electric Fields

Normal operation of the **rem**edē System can be affected by magnetic, electrical and electromagnetic signals with sufficient strength or with characteristics similar to respiratory activity. Consult with Respicardia if the patient will be in an area where contact with current carrying conductors is possible or near high powered electromagnetic fields caused by equipment such as arc welding units, induction furnaces, induction stoves, resistance welders, radio or microwave transmitters, and linear power amplifiers.

1.7.3.2 Cellular Phones

Normal operation of the **rem**edē System may be affected by cellular phones. Maintain a minimum separation of 25 cm (10 in) between a cellular phone and the **rem**edē System, even if the cellular phone is not on.

1.7.3.3 Electronic Article Surveillance (EAS)

Electronic article surveillance equipment such as retail theft prevention systems, as well as airport metal detectors, may interfere with the **rem**edē System. Advise patients to walk directly through an EAS system and not remain near an EAS system longer than necessary. Where possible, alert security personnel of the implanted **rem**edē System and request a manual search.

1.7.3.4 Common Radiofrequency Sources (e.g. RFID)

Normal operation of the **rem**edē System may be affected by common radiofrequency sources. Patients should minimize time around radiofrequency sources, such as RFID, when recognized they are nearby and operators of the **rem**edē System external components should maintain a separation distance of 40cm from RFID systems.

1.7.3.5 Static Magnetic Fields

Patients should avoid equipment or situations where they would be exposed to static magnetic fields greater than 10 gauss or 1 mT. Static magnetic fields may suspend therapy until next scheduled therapy session. Sources of static magnetic fields include, but are not limited to, stereo speakers, bingo wands, extractor wands, magnetic badges, or magnetic therapy products.

1.7.3.6 Wi-Fi

Do not use or enable Wi-Fi on the **rem**edē System Programmer to protect the system from cybersecurity risks.

1.7.4 remedē® System Therapy Hazards

1.7.4.1 Risk of Arrhythmia

The stimulation lead should be placed in the right brachiocephalic vein or the left pericardiophrenic vein. Based on clinical study of leads placed in these locations, it is highly unlikely the heart would be electrically impacted by the levels of stimulation available in the **rem**edē System (≤10 mA, 300 μs). Based on clinical experience and animal testing experience with displaced leads, it is unlikely that a displaced lead would cause significant arrhythmias.

1.7.4.2 Muscle Stimulation in Unipolar Configuration

Under certain circumstances, such as high-output unipolar stimulation, therapy induced muscle stimulations may occur at the pocket site of the implanted device. This condition is mitigated by appropriate programming of the stimulation parameters by qualified medical personnel in conjunction with patient feedback.

1.7.4.3 Component Failure

As with any active implantable electronic system, the **rem**edē® System might unexpectedly fail or stop working at any time due to random component fault, battery failure, exposure to extreme environmental interferences or environmental conditions. These factors may reduce system longevity, effectiveness and cause change in the performance characteristics.

1.8 Adverse Effects

Possible adverse effects include, but are not limited to, the following:

Implant Procedure-Related

- Adverse contrast dye reaction such as allergic reaction, pulmonary edema, or worsening renal function
- Adverse reaction to radiation exposure
- Thromboembolism
- Air embolism
- Bleeding
- Cardiac perforation including tamponade
- Hematoma, seroma, local bruising or swelling
- Hypotension
- Local wound healing issues at device implant site including wound dehiscence, pocket erosion, extrusion, movement of implanted device, keloid formation
- Pneumothorax
- Hemothorax
- Vascular damage, e.g., venous dissection, perforation

Lead and System-Related

- Adverse biocompatibility reaction to the implanted system
- Infection
- Lead breakage
- Lead dislodgement
- Lead not connected or secured appropriately in device header
- Implantable device malfunction
- Requirement for more energy to stimulate the nerve or ineffective stimulation
- Venous occlusion

Therapy-Related

- Crosstalk with another implanted device

- Disrupted sleep
- Muscle fatigue or discomfort in diaphragm, chest or abdomen from appropriate stimulation
- Nerve dysfunction
- Perturbation of blood gases causing hypoxia, hypercapnea and/or hypocapnea
- Inappropriate sensations
- Worsening heart failure, respiratory status or overall health

Other Procedure, System or Therapy-Related

- Anxiety
- Arrhythmia, including ventricular fibrillation
- Death
- Depression
- Hypotension
- Pain
- Skin irritation or local allergic reaction
- Thrombus or embolism, potentially leading to pulmonary embolism or stroke

1.9 Clinical Data Summary

1.9.1 Pivotal Trial of the remedē® System

The **rem**edē System was evaluated in a prospective, multicenter, randomized trial at study centers in the United States, Germany, and Poland for the indication of transvenous stimulation of the phrenic nerve for the treatment of central sleep apnea (CSA).

1.9.2 Patients Studied

The study enrolled 151 central sleep apnea patients who underwent an implant procedure. Of the 151 implant attempts, 147 (97%) were successful. The study endpoints were evaluated based on intent to treat. The patient demographics for the **rem**edē System Pivotal Trial are included in Table 1.

Table 1 Baseline Demographics

Baseline Measure	Mean N=151
Age (years)	65
Body Mass Index, kg/m2	31
Ejection Fraction, %	40
AHI, events/hour	46
CAI, events/hour	28
	n (%)
Male	135 (89%)
Race	
Black or African American	6 (4%)
Unknown	1 (1%)
White	144 (95%)

1.9.3 Study Design and Methods

The **rem**edē® System Pivotal Trial was a multicenter, prospective randomized trial conducted at 31 centers: 24 United States, 6 Germany, and 1 Poland. Prior to baseline assessments, patients were medically stable for 30 days in addition to having guideline recommended therapy appropriate for their clinical condition. Potential patients were identified by chart reviews and direct physician referrals. Pre-screening was performed via in-home sleep testing (polygraphy [PG]) or review of PSGs completed for clinical reasons.

Following pre-screening, potentially eligible patients prospectively underwent a qualifying overnight, attended PSG within 40 days prior to implant. Eligibility required the following PSG results: apnea-hypopnea index (AHI) ≥20 events/hour of sleep, central apneas (CAI) ≥50% of all apneas and at least 30 central apnea events throughout the night, and an obstructive apnea index (OAI) ≤20% of the total AHI. Key exclusion criteria included factors prohibitive of system implantation, phrenic nerve palsy, Stage D heart failure, a cerebrovascular event within 12 months, CSA secondary to opioids, and advanced renal disease.

All patients undergoing an implant attempt were randomized 1:1 to phrenic nerve stimulation (treatment) or control. The investigational system was implanted in both the treatment and control groups. All patients had a 1-month study visit after implantation that determined the schedule for subsequent follow-up at 3 month intervals. The system was activated in the treatment group at the 1-month visit according to a proprietary algorithm that applied a

stimulation pattern which enabled full diaphragmatic contraction while the patient continued to sleep. A full night PSG was completed 6 months following the 1 month visit in all subjects to assess the primary effectiveness endpoint. The system remained off in the control group through the 6-month effectiveness assessment, after which therapy was initiated and remained on.

The primary effectiveness endpoint was a comparison of the proportions of patients in the treatment versus control groups achieving a reduction in AHI of ≥50% from baseline to 6 months. The primary safety endpoint was freedom from serious adverse events associated with the implantation procedure, the system, or delivered therapy in the combined study groups through 12 months. A serious adverse event was defined as any adverse event that led to death, led to a serious deterioration in the health of the subject, resulted in a life-threatening illness or injury, resulted in a permanent impairment of a body structure or a body function, required inpatient hospitalization or prolongation of existing hospitalization, resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function , or led to fetal distress, fetal death or a congenital abnormality or birth defect.

1.9.4 Study Results

1.9.4.1 Safety

1.9.4.1.1 Primary Safety Endpoint

The percentage of subjects free from serious adverse events (SAE) associated with the implant procedure, the **rem**edē® system, or the delivered therapy through the 12 month visit was 91% [95% exact CI (86%, 95%)]. No statistical hypothesis testing was performed on this endpoint (Table 2).

Table 2 Summary of Freedom from Related SAEs through 12 Month Visit (ITT)

Variable	Pooled[1] (N=151)
Freedom from related SAEs	91% (138) (86%, 95%)
[1] Percent (n) and 95% exact confidence interval.	

Thirteen subjects (9%) each reported a single implant procedure, **rem**edē System, or delivered therapy related SAE. Table 3 displays the number of each type of event reported, along with the number and percentage of subjects who experienced the event.

Table 3 Summary of Serious Adverse Events by Relation to Implant Procedure, remedē® System, or Delivered Therapy through 12 Months

	Pooled (N=151)							
	Implant, System and/or Therapy Related[1,2]		Implant Procedure Related		System Related		Delivered Therapy Related	
Event	n Events	% (n) Subjects	n Events	% (n) Subjects	n Events	% (n) Subjects	n Events	% (n) Subjects
ANY EVENT	13	9% (13)	9	6% (9)	6	4% (6)	2	1% (2)
IMPENDING POCKET EROSION	2	1% (2)	1	1% (1)	1	1% (1)	0	0% (0)
IMPLANT SITE INFECTION	2	1% (2)	2	1% (2)	0	0% (0)	0	0% (0)
LEAD DISLODGEMENT	2	1% (2)	2	1% (2)	2	1% (2)	0	0% (0)
CONCOMITANT DEVICE INTERACTION	1	1% (1)	0	0% (0)	1	1% (1)	1	1% (1)
ELEVATED TRANSAMINASE	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
EXTRA-RESPIRATORY STIMULATION	1	1% (1)	0	0% (0)	0	0% (0)	1	1% (1)
IMPLANT SITE HEMATOMA	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
LEAD COMPONENT FAILURE	1	1% (1)	0	0% (0)	1	1% (1)	0	0% (0)
LEAD DISPLACEMENT	1	1% (1)	1	1% (1)	1	1% (1)	0	0% (0)
NON-CARDIAC CHEST PAIN	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)

[1]Relationship defined as probably or definitely related.
[2]Events and subjects with events may be counted as implant procedure, system and therapy related so may not add up to the combined events or subjects.

1.9.4.1.2 Non-Serious Related Adverse Events

Forty-eight percent (48%) of subjects experienced a non-serious event related to the implant procedure, the **rem**edē® System or delivered therapy. Table 4 displays the number of each type of event reported, the number and percentage of subjects who experienced the events, and the relationship of the event to the implant procedure, the **rem**edē System or delivered therapy.

