Study Protocol

**Protocol Title:** A **Pro**spective, Multi-Center, Open L**a**bel, Single Arm Clinical **Tri**al E**v**aluating the Safety and **E**fficacy of the Cordella™ Pulmonary Artery Sensor System in New York Heart Association (NYHA) Class III **H**eart **F**ailure Patients

Brief Title: PROACTIVE-HF IDE Trial Heart Failure NYHA Class III

Unique Protocol ID: ETX-HFS-PA-03

NCT04089059

08 November 2023

**Clinical Trial Protocol / Clinical Investigational Plan (CIP)**

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| Protocol Number/ CIP: | ETX-HFS-PA-03 IDE Trial |
| Title: | A **Pro**spective, Multi-Center, Open L**a**bel, Single Arm Clini**c**al **T**r**i**al E**v**aluating the Safety and **E**fficacy of the Cordella™ Pulmonary Artery Sensor System in New York Heart Association (NYHA) Class III **H**eart **F**ailure Patients (PROACTIVE- HF Trial) |
| Investigational Product Name: | Cordella Pulmonary Artery Sensor System |
| Version: | 11.0 (Final) |
| IDE Number: | G190020 |
| Date: | 08 November 2023 |

## ADMINISTRATIVE INFORMATION

### Sponsor Contacts

Medical, Clinical and Operational Support

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| Sponsor Name: | Endotronix Inc |
| Sponsor Address: | 1415 West Diehl Road<br>Suite #500W,<br>Naperville, IL 6056<br>3USA |
| Sponsor Name (EU only): | Endotronix, Ireland Limited |
| Sponsor Address (EU only): | DCU Alpha Innovation Center<br>Old Finglas Road, Glasnevin<br>Dublin 11, D11 KXN4<br>Ireland |
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Manufacturing

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| Manufacturing Name: | Endotronix Inc. |
| Manufacturing Address: | 1415 West Diehl Road<br>Suite #500W<br>Naperville, IL 60563 |

**PROTOCOL ADMINISTRATIVE INFORMATION**

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| Protocol/ CIP Number: | ETX-HFS-PA-03 |
| Revision Number: | 11.0 Final |
| Protocol/ CIP Date: | 08 November 2023 |
| IDE Number: | G190020 |
| Investigational Product: | Cordella™ Pulmonary Artery (PA) Sensor System |

**AMENDMENT HISTORY**

| Date | Amendment Number | Amendment Type |
|---|---|---|
| 05 September 2019 | 2.0 | The following specific revisions made to the protocol sections are described below:<br>- Section 8.1.21: Updated text to clarify that for each unscheduled call for a treatment subject an unscheduled call for a control subject needs to be performed<br>- Section 10.3: Updated text to reflect the change in the primary analysis to negative binomial regression of events per unit time as a function of the Treatment Arm.<br>In addition, TOC was updated to reflect the correct sections and page numbers. The headers and footers were updated to reflect the current revision number and the current version date. These changes are not specified individually as they are administrative or formatting only. |
| 15 October 2019 | 3.0 | The following specific revisions made to the protocol sections are described below:<br>- Sections 1.3 and 10.5 have been updated to reflect the correct Safety Endpoints at 12 month.<br>- Section 6.3 has been updated to reflect the revised study start.<br>- Section 8.17, 8.3.2, 8.3.3, 8.3.4, 8.3.5, 8.3.6, 8.3.7, 8.3.8, 8.3.9 has been updated to clarify full and abbreviated physical examinations during the trial.<br>- Section 8.1.9 has been updated to reflect the correct schedule of Assessment for NT-pro BNP.<br>- Sections 8.1.10 and 14.1 have been updated to reflect the correct schedule of Assessment for Echocardiogram.<br>- Sections 8.1.8, 8.3.3, 8.3.4, 8.3.5, 8.3.9 and 14.1: Updated to reflect the change that subjects in both Arms will be instructed to taking PAP measurements |