Table 4 Summary of Related non-Serious Adverse Events and Observations through 12 Months

	Pooled (N=151)							
	Implant, System and/or Therapy Related[1,2]		Implant Procedure Related		System Related		Delivered Therapy Related	
EVENT	n Events	% (n) Subjects	n Events	% (n) Subjects	n Events	% (n) Subjects	n Events	% (n) Subjects
ANY EVENT	105	48% (73)	30	17% (25)	11	7% (11)	67	35% (53)
DIAPHRAGMATIC STIMULATION DISCOMFORT	48	25% (38)	0	0% (0)	1	1% (1)	48	25% (38)
EXTRA-RESPIRATORY STIMULATION	15	9% (14)	0	0% (0)	0	0% (0)	15	9% (14)
IMPLANT SITE PAIN	7	5% (7)	7	5% (7)	0	0% (0)	0	0% (0)
IMPLANT SITE HEMATOMA	5	3% (4)	5	3% (4)	0	0% (0)	0	0% (0)
IMPLANT SITE BRUISING	4	3% (4)	4	3% (4)	0	0% (0)	0	0% (0)
ELEVATED LEAD IMPEDANCE	3	2% (3)	1	1% (1)	3	2% (3)	0	0% (0)
ELEVATED THRESHOLDS	2	1% (2)	0	0% (0)	2	1% (2)	0	0% (0)
IMPLANT SITE INFLAMMATION	2	1% (2)	2	1% (2)	0	0% (0)	0	0% (0)
INSOMNIA	2	1% (2)	0	0% (0)	0	0% (0)	2	1% (2)
PROGRAMMING ERROR	2	1% (2)	0	0% (0)	1	1% (1)	1	1% (1)
VENOUS THROMBOSIS	2	1% (2)	0	0% (0)	2	1% (2)	0	0% (0)
BACK PAIN	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
CONCOMITANT DEVICE INTERACTION	1	1% (1)	0	0% (0)	0	0% (0)	1	1% (1)
DIARRHEA	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)

	Pooled (N=151)							
	Implant, System and/or Therapy Related[1,2]		Implant Procedure Related		System Related		Delivered Therapy Related	
EVENT	n Events	% (n) Subjects	n Events	% (n) Subjects	n Events	% (n) Subjects	n Events	% (n) Subjects
DISSECTION OF SUBCLAVIAN VEIN	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
HYPOXIA	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
IMPLANT SITE ERYTHEMA	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
IMPLANT SITE INFECTION	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
IMPLANT SITE SWELLING	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
INADEQUATE LEAD POSITION	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
LEAD DISLODGEMENT	1	1% (1)	1	1% (1)	1	1% (1)	0	0% (0)
LEAD DISPLACEMENT	1	1% (1)	0	0% (0)	1	1% (1)	0	0% (0)
SUTURE IRRITATION	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
URTICARIA	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)

[1]Relationship defined as probably or definitely related.
[2]Events and subjects with events may be counted as implant procedure, system and therapy related so may not add up to the combined events or subjects.

1.9.4.1.3 System Explants

Explants of the **rem**edē® System occurred in 5.3% (8/151) of subjects. Details are provided in Table 5.

Table 5 Summary of System Explants

Number of Subjects	Reason for System Explant
2	Investigational device implant site infection
2	Elective explant[1]
1	Device battery depletion – expected
1	Lead component failure[2]
1	ICD pocket infection (ICD and **rem**edē System shared a common venous entry point requiring explant of both systems)
1	Failed stimulation lead modification procedure

[1]One subject chose to exit due to an intervening medical condition (depression) and one subject withdrew consent and requested a system explant
[2] Failure of one constituent part of the lead

1.9.4.1.4 Trial Withdrawals

A total of 43 subjects had exited the trial as of the datalock. Table 6 displays the reasons for trial discontinuation.

Table 6 Summary of Reasons for Trial Withdrawals

	Treatment (N=73)	Control (N=78)	Pooled (N=151)
Exit reason	**% (n) Subjects**	**% (n) Subjects**	**% (n) Subjects**
Physician-initiated withdrawal	1% (1)	3% (2)	2% (3)
Subject Death	15% (11)	14% (11)	15% (22)
Subject Lost to Follow-Up	1% (1)	1% (1)	1% (2)
Subject-initiated withdrawal	8% (6)	5% (4)	7% (10)
System explanted[1]	7% (5)	1% (1)	4% (6)
Total	33% (24)	24% (19)	28% (43)

[1]2 subject-initiated withdrawals also underwent system explant

Subjects exited for the following reasons:

- Physician-initiated withdrawals for three (3) subjects
    - Two (2) due to intervening medical conditions
    - One (1) exit from the trial subsequent to a failed implant attempt

- Subject death for 22 subjects
- Lost to follow-up for two (2) subjects
    - One (1) subject after an unsuccessful implant attempt
    - One (1) subject became unreachable despite multiple attempts by the investigational site to contact the subject

      Note: Neither subject had therapy initiated at the time of being lost to follow-up
- Subject-initiated withdrawals for ten (10) subjects
    - Four (5) subjects withdrew due to intervening medical issues
    - Three (3) subjects withdrew due to relocating away from study site
    - Two (2) withdrew consent subsequent to failed implant attempts
- Withdrawal due to explanted **rem**edē® Systems occurred in six (6) subjects. Two (2) subject-initiated withdrawals also had the system explanted as outlined in Section 1.9.4.1.3

1.9.4.2 Effectiveness

The primary effectiveness endpoint was a comparison of the proportions of patients in the treatment versus control groups achieving a reduction in AHI of ≥50% from baseline to 6 months. The proportion of patients achieving ≥ 50% reduction in AHI and the 95% confidence interval (CI) for the Treatment group was 51% (35/68) [95% CI (39%, 64%)] compared to 11% (8/73) [95% CI (5%, 20%)] for the Control group, resulting in a difference of 41% [95% CI (25%, 54%)] (Table 7). This result was statistically significant (p<.0001), demonstrating that active therapy with the **rem**edē System is superior to Control (inactive therapy) in achieving a 50% reduction in AHI.

Table 7 Summary of the Comparison of the Proportion of Patients with ≥ 50% Reduction in AHI at 6 Months (Modified ITT)

Variable	Treatment[1]	Control	Difference	P-value[2]
AHI reduced ≥ 50%	51% (35/68) (39%, 64%)	11% (8/73) (5%, 20%)	41% (25%, 54%)	<.0001

Percent (n/N) and 95% Exact Confidence Interval.

[1]Includes 7 patients imputed as not achieving ≥ 50% reduction in AHI.

[2] P-value from 1-sided Fisher's Exact Test.

1.9.4.3 Conclusion

The data support the reasonable assurance of safety and effectiveness of this device for treatment of moderate to severe CSA in adults.

1.10 Storage and Handling

Respicardia sterilizes the IPG and stimulation leads with ethylene oxide (EtO) prior to shipment.

The materials used are biologically compatible, but they are nevertheless prone to attract foreign particles. Avoid any contamination before introduction of the IPG or leads into the body.

Inspect the sterile package and contents prior to opening to ensure it is intact and contains a proper sterile use by date. The IPG, stimulation leads, and packaged accessories are intended for one (1) time use only and cannot be resterilized, do not implant product from a damaged or opened package.

Store and transport the **rem**edē® System in a dry place and within the recommended environmental temperature limits displayed in Table 8 below.

Table 8 Environmental Temperature Limits

remedē® System	Temperature Ranges
remedē IPG	0ºC (32ºF) and 50ºC (122ºF)
respi**stim®** R, L, LQ, LQS Leads	5ºC (41ºF) and 30ºC (86ºF)
remedē System Programmer	-20ºC (-4ºF) and 70ºC (158ºF)
Programming Wand	-20ºC (-4ºF) and 70ºC (158ºF)
eIPG	0ºC (32ºF) and 50ºC (122ºF)

Do not implant the IPG if it has been dropped on a hard surface from a height of 30 cm (12 in) or greater.

Only appropriate sterile implant techniques should be used to handle the **rem**edē System once removed from the sterile packaging.

1.10.1 Stimulation Leads

Avoid severe bending, kinking, stretching or aggressive handling with surgical instruments as this may cause permanent damage to the lead. Only appropriate sterile implant techniques should be used to handle the stimulation lead once removed from sterile packaging.

Published literature suggests that certain upper extremity activities can cause damage to the leads and possible failure of the leads. Active people, particularly those who perform repetitive upper extremity exercise at work or play should be cautioned that they could subject leads to damaging stress.

1.11 Clinician Training

Prior to implanting the **rem**edē System**,** implanting physicians will receive instruction on implant tools and techniques, anatomical considerations, and instruction on concomitant device testing. Clinicians will receive training related to therapy management including the initiation of therapy, titration, and use of the programmer.

1.12 remedē® System Implant

This section describes the general implant procedure of the **rem**edē System. Both respi**stim** L (left) and respi**stim** R (right) stimulation lead placements described in 1.11.3.2 have been shown to be equally effective and safe. Similar to cardiac device transvenous lead implant procedures, the implanting physician will determine the appropriate stimulation lead placement based on visualizing the anatomy under fluoroscopy, gaining access to the vessels, navigating the lead to a stable location within the desired vessel, and electrically stimulating the nerve. Provided the anatomy is suitable for a respi**stim** L (left) lead placement, the physician should attempt to place this lead since the **rem**edē IPG battery longevity is typically greater with this system configuration.

1.12.1 Mitigation Strategies for Managing the Risk of Infection During remedē® System Implant, Replacement and Explant Procedures

The following recommendations should be followed in order to minimize the risk of infection during the remedē System implant, replacement and explant procedures.

- Use rigorous aseptic methods including antiseptic skin preparation
- Administer prophylactic and post-operative antibiotics
- Use antiseptic flush in the pocket
- Use local antimicrobial agents

1.12.2 Implantable System

- **rem**edē System IPG
- respi**stim®** L, LQ, LQS, or R stimulation lead
- IS-1 compatible bipolar transvenous lead for sensing

1.12.3 remedē® System Implant Procedure

The **rem**edē System Implant includes the following steps:

- Locate target vessel and deploy the stimulation lead
- Test for phrenic nerve capture and secure the stimulation lead
- Deploy the sensing lead
- Perform final testing
- Create pocket, insert leads into the IPG and secure the IPG in the pocket
- Concomitant testing (if applicable)

1.12.3.1 Locate the Target Vessel

- Gain venous access using the right axillary, cephalic or subclavian vein using standard techniques.
- Select a puncture site near the lateral border of the first rib when utilizing a subclavian approach and avoid penetrating the subclavius muscle

Caution: Do not insert the lead under the medial one-third region of the clavicle; lead damage from clavicle/first rib entrapment or chronic dislodgment of the lead is possible if the lead is implanted in this manner. It is recommended to introduce the lead into the subclavian vein near the lateral border of the first rib.