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| | | in supine position at all study visits.<br>- Section 14.1 has been updated to reflect the correct schedule of Assessment for V2.<br>In addition, TOC was updated to reflect the correct sections and page numbers. Some minor typos have been corrected. The headers and footers were updated to reflect the current revision number and the current version date. These changes are not specified individually as they are administrative or formatting only. |
| 11 February 2020 | 4.0 | The following specific revisions made to the protocol sections are described below:<br>- Appendix 14.5 has been updated to reflect a change in the mPAP target range<br>In addition, TOC was updated to reflect the correct sections and page numbers. Some minor typos have been corrected. The headers and footers were updated to reflect the current revision number and the current version date. These changes are not specified individually as they are administrative or formatting only. |
| 13 May 2020 | 5.0 | The following specific revisions made to the protocol sections are described below:<br>- To align with updated labelling documentation the entire document has been updated as follows:<br>o Change CHFS to Cordella System<br>o Change myCordella Hub to myCordella Tablet<br>- Protocol Synopsis, Section 6.5, 8.3.4 and Appendix 14.1 have been updated to reflect that Study Visit 4 will be performed as remote/ virtual Telemonitoring visit<br>- Exclusion Criteria #3 has been updated in Protocol Synopsis and Section 7.5<br>In addition, TOC was updated to reflect the correct sections and page numbers. Some minor typos have been corrected. The headers and footers were updated |

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| | | to reflect the current revision number and the current version date. These changes are not specified individually as they are administrative or formatting only. |
| 09 December 2020 | 6.0 | The following specific revisions made to the protocol sections are described below:<br>- Protocol Synopsis, Section 6.2, 6.4 and 7.6 have been updated to reflect that the number of sites has been updated to 90 sites in the United States and Europe<br>- Protocol Sections 4.1 Potential Risks, 9.14 Anticipated Adverse Events and 15 have been updated to align with the updated labeling<br>- Protocol Section 6.3 to update the completion date of the Trial Enrollment<br>- Sections 8.14 and 14.1 have been updated to reflect a change in collection of Health Economic Data<br>In addition, TOC was updated to reflect the correct sections and page numbers. Some minor typos have been corrected. The headers and footers were updated to reflect the current revision number and the current version date. These changes are not specified individually as they are administrative or formatting only. |
| 11 November 2021 | 7.0 | The following specific revisions made to the protocol sections are described below:<br>- The trial design is being changed from a randomized- controlled trial design to an open-label single arm trial design, therefore the following sections have been updated accordingly: Protocol/ CIP Synopsis, Section 1.3, 5, 6, 7.2, 7.3, 7.6, 10, 13.12 and 15<br>- To reflect the change from randomized to an open-label trial, trial procedures and methods have been updated in Protocol/ CIP Synopsis, Section 8.1.1, 8.1.5,8.1.18, 8.1.20, 8.1.21, 8.3.2 and 8.3.6. Methods was updated to include 3 Cohorts. Cohort #1 will not be part of the primary endpoint analysis |

as these patients have already had follow-up visits as patients in the previous Control Arm. To harmonize all patients in the study, data for the primary endpoints will only be collected for patients who receive treatment from onset (i.e., Cohorts #2 and #3).

- Updating ISO 14155-2011 to the new version 14155:2020
- Due to the fact that European sites are added to the trial the following sections have been updated to account for EU specific requirements:
  - Added European Contact Details
  - Adding Clinical Investigational Plan (CIP) throughout the document
  - Adding Competent Authority (CA) and Independent Ethics Committee (IEC)), throughout the document
  - Added section 8.1.4 on informing GPs
  - Updated Adverse Event sections 9.1, 9.1.4, 9.2 and 9.3
  - Added section 9.3.2 on Regulatory Reporting Requirements
  - Added Appendix 14.7
- Intended Use & Indications for Use have been revised in Protocol/ CIP Synopsis and section 1.4
- Protocol/ CIP Synopsis, Section 6.2, 6.4 and 7.6 have been updated to reflect that the number of sites has been updated to 120 sites in the United States and Europe
- Exclusion Criteria in Protocol/ CIP Synopsis and section 7.5 have been updated:
  - Exclusion Criteria 19- to provide more clarity
  - Added Exclusion Criteria 20 as per required by German Competent Authority (BfArM)
- Section 1.2 and 15 have been updated to reflect recent updates and publications on Pulmonary Artery Pressure (PAP)

- Section 3.2 and 15 to update on the progress of all ongoing clinical trials at Endotronix
- Additional secondary efficacy endpoints have been added to Protocol/ CIP Synopsis, section 5.1 and 10.4
    - Added new Secondary Efficacy Endpoints # 3, # 4 and # 8
    - Updated Secondary Efficacy Endpoints # 11
- Section 6.3 has been updated to reflect revised timelines
- Subject compliance on the Cordella System is very satisfactory, therefore we updated sections 6.5, 8.1.15, 8.1.20 and 8.3.2 to reflect that the Cordella System and Training will be provided at V2/ Implant Visit
- Addition of an optional Subject Survey with new section 8.1.21 and update to section 8.4.4, 8.4.6, 14.1 and new Appendices 14.7 and 14.8
- Revision to section 8.1.21 and 14.1 with regards to subject contact schedule with addition of optional Subject and Site Surveys on PAP and new Appendices 14.8 and 14.9
- Added section 9.1.3 Device Deficiency (DD) Definition for consistency
- Appendix 14.5 Cordella PA Sensor Treatment Guidelines were updated to reflect the recent addition of the use of SGLT-2 inhibitors for HF Management
- Small clarifications have been made to the following sections:
    - 6.2 to clarify total subject enrollment per site
    - 7.7.1 Screen Failure criteria was clarified
    - 8.1.9 BUN and Urea Laboratory Test can be performed
    - 8.1.16 additional PAP measurements may be taken seated/ supine within 24 hours after implant

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| | | ○ 8.1.18 PAP Measurements for FUP visits may also be taken at home by the subject<br>○ 8.3.2 follow-up for safety in case an implant was not completed<br>○ Throughout section 8 and 14.1 changed sitting to seated for clarification<br>- In addition, TOC was updated to reflect the correct sections and page numbers. Some minor typos have been corrected. The headers and footers were updated to reflect the current revision number and the current version date. These changes are not specified individually as they are administrative or formatting only. |
| 08 June 2022 | 8.0 | The following specific revisions made to the protocol sections are described below:<br>- The Performance Goal (PG) for the primary and first secondary endpoint was revised for this trial and therefore the sample size increased to 450 implanted subjects (Cohort #2 and Cohort #3). In the protocol the following sections have been updated accordingly: Protocol/ CIP Synopsis, Section 6.1, 6.2, 6.5, 7.6, 10.3, 10.4 and 10.5.<br>- Number of Cohort #1 subjects (cross- over from former Control Arm) was updated to 85 subjects in the following sections: Protocol/ CIP Synopsis, Section 6.1 and 6.2.<br>- Protocol/ CIP Synopsis, section 6 and figure 8 have been updated to provide clarification with regards to timing of unblinding of Cohort #2 and Cohort #3 subjects.<br>- Protocol Sections 4.1 Potential Risks, 8.2 Device Explant and 9.14 Anticipated Adverse Events have been updated to provide clarification on one specific risk.<br>- Section 6.2 has been updated to further specify subject disposition.<br>- Enrollment will now finish in Q4 2022, section 6.3 has been updated accordingly. |

- Inclusion Criteria # 4 in Protocol/ CIP Synopsis and section 7.4 has been updated to reflect the inclusion of (European Society of Cardiology) ESC Guidelines for the EU part of the trial.
- Protocol/ CIP Synopsis , section 7.6, 8.1.1, 8.1.13, 8.1.15, 8.3.1 and 14.1 have been updated to indicate that subject training on and distribution of the commercial Cordella System (myCordella™ Tablet & Peripherals) will occur at Screening Visit (Visit 1).
- Baseline KCCQ will be performed as soon as the subject receives their Cordella System during the Screening Visit. Protocol/ CIP Synopsis, sections 6.5, 7.6, 8.1.13, 8.1.15, 8.3.1, 8.3.2 and 14.1 have been updated to reflect this change. The threshold for chest circumference for providing a CT-scan for review has been reduced from 59 inch/ 1500 mm to 55 inch /1400 mm, section 8.1.7 has been updated accordingly.
- Section 8.3 has been updated to remove temperature collection as its not needed for safety purposes
- Section 8.3.1 and 14.1 have been updated to add which study procedures have to be repeated in case a subject will be implanted > 30 days after visit 1
- Further clarification has been made on the safety endpoints in section 10.5
- Section 11.7.1.1 has been updated to provide further clarity on responsibilities on indemnification/ insurance.
- For EU only, section 13.12 has been added to cover the end of the trial.
- Small corrections have been made to sections 4.2 and 14.5
- Appendix 14.7 has been updated to add the following:
  - Added Adverse Event Causality Assessment for the EU