- Insert a guiding catheter and position within the left brachiocephalic vein. Refer to Figure 6 below for a pictorial description of typical venous anatomy.

- Obtain a venogram to visualize target vein ostium.

Caution: When locating the target vein ostium with the guiding catheter, do not force the catheter tip forward if resistance is felt.

Caution: Excessive amount and/or rate of contrast dye injection can cause extravasation of contrast dye or vessel dissection.

- Cannulate the vein and visualize with selective venogram (for the left pericardiophrenic vein).

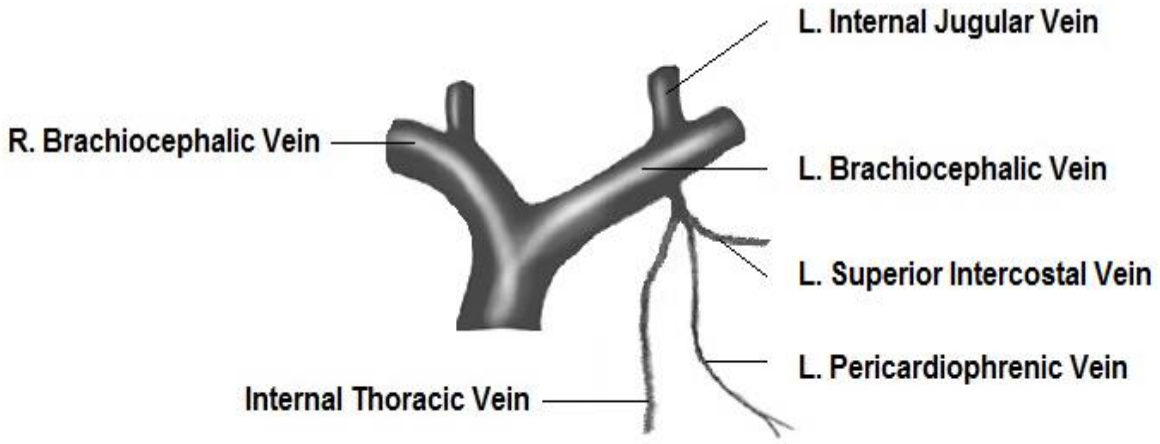

Figure 6 Typical Left Pericardiophrenic Vein Anatomy

1.12.3.2 Deploy the Left or Right Stimulation Lead

1.12.3.2.1 Left Pericardiophrenic Stimulation Lead

- Insert respi**stim®** L, LQ, or LQS stimulation lead over a 0.014 inch guide wire and advance to desired position within the left pericardiophrenic vein
- Use care when inserting a guide wire into the lead to avoid penetrating the lead wall or damaging the lead conductor coil.

  ***Note*:** Flushing a clotted lead can compromise the integrity of the stimulation lead. If clotting is suspected, remove the lead from the body and soak in heparinized saline. Insert a guide wire into the proximal or distal end of the stimulation lead and advance to clear the lumen.

  Note: Guide wires should be handled with care at all times. A damaged guide wire may not behave as expected and could result in damage to the lead or vasculature.

1.12.3.2.2 Right Brachiocephalic Stimulation Lead

- Select the appropriate right stimulation lead model for the diameter of the brachiocephalic vein (See Appendix III). A lead that is too small for the vessel can result in weak or ineffective diaphragmatic stimulation
- Ensure the stylet is fully advanced within the lead to the distal end of the lumen before inserting the right stimulation lead
- Use care when inserting the stylet to avoid damaging the lead wall or conductor coil. It may be necessary to straighten the helical shape of the lead to fully advance the stylet
- Place the lead through an introducer sheath and advance until the distal end of the lead is at the level of the superior vena cava or right atrium
- Retract the stylet gradually and apply counterclockwise rotation to the lead body to allow the helical shape to form
- Apply gentle traction and counterclockwise rotation as needed to position the electrodes along the lateral wall of the vessel
- Do not allow the proximal and distal helixes to collapse and make contact as this will not provide a stable lead position
- Assess the stability of the lead position by requesting that the patient breathe deeply or cough during fluoroscopic observation

Note: Motion of the lead synchronous with cardiac systole may suggest that the lead is near the right atrium and should be repositioned.

1.12.3.3 Test for Phrenic Nerve Capture

Patient stimulation testing requires communication with the patient to ensure an appropriate stimulation response. Physicians should deliver procedural sedation that allows for this communication. See Table 9 below for recommended stimulation threshold and impedance values.

- Evaluate stimulation lead impedance
- Perform stimulation threshold testing
    - Once the stimulation lead has been placed in the desired location, make sure the stylet or guide wire is retracted sufficiently to expose lead bias, if applicable, allowing the lead to engage the vessel in a natural way.
    - Select an electrode testing configuration (cathode-anode electrode pair) and connect the stimulation lead to the **rem**edē® eIPG

    Caution: Connect the sterile cable to the **rem**edē eIPG before connecting to the stimulation lead.

Caution: Do not touch the exposed metal of the stimulation lead connector end or the exposed metal of the cable alligator clips. Do not allow the exposed metal of the stimulation lead connector end or the exposed metal of the cable alligator clips to contact electrically conductive or wet surfaces.

Caution: Protect any unused alligator clip(s) from contact with any conductive surface or current leakage source.

- Set the eIPG stimulation amplitude, pulse width and frequency based on the stimulation lead implanted
  - respi**stim®** L (left) stimulation lead
    - Amplitude = 2 mA
    - Pulse Width = 150 µsec
    - Frequency = 20 Hz
  - respi**stim®** R (right) stimulation lead
    - Amplitude = 5 mA
    - Pulse Width = 300 µsec
    - Frequency = 40 Hz
- Deliver a single test pulse
- Increase or decrease the stimulation current incrementally as needed until a moderately strong diaphragmatic contraction is observed by means of abdominal palpation or fluoroscopic visualization
  - If an inadequate response or no response is detected, the implanting physician should select a new electrode pair (for R, LQ and LQS leads) and repeat the stimulation threshold test before repositioning the stimulation lead
  - If an inadequate or no response persists, the stimulation lead should be repositioned and the stimulation threshold test sequence repeated until the desired response is achieved
- Test for extra respiratory sensations (ERS) at levels above the stimulation threshold
  - ERS or sensations during stimulation other than diaphragmatic contraction are the result of stimulating nerves beyond the phrenic nerve
  - Reposition the lead if unable to avoid ERS through electrode selection or limitation of IPG output

Table 9 Recommended Stimulation Threshold and Impedance Values

Stimulation Lead	Stimulation Threshold	Stimulation Lead Impedance	Criteria for stimulation threshold
Left	<4mA	400 – 2000 Ω	Clear evidence of diaphragmatic movement determined via palpation or fluoroscopy
Right	<5mA	200 – 800 Ω	

1.12.3.4 Secure the Stimulation Lead

- The guiding catheter (respi**stim®** L, LQ or LQS) or introducer sheath (respi**stim®** R) must be removed prior to securing the stimulation lead. For detailed instructions on removing the guiding catheter refer to the manufacturer's Instructions For Use (IFU).
- Ensure sufficient lead slack is provided within the venous system to allow for strain relief during changes in body position to reduce the risk of lead dislodgement.
- Position the first ligature sleeve immediately proximal to the point of venous access and secure the ligature sleeve to the lead using permanent, non-absorbable sutures; anchor the ligature sleeve to the fascia or other suitable subcutaneous tissue using permanent, non-absorbable sutures.
- For respi**stim** R leads**,** place a second suture sleeve a minimum of 10 cm proximal to the first suture sleeve with a strain relief loop between the first and second sleeve for stability.
- Maintain the guide wire or stylet within the lumen of the stimulation lead while securing the ligature sleeve to the lead body and anchoring to tissue in order to prevent damage to the stimulation lead insulation and conductor coil.
- Do not use excessive force when tying sutures on ligature sleeves.
- Do not kink, twist, or torque the lead while anchoring the ligature sleeve, as doing so could cause electrode movement.
- Do not tie a suture directly to the lead body.

Note: Inadequate strain relief between proximal and distal ligature sleeves (if multiple ligature sleeves are present) or between ligature sleeve and IPG pocket can increase the risk of chronic flex damage to the lead.

1.12.3.5 Deploy Sensing Lead

- Deploy the sensing lead into a branch vein off the main tributary of the azygos vein using standard techniques

Note: The respi**stim** lead or any commercially available bipolar IS-1 compatible lead can be utilized for sensing

1.12.3.6 Create Pocket, Insert Leads and Secure IPG

Note: For optimal performance of the 3-axis position sensor, care should be taken to ensure the pocket is tight forming and **aligned vertically** (Figure 7).

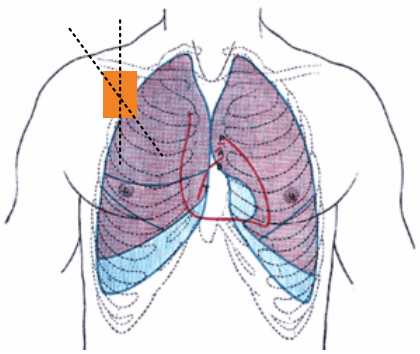

Figure 7 Recommended IPG Pocket Location

The **rem**edē IPG has four IS-1 bipolar connector ports in the header block, three for connecting stimulation leads and one for a sensing lead. The three stimulation lead ports are labeled **1-2**, **3-4** and **5-6** corresponding to the following stimulation lead electrodes (Figure 8). The single IS-1 bipolar connector sensing lead port is labeled **S** and allows for the insertion of a bipolar sensing lead (also Figure 8):

Figure 8 The remedē® IPG Connector Block and Port Diagram

1-2 corresponds to electrode 1 (distal) and electrode 2

3-4 corresponds to electrode 3 and electrode 4

5-6 corresponds to electrode 5 and electrode 6 (proximal)

S corresponds to the sensing lead

Note: For easier lead insertion, insert terminal S into Sense IS-1 and lower stimulation port (5-6) IS-1 connectors first.

The distal end electrodes of the respi**stim** L Stimulation Lead correspond to the IS-1 connections detailed in Figure 9 with electrode 1 being the most distal electrode and electrode 2 being the most proximal electrode.

Figure 9 respi**stim® L Stimulation Lead Connections**

The electrodes of the respi**stim** LQ and LQS Stimulation Leads correspond to the IS-1 connections shown in Figure 10 with electrode 1 being the most distal electrode and electrode 4 being the most proximal electrode. The IS-1 terminal containing the serial number marking corresponds to electrode 1-2.