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| | | ○ Added Safety Reporting Requirements for the EU as per EU (Medical Device Regulations) MDR.<br>- Appendix 14. 9 Subject Survey was updated with small corrections<br>In addition, TOC was updated to reflect the correct sections and page numbers. Some minor typos have been corrected. The headers and footers were updated to reflect the current revision number and the current version date. These changes are not specified individually as they are administrative or formatting only. |
| 01 September 2022 | 9.0 | The following specific revisions made to the protocol sections are described below:<br>- Protocol/ CIP Synopsis , section 5.2 and 10.5 have been updated to indicate that one (1) additional secondary safety endpoint has been added<br>- The Performance Goal (PG) for the primary and first secondary efficacy endpoints was revised for this trial. In the protocol the following sections have been updated accordingly: Protocol/ CIP Synopsis, Section 10.3 and 10.4.<br>- Primary Endpoint Analysis has been finalized for SIRONA 2; therefore Section 3.2 has been updated<br>- Enrollment will now finish in Q4 2022, section 6.3 has been updated accordingly.<br>- Reference 52 and 53 have been added<br>- Exclusion # 6 in Protocol/ CIP Synopsis and section 7.5 has been changed to support the fact that F patients who have repaired congenital heart disease conditions would benefit from participating in the PROACTIVE-HF trial.<br>- Sections 8.1.2, 8.1.10, 8.3.1 and 14.1 have been updated to change that the Screening Echocardiography may also be obtained within 6 months of Study Visit 1<br>- The timing of the initial NYHA Classification Assessment has been clarified in sections 8.31 and 14.1. |

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| | | In addition, TOC was updated to reflect the correct sections and page numbers. Some minor typos have been corrected. The headers and footers were updated to reflect the current revision number and the current version date. These changes are not specified individually as they are administrative or formatting only. |
| 16 December 2022 | 10.0 | The following specific revisions made to the protocol sections are described below:<br>- The responsible Medical Officer has been updated<br>- Increase of FUP time for all subjects to Year 5, therefore the following sections have been updated accordingly:<br>o CIP Synopsis<br>o Section 6, 6.3 and 6.5<br>o Sections 7.7.2<br>o Sections 8.1, 8.1.7, 8.1.8, 8.1.9, 8.1.10, 8.1.12, 8.1.22<br>o Sections 8.3.8<br>o Sections 10.4.1 and 10.4.2<br>o Section 14.1 and 14.3<br>In addition, TOC was updated to reflect the correct sections and page numbers. The headers and footers were updated to reflect the current revision number and the current version date. These changes are not specified individually as they are administrative or formatting only. |
| 08 November 2023 | 11.0 | The following specific revisions made to the protocol sections are described below:<br>- Change of sponsor/ manufacturing address to 1415 West Diehl Road, Suite #500W, Naperville, IL 60563<br>- A clarification has been made to Secondary Efficacy Endpoint #3; therefore the following sections have been updated accordingly:<br>o CIP Synopsis<br>o Section 5.1 and 10.4 |

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| | In addition, TOC was updated to reflect the correct sections and page numbers. The headers and footers were updated to reflect the current revision number and the current version date. These changes are not specified individually as they are administrative or formatting only. |

**SPONSOR PROTOCOL/ CIP APPROVAL**

The study will be carried out in accordance with the highest respect for the individual participants in accordance with the requirements of this protocol/ CIP and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Organization of Standardization (ISO) 14155:2020- Clinical investigation of medical devices for human subjects – Good Clinical Practice

All applicable local laws and regulations, including, without limitation, data privacy laws and regulations.

**SIGNATURES**

| **Sponsor Signatory:** | **Signature:** | **Date:** |
|---|---|---|
| Name & Title | Peter Branecky, MD, Sr. Medical Director, Endotronix Inc. | |
| Name & Title | Andrea Sauerland, VP Clinical Operations Endotronix Inc. | |
| Name & Title | Lisbert Avila- Yu, SVP Quality Affairs & Regulatory Endotronix Inc. | |

# Pages from ETX-HFS-PA-03 final V11.0 08Nov23 clean

Final Audit Report 2023-11-09

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| Created: | 2023-11-08 |
| By: | Andrea Sauerland (andrea.sauerland@endotronix.com) |
| Status: | Signed |
| Transaction ID: | CBJCHBCAABAA2ooCGCeTn5C3iy3kDXnstlAAKMQ78CeS |

## "Pages from ETX-HFS-PA-03 final V11.0 08Nov23 clean" History

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Agreement completed.