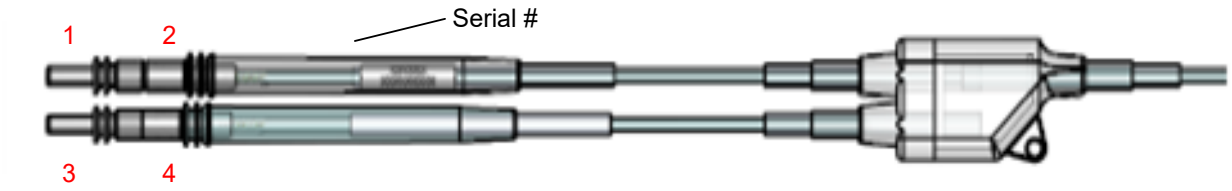

Figure 10 respi**stim® LQ and LQS Stimulation Lead Connections**

The electrodes of the respi**stim** R Stimulation Leads correspond to the IS-1 connections shown in Figure 11 with electrode 1 being the most distal electrode and electrode 6 being the most proximal electrode. The IS-1 terminal containing the serial number marking corresponds to electrode 1-2.

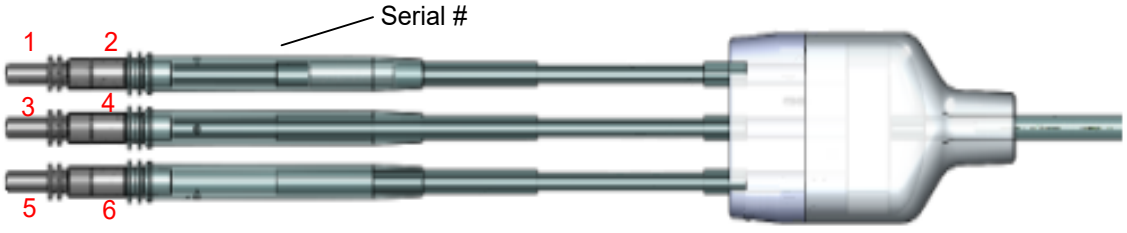

Figure 11 respi**stim® R Stimulation Lead Connections**

Caution: Verify that the lead connections are secure. Loose lead connections may result in inappropriate sensing and/or failure to deliver stimulation therapy.

Caution: Use only the wrench supplied with the device. The wrench is designed to prevent damage to the device from over tightening a setscrew.

Caution: Counterclockwise rotation of a set screw may cause the set screw to disengage from the connector block.

Caution: If a multipolar stimulation lead is not implanted, pin plugs provided with the device must be secured in the unused stimulation ports to avoid damage to the device.

- Do not kink, twist, or braid the lead connectors with other leads, as doing so could cause lead insulation abrasion or conductor damage.
- Do not bend the lead near the lead-header interface. Improper insertion can cause insulation or connector damage.
- **Prior to placing the IPG in the pocket,** wrap any excess lead length loosely behind the IPG by rotating as shown in Figure 12.
- Place the IPG and excess lead wrap in the IPG pocket with the IPG connector closest to the pocket incision and with the **device labeling facing up toward the skin.**
- Do not coil the leads. Coiling will twist the lead bodies and may result in lead dislodgment.

Figure 12 Proper Rotation of IPG to Wrap Excess Lead Length

- Test lead impedance **after** connecting the leads to the IPG
- **Secure the rem**edē® **IPG in the pocket** in order to minimize the risk of migration and mechanical interaction with the lead

1.12.4 Concomitant Cardiac Device Testing (if applicable)

Testing for concomitant cardiac device interaction at the time of **rem**edē System implant for patients with a pre-existing cardiac device is recommended. Concomitant device interaction testing should be repeated prior to therapy initiation and anytime the **rem**edē System or the cardiac device system is modified. The following steps are required to complete concomitant device interaction testing:

1. Disable high voltage cardiac therapies on the cardiac device if applicable
2. Program cardiac device sensing to the most sensitive setting and prepare for monitoring electrogram (EGM) and device marker channels
3. Set up **rem**edē® System stimulation test (2 sec duration)
    a. Acute/new **rem**edē System:
        i. Left stimulation lead: pulse width 150µs, frequency 20 Hertz
        ii. Right stimulation lead: pulse width 300µs, frequency 40 Hertz
    b. Chronic **rem**edē System:
        i. Use programmed pulse width and frequency settings
4. Deliver 2-3 stimulation pulses at 2 times the stimulation threshold
5. Observe cardiac device EGM and marker channels for evidence of detection of **rem**edē System stimulation pulses
6. Testing should be completed with both an intrinsic (sensed) rhythm and during forced ventricular pacing

1.12.5 Postoperative Care

Follow up according to normal postoperative care procedures. A 7 to 14 day check of the surgical incision healing is recommended.

To allow for stabilization and healing after the implant procedure, the **rem**edē System therapy should not be enabled for approximately 1 month following implant.

Regular patient follow-up should be scheduled to monitor the condition of the IPG battery and to confirm that therapy settings are appropriately programmed.

Intermittent or continuous loss of stimulation or sensing can be caused by a displacement of the electrode, unsatisfactory electrode position, breakage of the conductor or its insulation, an increase in thresholds, or poor electrical connection to the pulse generator.

1.12.6 Physician Instructions to Patient

Information regarding the **rem**edē System should be provided to patients including the warnings and precautions provided on page 13. Patients should also be instructed as follows:

- It is normal to feel some discomfort from the surgical incision and to have some pain at the implant site for 2 – 6 weeks.
- It is best to limit the mobility of the right arm (or left arm if left-sided device placement) and avoid lifting the arm above shoulder level for several weeks after the implant procedure. This time period allows the leads and IPG to affix more securely in place and such movements could impair the healing process.

- Repetitive upper extremity activities and exercise can cause damaging stress and possible failure to permanent implanted leads. Active patients should be cautioned to avoid physical activities that could damage the implant site or the implanted system.
- Inform general practitioners and consulting physicians that the patient has an implanted stimulation system
- Carry the Device/Subject Identification Card at all times

1.12.7 Patient Registration

Complete a **rem**edē® System registration form following implant of the **rem**edē System. This form serves as a permanent record of facts related to the implanted system. A copy of this form should be returned to Respicardia. Refer to the last page of this manual for contact information.

1.12.8 Surgical Revision and Explant

1.12.8.1 Lead Repositioning

If the stimulation lead becomes displaced and phrenic nerve capture cannot be obtained by programming stimulus to other electrodes, an effort to reposition the affected lead should be attempted as soon as possible. Care should be taken to avoid damage to the implanted IPG, stimulation lead, sensing lead and surrounding tissues during the replacement procedure. If the displaced lead is unable to be repositioned and must be explanted, the lead should be returned to Respicardia for analysis and/or disposal.

1.12.8.2 IPG Replacement

The IPG should be replaced when IPG battery has been depleted and either the elective replacement indicator (ERI) or end of life (EOL) indicator is displayed on the **rem**edē System Programmer. Care should be taken to avoid damage to the implanted leads during the replacement procedure. Confirm proper function and programming of the **rem**edē System following replacement. The explanted IPG should be returned to Respicardia for analysis and/or disposal.

1.12.8.3 System Explant

The decision to remove the **rem**edē System is the responsibility of the physician and patient and should be determined on a case by case basis. The risks associated with system removal and/or abandonment should be considered. If the IPG is removed but the leads are left in place, the proximal connectors of the leads should be capped to minimize tissue irritation and induced currents. Any explanted system components should be returned to Respicardia for analysis and/or disposal.

1.13 Using the remedē® System Programmer

1.13.1 remedē® System Programmer

The **rem**edē System Programmer (Figure 13) includes:

- **rem**edē System Programmer tablet display with **rem**edē Programmer Software Application
- **rem**edē System Programmer wand
- Medical grade power supply

Figure 13 remedē **System Programmer Tablet Display (Model 1002A)**

1.13.1.1 remedē® System Programmer Tablet Display

The System **rem**edē Programmer tablet display is an interactive touch screen tablet controlled using the attached stylus. The external buttons and ports used by the **rem**edē System are labeled along the border of the tablet display (On/Off, USB, and Power Plug). Other external buttons or controls on the tablet display are not used when programming the **rem**edē System (see Figure 14).

Figure 14 remedē System Programmer Tablet Display

Connections: (1) Power input jack, (2) USB – do not use for Wi Fi connection, (3) Audio output jack, (4) SD memory slot with cover.

> ***Note:*** Connections 1 and 2 are required for power and **rem**edē System connectivity. The power input jack may be plugged into the provided medical grade power supply.

1.13.1.2 remedē® System Programmer Wand

The **rem**edē System Programmer wand (Figure 15) provides a communication link between the programmer tablet display and the device. The programming wand must be held over the device to interrogate or program. The programmer wand is connected to the programmer tablet display via the USB port.

Figure 15 The remedē System Programmer Wand

1.13.1.3 Medical Grade Power Supply

The **rem**edē System Programmer is powered using the provided medical grade power supply and power cable.

> ***Caution:*** – Use only the provided programmer power supply. Do not use the programmer power supply to power any other electronic devices. Never power the

remedē System Programmer using an extension cord, power strip or other multiple outlet cable.

1.13.1.4 Connecting External Non-Respicardia Devices

Peripheral equipment connected to the programmer tablet display must be certified according to applicable International Electrotechnical Commission (IEC) standards for medical equipment. The system, formed by connecting peripheral equipment to the programmer, must comply with IEC 60601-1 for medical electrical systems. It is the responsibility of the user connecting the peripheral equipment to comply with IEC standards. It is the responsibility of the user to keep peripheral equipment that is certified to IEC 60950 at least two meters away from the patient. Contact the peripheral equipment manufacturer for information about IEC certification.

Caution: – To avoid a potential safety hazard, do not connect the **rem**edē System Programmer to any non-certified outlet powered device (such as an external printer) during a patient session.

1.13.1.5 External USB/CAT5 Extension

An external USB/CAT5 extension kit may be used with the **rem**edē System Programmer to allow for extended programmer use in a sleep lab control room during a sleep study (up to 150 ft. away from patient room). Use only an external USB/CAT5 extension kit that is compliant with IEC 60601-1 for medical electrical systems, compatible with USB 2.0 and provides power on the remote end of the extension.

1.13.2 Preparing for a Clinical Programming Session

1.13.2.1 Powering On the Programmer

The **rem**edē System Programmer tablet display should be plugged in to an electrical outlet using the provided medical grade power supply. To power on the **rem**edē System Programmer, press and hold the power button for at least 2 seconds until the blue LED next to the power button illuminates indicating power is on.

1.13.2.2 Starting the Software Application

When initially powered on, the **rem**edē System Programmer will automatically launch the **rem**edē System Programmer Software Application. The user may also select the Respicardia **rem**edē icon (Figure 16) from the desktop to start the **rem**edē System Programmer Software Application.

Figure 16 The remedē® System Software Application Icon

1.13.2.3 Navigating the Software Application

Figure 17 remedē System Software Application Screen

Title Bar

The title bar (Figure 17) is displayed at the top of the window. It identifies the software application currently running (Respicardia Programmer), the device serial number and displayed data source, which can be from an implanted device or a saved file set.

Menu Bar

The Menu Bar (Figure 17) is displayed under the title bar. It contains the **rem**edē System Programmer commands grouped under the File, View, Log, Tools and Help pull down menu headings. Selecting the Menu Bar item with the touch pen will open the corresponding pull down menu.

Toolbar

The toolbar (Figure 17) is displayed under the Menu Bar and offers shortcuts to frequently used functions from the File, Log, and Tools pull down menus from the Menu Bar. The toolbar also provides direct access to the mode to allow the user to quickly program between off, therapy and monitor modes. Selecting a button on the toolbar with the stylus will initiate the chosen task. See Table 10 below for **rem**edē System Software Application toolbar icons.

Table 10 remedē® System Software Application Toolbar Icons

	New Device		Read Impedance
	Open Saved Settings		Threshold Testing
	Print Current Settings		Activate Therapy
	Browse Current Log		Suspend Therapy
	Marker Detail		Set IPG Time
	Open Log File		Activity & Pitch Report
	Add Log Bookmark		Full Report
	Marker Mode		Urgent Off

Parameter Window

The Parameter Window (Figure 17) contains all programmable parameters used to configure **rem**edē System therapy. Once the **rem**edē IPG is interrogated, the currently programmed settings are displayed in a tab format within the Parameter window. The parameters are grouped using a tab format with the following headings: Summary, Therapy, Stimulus, Weekly Titration, Nightly Titration, Sensors, Tools, Lab Parameters, Lab Status, and LOG Configuration. Selecting a tab heading will allow the user to view to the corresponding programmable parameters and their current values.

Programming Window

The Programming Window (Figure 17) allows a user to interrogate the device, directly execute a programming command and cancel pending programming changes that have not been executed or undo a previous programming command. A message field is located beneath the programming window buttons that details parameter value conflicts, if applicable.

Log Window

The Log Window (Figure 17) contains a message field detailing history log of all interactions between the device and programmer during a clinical programming session. Each log entry will contain the following format: description, status, date and time. The date and time correspond to the programmer clock. If the programmer clock is different from the clock maintained by the implanted device, a message will appear upon initial interrogation. If applicable, additional log entry information may be viewed by double tapping the specific log entry.

Marker Window

The Marker Window (Figure 17) may be used to graphically view live data collected by the device or to review previously collected waveforms and data. Two channels may be selected for viewing at a time.

Status Bar

The Status Bar (Figure 17) indicates any current communication event (for example, interrogation, programming and ready). The Status Bar may also be used to indicate the function of any buttons as the description will be displayed when the pointer is held over a button.

1.13.2.4 Positioning and Using the Programming Wand

During a clinical programming session, telemetry communication between the **rem**edē® System Programmer and the **rem**edē IPG requires the programming wand to be positioned over the patient's implanted device. The programming wand must be in place over the implanted device for the duration of the programming session. Lifting or moving the programming wand out of telemetry range will interrupt or end any tests or operations in progress. Replacing the wand may allow the user to resume progress saving wave or log data, while other functions may need to be restarted.

The programming wand contains a number of LEDs to indicate proper position and function. A green power on LED indicates the programming wand is connected to the **rem**edē System Programmer display and powered. A series of red, yellow, and green LEDs indicate telemetry signal strength with green indicating best communication, yellow indicating

adequate communication, and red or no LED illumination indicating poor or no communication. The programming wand should be repositioned in the case of red or no LED illumination.

***Note*:** Best signal strength will be found when the distance between the Programming Wand and implanted device is less than 2.5 cm (1 inch).

1.13.2.4.1 Effect of Programming Wand on Concomitant Devices

The **rem**edē System Programmer Wand does not contain a strong magnet. Placing the Programming Wand over a concomitantly implanted device is unlikely to have an effect on the operation and programming of the concomitant device.

1.13.2.5 Interrogating the remedē® *IPG*

Position the Programming Wand directly over the implanted device and verify sufficient signal strength for proper communication. Select the interrogate button from the **rem**edē System Software Application (Figure 18) using the attached stylus or by selecting Interrogate under the File pull down menu on the Menu Bar. The interrogate button will illuminate in blue if no active programming session is in progress. After successfully completing the interrogation, the Summary Tab and associated parameters will appear displaying current device status and programmed settings.

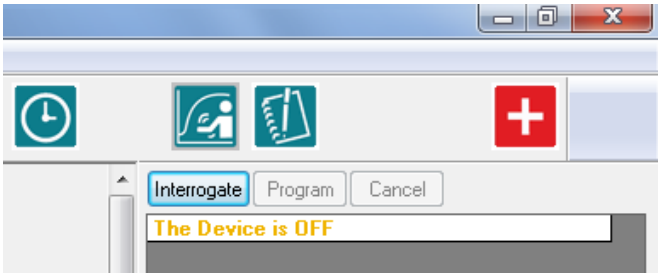

Figure 18 Interrogate Button

1.13.2.5.1 Battery Status

The measured battery voltage will be displayed with one of the following battery status indicator messages:

Good	The measured battery voltage level is above the elective replacement indicator level.
ERI	The elective replacement indicator (ERI) is triggered after 3 consecutive battery measurements are less than 2.60V. The **rem**edē IPG will continue to operate as programmed but replacement should be scheduled as soon as possible. Approximately 3.3 weeks of normal operation remain once ERI is triggered.
EOL	The end of life indicator (EOL) is triggered when 3 consecutive battery measurements are less than 2.50V. Stimulation therapy is disabled when the battery reaches EOL and the **rem**edē IPG should be replaced immediately.

1.13.2.6 Urgent Off Command Using the Programming Wand

The urgent off command is a safety feature that overrides all functions in effect and immediately disables stimulation therapy and programs the device to the off mode. The urgent off command may be initiated using the programming wand by selecting and holding the urgent off button for at least 2 seconds (Figure 19). An orange LED above the urgent off button will illuminate and flash 5 times to indicate successful programming. If not successful, the programming wand will automatically make one additional attempt to program the urgent off command. In this case the user should ensure the programming wand is positioned over the device with sufficient telemetry signal strength.

Figure 19 remedē® **System Programmer Wand Urgent Off Button**

Once the **rem**edē IPG has been interrogated, the user may also initiate the urgent off command by selecting Urgent Off from the Tools pull down menu on the Menu Bar or by selecting the urgent off icon from the toolbar (Figure 17).

Note: – The programming wand may be connected to any powered USB port to program the urgent off command and does not require the **rem**edē System Software Application.

1.13.2.7 Therapy Suspension Using a Magnet

The **rem**edē® System stimulation therapy can be suspended by placing a strong magnet over the implanted device (within 6 cm) in the event that the programming wand is unavailable. A magnetic sensor in the IPG can sense the presence of a strong, external magnetic field (most commonly generated by using a standard pacemaker donut magnet). The minimum magnetic field strength required to activate the magnet sensor is 25 Gauss as measured at the surface of the **rem**edē System device. The magnet must be held in place for a minimum of 10 seconds to allow the **rem**edē System to detect the magnetic field and confirm its presence. Once a magnetic field has been detected, the **rem**edē System automatically suspends stimulation therapy. Once the magnetic field has been removed, stimulation therapy will resume at the next Scheduled Sleep Start Time (typically the next night when stimulation therapy is scheduled to start).

1.14 remedē® System Limited Warranty

A. LIMITED WARRANTY. RESPICARDIA, INC. ("SELLER") PROVIDES TO THE ORIGINAL PURCHASER OF THE PRODUCT ("BUYER") THE FOLLOWING LIMITED WARRANTY FOR THE REMEDĒ® SYSTEM, COMPRISED OF THE IMPLANTABLE NEUROSTIMULATOR ("STIMULATOR"), WIRES FOR SENSING AND STIMULATION ("LEADS"), A PORTABLE HANDHELD TABLET ("TABLET") A PATIENT WAND PROGRAMMING ("WAND"), AND THE PROPRIETARY REMEDĒ® SYSTEM MOBILE APP WHICH IS INSTALLED ON THE TABLET ("APP"). EACH OF THE STIMULATOR AND LEADS IS A "COMPONENT." EACH OF THE TABLET AND WAND IS A "THIRD PARTY PRODUCT".

I. (A) EACH COMPONENT AND THIRD PARTY PRODUCT OF A SYSTEM WHEN DELIVERED TO BUYER WILL BE NEW, OF HIGH QUALITY, AND FREE FROM MATERIAL DEFECTS AND CONSISTENT WITH THE DOCUMENTATION PROVIDED; AND (B) THE APP WILL PERFORM SUBSTANTIALLY IN ACCORDANCE WITH THE DOCUMENTATION ACCOMPANYING THE SYSTEM.

II. SHOULD THE APP FAIL TO PERFORM SUBSTANTIALLY IN ACCORDANCE WITH THE DOCUMENTATION WITHIN ONE YEAR, SELLER'S SOLE OBLIGATION AND BUYER'S SOLE REMEDY WILL BE FOR SELLER TO, AT ITS OPTION: (A) REPLACE OR REPAIR (INCLUDING AT SELLER'S OPTION BY REMOTE UPDATE) THE NON-CONFORMING APP OR ANY NON-CONFORMING PORTIONS THERETO WITH AN APP THAT CONFORMS TO THE DOCUMENTATION; OR (B) ISSUE A CREDIT TO BUYER. FOR CLARITY, THE APP IS LICENSED, NOT SOLD, TO BUYER, AND SELLER RETAINS ALL INTELLECTUAL PROPERTY RIGHTS IN AND TO THE APP.

III. SHOULD ANY COMPONENT FAIL TO FUNCTION WITHIN NORMAL USE DUE TO DEFECT IN MATERIALS OR WORKMANSHIP WITHIN A PERIOD OF TWO (2) YEARS COMMENCING WITH THE DELIVERY OF THE SUCH COMPONENT TO THE BUYER, SELLER'S SOLE OBLIGATION AND BUYER'S SOLE REMEDY WILL BE FOR SELLER TO, AT ITS OPTION (A) REPAIR OR REPLACE THE APPLICABLE COMPONENT; (B) PROVIDE A FUNCTIONALLY COMPARABLE REPLACEMENT COMPONENT AT NO CHARGE; OR (C) ISSUE A CREDIT TO BUYER. SHOULD ANY THIRD PARTY PRODUCT FAIL TO FUNCTION WITHIN NORMAL USE DUE TO DEFECT IN MATERIALS OR WORKMANSHIP WITHIN A PERIOD OF ONE (1) YEAR COMMENCING WITH THE DELIVERY OF THE SUCH THIRD PARTY PRODUCT TO THE BUYER, SELLER'S SOLE OBLIGATION AND BUYER'S SOLE REMEDY WILL BE FOR SELLER TO, AT ITS OPTION (A) REPAIR OR REPLACE THE APPLICABLE THIRD PARTY PRODUCT; (B) PROVIDE A FUNCTIONALLY COMPARABLE REPLACEMENT THIRD PARTY PRODUCT AT NO CHARGE; OR (C) ISSUE A CREDIT TO BUYER.

IV. IF SELLER CHOOSES TO ISSUE A CREDIT TO BUYER FOR A COMPONENT OR THIRD PARTY PRODUCT, THE CREDIT SHALL BE THE LESSER OF THE NET INVOICED PRICE OF THE ORIGINAL COMPONENT OR THIRD PARTY PRODUCT, OR THE CURRENT FUNCTIONALLY COMPARABLE COMPONENT OR THIRD PARTY PRODUCT OR REPLACEMENT COMPONENT OR THIRD PARTY PRODUCT. IF SELLER CHOOSES TO ISSUE A CREDIT TO BUYER FOR THE APP, THE CREDIT SHALL

BE EQUAL TO THE FEES PAID FOR THE TABLET. FOR COMPONENTS OR THIRD PARTY PRODUCTS THAT ARE USED WITH A SPECIFIC PATIENT, BUYER AGREES TO REFLECT THE CREDIT ON THE APPLICABLE PATIENT'S BILL AND REPORT THE CREDIT TO THE APPLICABLE PAYOR.

V. IN ORDER TO QUALIFY FOR THE LIMITED WARRANTY SET FORTH HEREIN, THE FOLLOWING CONDITIONS MUST BE MET: (A) THE COMPONENT OR THIRD PARTY PRODUCT MUST NOT HAVE BEEN REPAIRED OR ALTERED OUTSIDE OF SELLER'S FACILITY OR IN ANY WAY WHICH IN THE SOLE OPINION OF SELLER IMPACTS THE SYSTEM'S STABILITY AND RELIABILITY; (B) THE COMPONENT OR THIRD PARTY PRODUCT MUST NOT HAVE BEEN SUBJECT TO ABUSE, LACK OF PROPER MAINTENANCE, NEGLIGENCE, ACCIDENT, MOVEMENT, OR ADJUSTMENT OF EQUIPMENT BY PERSONNEL NOT AUTHORIZED BY SELLER; (C) THE COMPONENT OR THIRD PARTY PRODUCT MUST HAVE BEEN PUT INTO USE PRIOR TO ANY LABELED "USE BEFORE" DATE; (D) THE COMPONENT OR THIRD PARTY PRODUCT MUST HAVE BEEN USED IN ACCORDANCE WITH SELLER'S INSTRUCTIONS AND THE LABELING, AND MAY NOT HAVE BEEN USED FOR A PURPOSE NOT INDICATED ON THE LABELING; AND (E) NEITHER THE APP NOR ANY OTHER SOFTWARE OR FIRMWARE ON ANY COMPONENT OR THIRD PARTY PRODUCT MAY HAVE BEEN MODIFIED IN ANY WAY BY ANY PERSON OTHER THAN SELLER. FURTHERMORE, DEFECTS ARISING IN WHOLE OR PART AS A RESULT OF NORMAL WEAR AND USAGE, IMPROPER OR INADEQUATE MAINTENANCE, INTERRUPTIONS OR UNSUITABLE POWER OR COMMUNICATION SOURCES OR CONNECTIVITY, ENVIRONMENTAL CONDITIONS, ACCIDENT, MISUSE, ABUSE, IMPROPER INSTALLATION, MODIFICATION, REPAIR, STORAGE OR HANDLING, OR ANY OTHER CAUSE NOT THE FAULT OF SELLER ARE NOT COVERED BY THIS LIMITED WARRANTY.

VI. THE LIMITED WARRANTY DOES NOT APPLY TO EXPIRATION OF COMPONENT OR THIRD PARTY PRODUCTS PARTS WITH A LIMITED LIFETIME, SUCH AS THE BATTERY. SELLER HEREBY ASSIGNS TO BUYER ANY AND ALL MANUFACTURERS' OR SUPPLIERS' WARRANTIES, GUARANTEES, REPRESENTATIONS, SERVICES AGREEMENTS AND INDEMNITIES, APPLICABLE TO ANY THIRD PARTY HARDWARE OR SOFTWARE DELIVERED BY BUYER IN CONNECTION WITH THE SYSTEM, TO THE EXTENT ASSIGNABLE BY SELLER.

B. CLAIMING THE LIMITED WARRANTY. PLEASE CONTACT SELLER'S SERVICE DEPARTMENT OR THE AUTHORIZED REPRESENTATIVE BY MAIL OR PHONE PRIOR TO RETURNING A COMPONENT OR THIRD PARTY PRODUCT FOR FURTHER INSTRUCTIONS. WHEN RETURNING A COMPONENT OR THIRD PARTY PRODUCT, BUYER MUST INCLUDE A COMPLETE DESCRIPTION OF THE ALLEGED COMPONENT OR THIRD PARTY PRODUCT FAILURE ACCOMPANIED BY A PROOF OF PURCHASE ATTACHED TO THE COMPONENT OR THIRD PARTY PRODUCT. IN ORDER TO QUALIFY FOR THE LIMITED WARRANTY SET FORTH HEREIN, BUYER MUST RETURN THE COMPONENT OR THIRD PARTY PRODUCT TO SELLER WITHIN THIRTY (30) DAYS AFTER DISCOVERY OF DEFECT. SELLER WILL BEAR THE COSTS AND RISKS OF LOSS WITH ANY RETURN TRANSPORT TO SELLER. BUYER WILL BEAR THE COSTS AND RISKS OF THE RETURN TRANSPORT FOR REPLACEMENT OR REPAIRED COMPONENTS OR THIRD PARTY PRODUCTS, PROVIDED HOWEVER, THAT BUYER

SHALL BE LIABLE TO SELLER FOR EXPENSES INCURRED IN CONNECTION WITH DIAGNOSING, REPAIRING AND/OR REPLACING ANY COMPONENT THIRD PARTY PRODUCT THAT WAS RETURNED OUTSIDE OF WARRANTY.

C. DISCLAIMERS AND LIMITATION OF LIABILITY. THE LIMITED WARRANTY IS LIMITED TO ITS EXPRESS TERMS. IN PARTICULAR:

I. EXCEPT AS EXPRESSLY PROVIDED BY THE LIMITED WARRANTY IN SECTION (A), SELLER MAKES NO OTHER REPRESENTATION OR WARRANTY, WITH RESPECT TO THE SYSTEM, ANY COMPONENT, ANY THIRD PARTY PRODUCT, OR THE APP, INCLUDING BUT NOT LIMITED TO, IMPLIED CONDITIONS OF FITNESS FOR A PARTICULAR PURPOSE, MERCHANTABILITY, NON-INFRINGEMENT, WARRANTIES ARISING FROM COURSE OF DEALING OR USAGE OF TRADE OR ANY OTHER MATTER. SELLER MAKES NO REPRESENTATIONS WHATSOEVER, WHETHER EXPRESS OR IMPLIED, TO ANY PERSON OTHER THAN THE BUYER. NO AGENT, EMPLOYEE OR REPRESENTATIVE OF SELLER HAS ANY AUTHORITY TO BIND SELLER TO ANY AFFIRMATION, REPRESENTATION OR WARRANTY EXCEPT AS STATED IN A WRITTEN DOCUMENT SIGNED BY AN AUTHORIZED OFFICER OF SELLER. ALL WARNINGS CONTAINED IN THE LABELING FOR THE SYSTEM ARE AN INTEGRAL PART OF THIS LIMITED WARRANTY.

II. SELLER IS NOT RESPONSIBLE FOR ANY INCIDENTAL, CONSEQUENTIAL DAMAGES BASED ON ANY DEFECT, FAILURE OR MALFUNCTION OF THE SYSTEM, ANY COMPONENT, ANY THIRD PARTY PRODUCT, OR THE APP, WHETHER THE CLAIM IS BASED ON WARRANTY, CONTRACT, TORT OR OTHERWISE. SELLER SHALL HAVE NO LIABILITY TO ANY PERSON FOR, AND BUYER HEREBY EXPRESSLY WAIVES, ALL REMEDIES AND DAMAGES RELATING TO INDIRECT, INCIDENTAL, CONSEQUENTIAL, SPECIAL OR PUNITIVE DAMAGES OF ANY DESCRIPTION, WHETHER ARISING OUT OF WARRANTY OR OTHER CONTRACT, NEGLIGENCE OR OTHER TORT, OR OTHERWISE, INCLUDING, WITHOUT LIMITATION, RESCISSION, DIFFERENCE IN VALUE DAMAGES, FORESEEABLE BUSINESS LOSSES, LOSS OF PROFITS AND RELIANCE DAMAGES. UNDER NO CIRCUMSTANCES SHALL SELLER'S LIABILITY HEREUNDER FOR ANY CAUSE EXCEED THE PURCHASE PRICE PAID BY BUYER FOR THE COMPONENT OR THIRD PARTY PRODUCT OUT OF WHICH SUCH CLAIM OR ACTION AROSE. THE PARTIES EXPRESSLY AGREE THAT THE EXCLUSIONS AND LIMITATIONS SET FORTH HEREIN ARE AGREED ALLOCATIONS OF RISK AND SHALL SURVIVE THE DETERMINATION OF ANY COURT OF COMPETENT JURISDICTION THAT ANY REMEDY PROVIDED HEREIN FAILS OF ITS ESSENTIAL PURPOSE.

III. THE EXCLUSIONS, DISCLAIMERS, AND LIMITATIONS SET FORTH HEREIN ARE NOT INTENDED TO, AND SHALL NOT BE CONSTRUED AS TO, CONTRAVENE MANDATORY PROVISIONS OF ANY APPLICABLE LAW OR REGULATION. IF ANY PART OF THIS SECTION IS HELD TO BE ILLEGAL OR UNENFORCEABLE BY A COURT OF COMPETENT JURISDICTION, THE PART SHALL BE MODIFIED SO AS TO BE ENFORCEABLE TO THE MAXIMUM EXTENT POSSIBLE. IF THE PART CANNOT BE MODIFIED, THEN THAT PART MAY BE SEVERED AND THE OTHER PARTS OF THE LIMITED WARRANTY SHALL REMAIN IN FULL FORCE AND EFFECT. THIS LIMITED

WARRANTY IS EXPRESSED FOR THE SOLE BENEFIT OF THE ORIGINAL USER WHO PURCHASES OR RECEIVES THE SYSTEM, COMPONENT, APP, OR THIRD PARTY PRODUCT, AND IS NOT TRANSFERABLE.

1.15 Appendix I: remedē® System IPG Specifications

1.15.1 Physical Characteristics

Table 11 remedē System IPG (Model 1001) Physical Description

Description	Value
Height	80 mm
Length	47.5 mm
Thickness	14.6 mm
Volume	39 cm^3
Mass	64 g
Materials exposed to tissue	Titanium, epoxy resin, silicone rubber

1.15.2 Lead Connectors

The **rem**edē Pulse Generator has been designed to accept 3.2 mm IS-1 lead connectors.

1.15.3 Radiopaque Identification

A radiopaque ID marker placed inside the **rem**edē IPG connector block allows the model number and year of manufacture to be identified by normal X-ray techniques. The identification is composed by the manufacturer's identification code (CCI), the model code (E) and the last two digits of the manufacture year (Figure 20).

Figure 20 remedē System IPG Radiopaque Identifier

1.15.4 Battery Information

Table 12 remedē® System IPG (Model 1001) Battery Information

Chemistry	Lithium Carbon Monofluoride (WG 9086)
Nominal Voltage	2.9 – 2.95 Volts (at 37ºC)
Capacity	2.2 Amp-hours (Ah)
Elective Replacement Indicator (ERI)	2.60 Volts
End of Life (EOL)	2.50 Volts

Table 13 remedē System IPG (Model 1001) – Battery Longevity Estimates

Settings Description	Low Energy Use Settings	Normal Energy Use Settings	High Energy Use Settings
Stimulation Amplitude	2 milliamperes (mA)	5 mA	10 mA
Therapy Dose	6 hours	7 hours	7 hours
Stimulation Pulse Width	60 micro seconds (µs)	150 µs	300 µs
Stimulation Frequency	20 hertz (Hz)	20 hertz (Hz)	40 hertz (Hz)
Stimulation Lead Impedance	1500 ohms (Ω)	1000 ohms (Ω)	500 ohms (Ω)
Stimulation Mode	Asynchronous	Asynchronous	Asynchronous
Stimulation Duty Cycle	50 %	50 %	50 %
System Measurements	Transthoracic Impedance, R-wave, Posture	Transthoracic Impedance, R-wave, Posture	Transthoracic Impedance, R-wave, Posture
Battery Longevity Estimate*	55 months	41 months	17 months
*Due to the anatomical relationship between the phrenic nerve and lead electrodes, patients implanted with the respi**stim®** L (left) stimulation lead typically have normal to high longevity estimates. Patients implanted with the respi**stim®** R (right) stimulation lead typically have normal to low longevity estimates.			

1.15.5 Programmable Settings

Table 14 remedē® System IPG (Model 1001) Programmable Settings

Parameter	Factory Value	Programmable Values	Increment
Therapy			
Mode	Off	Off, Therapy, Monitor	
Algorithm Mode	Asynchronous	Asynchronous, Synchronous	
Asynchronous Respiratory Rate	16 breaths per minute (bpm)	10 – 30 bpm	1 bpm
Stay in Monitor	Off	On, Off	
Asynchronous I:E Ratio	1.0	0.5 – 2.0	0.1
Synchronous Backup Ventilation	16 bpm	10 – 30 bpm	1 bpm
Synchronous Backup Only	Off	On, Off	
Synchronous Stimulation Duration	2.0 seconds (sec)	0.5 – 30.0	0.1 sec
Synchronous Delay	0.5 sec	0.1 – 4.0 sec	0.1 sec
Synchronous Blanking Period	0.4 sec	0.1 – 20.0 sec	0.1 sec
Scheduled Sleep Start (all days)	22:00 (HH:MM)	00:00 – 23:30 (HH:MM)	30 min
Scheduled Sleep Stop (all days)	06:00 (HH:MM)	00:00 – 23:30 (HH:MM)	30 min
Maximum Dose	8 hours (hrs)	00:30 – 12:00	30 min
Lack of Respiration Period	8.0 sec	0.5 – 30.0 sec	0.5 sec
Stimulation			
Amplitudes (Supine, Left, Right, Prone)	0.1 mA	0.0 – 10.0 mA	0.1 mA
Maximum Amplitudes (Supine, Left, Right, Prone)	0.1 mA	0.1 – 10.0 mA	0.1 mA
Pulse Width	150 µs	60 – 300 µs	30 µs
Frequency	20 Hz	10, 20 40 Hz	
Anode (+)	Electrode 2	Electrode 1, 2, 3, 4, 5, 6	
Cathode (-)	Electrode 1	Electrode 1, 2, 3, 4, 6, Can	

Table 14 remedē® System IPG (Model 1001) Programmable Settings

Parameter	Factory Value	Programmable Values	Increment
Suspension Window	1.0 min	0.0 – 5.0 min	0.5 min
Stimulation Duration Adaption	Off	On, Off	
Current Amplitude Adaption	Off	On, Off	
Continue at Imax	On	On, Off	
Ramps			
Rising Duration	30 %	0 – 100 %	10%
Falling Duration	10 %	0 – 100 %	10%
Baseline Amplitude	50 %	0 – 90 %	10%
Titration			
Nightly Titration (all intervals)	100 %	50 – 100 %	5 %
Nightly Titration Time	Absolute	Absolute, Relative	
Weekly Titration	Off	On, Off	
Week 2 … Week 8	0.0 mA	0.0 – 0.5 mA	0.1 mA
Sensors			
Activity Threshold	8	0 – 16	1
Activity Window	2.0 min	0.5 – 5.0 min	0.5 min
Sleep Latency	5 min	2 – 15 min	1 min
BioBreak Threshold	2 min	1 – 15 min	1 min
Pitch Threshold	50 degrees (deg)	5 – 90 deg	5 deg
Left – Supine Threshold	40 deg	0 – 170 deg	10 deg
Left – Prone Threshold	160 deg	10 – 180 deg	10 deg
Right – Supine Threshold	-40 deg	0 – -170 deg	10 deg
Right – Prone Threshold	-160 deg	-10 – -180 deg	10 deg
Transthoracic Impedance Measure			
Enable	On	On, Off	
Configuration	Sensing – Can	Sensing – Stim, Sensing – Can, Stim - Can	
R Wave			
Enable	On	On, Off	

Table 14 remedē® System IPG (Model 1001) Programmable Settings

Parameter	Factory Value	Programmable Values	Increment
Configuration	Can & Distal	Proximal & Distal, Can & Proximal, Can & Distal	
Sensitivity	1.0 millivolt (mV)	0.5 – 5.0 mV	0.5 mV
Refractory	200 millisecond (ms)	200 – 500 ms	50 ms
dEMG			
Enable	Off	On, Off	
Gain	Low	Low, Medium, High	
Configuration	Can & Distal	Proximal & Distal, Can & Proximal, Can & Distal	

1.16 Appendix II: respistim® L, LQ, and LQS Stimulation Lead Specifications

1.16.1 Physical Characteristics

Recommended Guiding Catheter 6 French minimum

Electrodes

- Material — Platinum/Iridium
- Electrode Surface Area — 12 millimeters^2
- Coating — None
- Steroid — None

Lead Diameter

- Body — 3.6 French
- Electrodes — 3.9 French
- Inside Diameter — 0.020 inch
- Insulation Material — Polyurethane 90A

Terminal

- Compatibility — IS-1
- Material — 316L Stainless Steel

Conductors

- Type — Co-axial design, hexafilar coil with coated wire

Table 15 respistim L, LQ, and LQS Lead Model Descriptions

respistim L		
Model		Length (centimeters)
2001		35
2002		45
2003		55
2004		70
respistim LQ		
Model		Length (centimeters)
5045		45
5055		55
5065		65
5085		85
respistim LQS		
Model		Length (centimeters)
4045		45
4055		55
4065		65
4085		85

1.17 Appendix III: respistim® R Lead Specifications

1.17.1 Physical Characteristics

Recommended Introducer 8 French

Electrodes

- Material — Platinum/Iridium
- Electrode Surface Area — 29 millimeters^2
- Coating — None
- Steroid — None

Lead Diameter

- Proximal Body — 4.8 French
- Distal Body — 7.0 French
- Inside Diameter — 0.020 inch
- Insulation Material — Polyurethane 90A

Terminal

- Compatibility — IS-1
- Material — 316L Stainless Steel

Conductors

- Type — Co-axial design, hexafilar coil with coated wire

Table 16 respistim R Model Descriptions

Model	Length (centimeters)	Distal Helical Spring Length (millimeters)	Distal Helical Spring Diameter (millimeters)
3101	60	25	20
3102	60	25	24
3103	60	35	20
3104	60	35	24
3105	60	45	20
3106	60	45	24
3201	80	25	20
3202	80	25	24
3203	80	35	20
3204	80	35	24
3205	80	45	20
3206	80	45	24

1.18 Appendix IV: Additional Programmer and eIPG Details

The programmer display is a commercially available tablet computer certified for use in a clinical environment as the **rem**edē® System Programmer. The programmer does not contain any user serviceable parts.

1.18.1 Power Supply

The **rem**edē System Programmer is provided with a medical grade power supply and power cable that fulfills the standard IEC 60601-1:2012. The power supply is rated as follows: 100-240 VAC, 2.0-1.0A, 50-60Hz.

Use only the power supply and power cable provided by Respicardia. The power supply provides electrical isolation to the patient and operator from electrical power mains.

1.18.2 Routine Cleaning

Always turn the **rem**edē System programmer OFF prior to cleaning.

When necessary, it is recommended that a soft cloth dampened with distilled water or isopropyl alcohol be used to wipe the exterior case of the programming wand. Do not use solvents or cleaning cloths containing chemical cleaning agents.

1.18.3 Cybersecurity Considerations

Do not attempt to install software on the **rem**edē System Programmer. Software installation may introduce viruses/ malware into the system and corrupt the system configuration. This may result in a malfunction or the inability to use the **rem**edē System Programmer.

The **rem**edē System Programmer wireless network (Wi-Fi) access has been disabled to enhance system cybersecurity robustness. Do not remove the **rem**edē System Programmer Micro SD port cover at any time.

Do not attempt to use Wi-Fi via a USB connection on the **rem**edē System Programmer. The **rem**edē System Programmer is not intended for use with any Wi-Fi connection.

1.18.4 eIPG Cable

The Respicardia eIPG is used with a sterile cable having two covered alligator clips on one end and two 2mm male shrouded connector pins on the opposite end. The cable should have a length of 2-3 meters.

1.19 Appendix V: remedē® System Programmer Electromagnetic Interference Information

The **rem**edē System may be subject to interference from other electrical equipment being operated in the near vicinity. Specifically, portable and mobile radiofrequency (RF) equipment can interfere with the normal operation of the programming system. This shall be taken into account in any situation where the equipment is not operating as expected. The **rem**edē System Programmer may be interfered by other equipment, even if that equipment complies with CISPR emission limits.

Table 17 Electromagnetic Emissions Guidance Declaration

<table>
<tr><th colspan="3">Guidance and manufacturer's declaration – Electromagnetic Emissions</th></tr>
<tr><td colspan="3">The remedē System Programmer is intended for use in the electromagnetic environment specified below.</td></tr>
<tr><td>Emissions Test</td><td>Compliance</td><td>Electromagnetic Environment – Guidance</td></tr>
<tr><td>RF emissions
CISPR 11</td><td>Group 1</td><td>The remedē System programmer uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause interference in nearby electronic equipment.</td></tr>
<tr><td>RF emissions
CISPR 11</td><td>Class B</td><td rowspan="3">The remedē System is suitable for use in all establishments, including domestic establishments and those directly connected to the public low voltage power supply network that supplies buildings used for domestic purposes.</td></tr>
<tr><td>Harmonic Emissions
IEC 61000-3-2</td><td>Class A</td></tr>
<tr><td>Voltage fluctuations/flicker emissions
IEC 61000-3-3</td><td>Complies</td></tr>
</table>

Table 18 Electromagnetic Immunity Guidance Declaration

Guidance and Manufacturer's Declaration – Electromagnetic Immunity			
The **rem**edē® System programmer is intended for use in the electromagnetic environment specified below. The **rem**edē System should not be used adjacent to or stacked with other equipment and that if adjacent or stacked use is necessary, the **rem**edē System should be observed to verify normal operation in the configuration in which it will be used.			
Immunity Test	**IEC 60601 Test Level**	**Compliance Level**	**Electromagnetic Environment – Guidance**
Electrostatic discharge (ESD) IEC 61000-4-2	±6 Kilovolt contact ±8 Kilovolt air	±6 Kilovolt contact ±8 Kilovolt air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30%.
Electrical fast transient/burst IEC 61000-4-4	±2 Kilovolt for power supply lines ±1 Kilovolt for input/output lines	±2.0 Kilovolt for power supply lines ±1 Kilovolt for input/output lines	Mains power should be that of a typical hospital environment. Do not operate motors or other electrically noisy equipment on the same mains circuit as the **rem**edē System Programmer.
Surge IEC 61000-4-5	±1 Kilovolt, differential mode ±2 Kilovolt, common mode	±1 Kilovolt, differential mode ±2 Kilovolt, common mode	Mains power quality should be that of a typical commercial or hospital environment.
Voltage dips, short interruptions and voltage variations on power supply input lines IEC 61000-4-11	‹5% U_T (›95% dip in U_T) for 0.5 cycle 40% U_T (60% dip in U_T) for 5 cycles 70% U_T (30% dip in U_T) for 25 cycles ‹5% U_T (›95% dip in U_T) for 5 sec	100% dip in U_T for 0.5 cycle 60% dip in U_T for 5 cycles 30% dip in U_T for 25 cycles 100% dip in U_T for 5 sec	Mains power quality should be that of a typical commercial or hospital environment. **Note:** If the user of the **rem**edē System Programmer requires continued operation during power interruptions, it is recommended that the **rem**edē System Programmer be powered from an uninterruptible power supply or battery.
Power frequency (50/60 Hz) IEC 61000-4-8	3 A/m	3 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
NOTE: UT_is the AC mains voltage prior the application of the test level.			

Table 19 Electromagnetic Immunity Guidance Declaration

Guidance and Manufacturer's Declaration – Electromagnetic Immunity			
The **rem**edē System programmer is intended for use in the electromagnetic environment specified below.			
Immunity Test	**IEC 60601 Test Level**	**Compliance Level**	**Electromagnetic Environment – Guidance**
Conducted RF IEC 61000-4-6	3 voltage root mean square (Vrms) 150 kilo hertz (KHz) to 80 mega hertz (MHz)	3 V	Portable and mobile RF communications equipment should be used no closer to any part of the **rem**edē System Programmer including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter. Recommended separation distance: $d = 1.17\sqrt{P}$ 150 kHz to 80 MHz $d = 1.17\sqrt{P}$ 80 MHz to 800 MHz $d = 2.33\sqrt{P}$ 800 MHz to 2.5 GHz where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and d is the recommended separation distance in meters (m). Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey,[a] should be less than the compliance level in each frequency range.[b] Interference may occur in the vicinity of equipment marked with the following symbol: 
Radiated RF IEC 61000-4-3	3 V/m 80 MHz to 2.5 giga hertz (GHz)	3V/m	
NOTE 1 At 80 MHz and 800 MHz, the higher frequency range applies. NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.			
[a] Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which the **rem**edē System Programmer is used exceeds the applicable RF compliance level above, the **rem**edē System Programmer should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as relocating the **rem**edē System Programmer. [b] Over the frequency range 150 kHz to 80 MHz, field strengths should be less than 3V/m.			

Table 20 Recommended Separation Distances Between Portable and Mobile RF Communications Equipment

Recommended separation distances between portable and mobile RF communications equipment and the **rem**edē® System programmer			
The **rem**edē System programmer is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or user of the **rem**edē System programmer can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the **rem**edē System programmer as recommended below, according to the maximum output power of the communications equipment.			
Rated maximum output power of transmitter W	Separation distance according to frequency of transmitter M		
	150 kHz to 80 MHz $d = 1.17\sqrt{P}$	80 MHz to 800 MHz $d = 1.17\sqrt{P}$	800 MHz to 2.5 GHz $d = 2.33\sqrt{P}$
0.01	0.12	0.40	1.47
0.1	0.37	0.71	1.97
1	1.17	1.27	2.62
10	3.7	2.25	3.50
100	11.7	4.0	4.66
For transmitters rated at a maximum output power not listed above, the recommended separation distance *d* in meters (m) can be estimated by using the equation applicable to the frequency of the transmitter, where *P* is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer. NOTE 1 At 80 MHz and 800 MHz, the higher frequency range applies. NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.			

1.20 Appendix VI: remedē® System Programmer Communications & Telemetry

1.20.1 Telemetry Data

Telemetry communication through magnetic induction with the programmer provides the means to view and set system parameters and collect device data obtaining the following information:

- All programmable parameters
- Patient information (IPG model/serial number, Lead model/serial number, Patient ID, Physician contact information, implant date, patient time zone)
- Battery voltage and condition indicator (Good, Early Replacement Indicator [ERI], and End of Life [EOL])
- Statistics that include sensing and stimulation events
- Stimulation lead impedance as well as historical record of these values

The **rem**edē System programmer communicates with the **rem**edē IPG using a proprietary telemetry communication protocol.

Table 21 Telemetry Transmission Characteristics

remedē System Programmer Transmission Characteristics to Implanted Device
ASK: "0" = tone absence, "1" = tone presence, Bit length = 0.305 ms 16-20 kHz carrier Range: ≤ 6 cm Power: $0.56W_{peak}$, $0.27W_{average}$

1.20.2 Troubleshooting

Telemetry communication through magnetic induction with the programmer may encounter situations that require user intervention. The following are potential communication issues that may occur and the action that should be taken by the user.

1.20.2.1 Loss of Communication with Programmer Wand

If a loss of communication between the Programmer Display and the Programmer Wand has occurred, a message indicating loss of interface connection will appear on the Programmer Display.

Action: Unplug the USB cable connecting the Programmer Wand to the Programmer Display and wait at least 5 seconds before reconnection.

- **Additional Information:** A loss of communication may be incurred by unplugging the USB cable or as a safety effect in the presence of excessive electromagnetic interference (EMI), an excessive electrostatic discharge (ESD), or other high energy burst (e.g. external defibrillation).

1.20.2.2 Loss of Marker Mode or Other Telemetry Error Messages

If a loss of communication between the Programmer Wand and the implanted device has occurred, a message indicating loss of telemetry connection will appear on the Programmer Display.

Action: Confirm the Programming Wand is within the secure communication zone and attempt telemetry operation again.

- **Additional Information**: A loss of communication may incur due to the Programming Wand not being within the secure communication zone or a result of the presence of excessive electromagnetic interference (EMI), excessive electrostatic discharge (ESD), or other high energy burst (e.g. external defibrillation).

1.20.2.3 Loss of Programmer Operating System Functions

If the Programmer Display experiences a functional error as related to the PC's Operating System the Windows system may report an error or cause the screen to become blue with reported error condition, or become non-responsive to any attempted input.

Action: The Programmer Display may be reset by pushing the recessed button on the backside of the PC tablet. Once the system returns to the Windows desktop, launch the **rem**edē® System Programmer Software Application and proceed with the programming session.

- **Additional Information**: A system error, while rare, may occur with the Windows Operating System of the **rem**edē System Programmer Display due to any number of reasons. If the error is repeated the user should contact Respicardia.

- Note: If any unforeseen problem arises that renders the programmer unable to perform normally, the user should contact Respicardia.

1.21 Appendix VII: Service and Disposal Information

1.21.1 Service

All servicing of the **rem**edē® System Programmer components shall be performed by Respicardia, Inc. personnel. For Customer service, contact the address below:

Respicardia, Inc.
12400 Whitewater Drive, Suite 150
Minnetonka, MN 55343 USA
Phone: (952) 540-4470
Fax: (952) 540-4485
E-mail: info@Respicardia.com
http://www.respicardia.com

1.21.2 Disposal

The **rem**edē IPG and leads that have been exposed to blood and/or body fluids shall be considered to be a potential biohazard and disposed of according to local environmental regulations. The **rem**edē System programmer, programming wand, and external IPG shall be considered as electronic waste and disposed of according to local environmental regulations.

Respicardia, Inc.
12400 Whitewater Drive, Suite 150
Minnetonka, MN 55343 USA
Phone: (952) 540-4470
Fax: (952) 540-4485
E-mail: info@Respicardia.com
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