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**INVESTIGATOR ACKNOWLEDGEMENT**

By signing this clinical protocol/CIP, I confirm that I have read the protocol/ CIP and agree that it contains all the necessary details for performing the study. I agree to conduct the study as outlined herein, complying with Good Clinical Practice, and all applicable regulatory requirements.

I will provide copies of protocol/CIP and all pertinent documents to all members of the study team responsible to me who assist in the conduct of the study. I will discuss this material with them to assure that they are fully informed and trained on the study conduct as well as use of the Investigational Device.

I will use only the informed consent form approved by the sponsor and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or its representative.

I also understand that this study will not be initiated without approval of the appropriate IRB/IEC, Competent Authority (CA) and that all administrative requirements of the governing body of the institution will be complied with fully.

I will obtain written informed consent from all participating subjects as specified in ICH Guideline for Good Clinical Practice; Section 4.8 and will fulfill all responsibilities for submitting pertinent information to the IRB/IEC.

I also agree to report all information or data in accordance with the protocol/CIP and, in particular, I agree to report without unjustified delay, all Adverse Events (Aes) and Serious Adverse Events (SAEs) that could have led to an Unanticipated Adverse Device Effect (UADE) or Unanticipated Serious Adverse Device Effect (USADE).

I further agree that Endotronix and/or designee will have access to any original source documents from which electronic case report form (eCRF) information may have been generated.

I also agree to have control over all clinical supplies (including investigational products) provided by Endotronix and/or designee and collect, account and handle all clinical specimens in accordance with the protocol/CIP.

I further agree not to originate or use the name of Endotronix and/or Cordella™ Heart Failure System and Cordella™ Pulmonary Artery Sensor System, or any of its employees, in any publicity, news release or other public announcement, written or oral, whether to the public, press or otherwise, relating to this protocol/CIP, to any amendment hereto, or to the performance hereunder, without the prior written consent of Endotronix Inc.

**Investigator Acknowledgement Signature**

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Signature Date

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Name (Print)

**PROTOCOL/ CIP SYNOPSIS**

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| **Protocol Title** | A Prospective, Multi-Center, Open- Label, Single Arm Clinical Trial Evaluating the Safety and Efficacy of the Cordella™ Pulmonary Artery Sensor System in New York Heart Association (NYHA) Class III Heart Failure Patients (PROACTIVE-HF Trial) |
| **Protocol Number** | ETX-HFS-PA-03/ IDE Trial |
| **Device Name** | Cordella™ Pulmonary Artery (PA) Sensor System (CorPASS) |
| **Device Description** | The Cordella PA Sensor System comprises seven (7) subsystems that operate together to take daily PA Pressure (PAP) readings at a patient's home and transmit the results to a care provider for evaluation.<br>1. Cordella Sensor<br>2. Cordella Delivery System<br>3. myCordella Patient Reader<br>4. Reader Dock<br>5. Cordella Calibration Equipment (CalEQ)<br>6. myCordella Tablet*<br>7. Cordella Data Analysis Platform (CDAP)<br>For use in the proposed clinical trial, Endotronix intends to use the system in conjunction with Endotronix's commercial Cordella Heart Failure System (Cordella System). The Cordella System collects, records, and transmits physiologic data and communications from the patient at home to clinician(s) for assessment, patient communication, and patient-centered heart failure (HF) management.<br>It contains the following components:<br>1. myCordella Patient App<br>2. myCordella Patient Management Portal (PMP)<br>3. myCordella Tablet*, **<br>4. Up to Three (3) commercially available Medical Devices that patients use at home to collect data: weight, blood pressure (BP), heart rate (HR) and blood oxygen saturation (SpO2)<br>* The myCordella Tablet for the Cordella System and CorPASS systems are one and the same.<br>** not a medical device in accordance with the 21st Century Cures Act. |

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| **Intended Use & Indications for Use** | **Cordella PA Sensor System**<br>The Cordella PA Sensor System is intended to measure, record, and transmit pulmonary artery pressure (PAP) data from NYHA Class III heart failure patients at home to clinicians for assessment and patient-centered heart failure management, with the goal of reducing heart failure hospitalizations. |
| **Study Objectives** | To demonstrate safety and efficacy of the Cordella PA Sensor System. |
| **Study Design** | This is a prospective, open- label, single arm, multicenter clinical trial to evaluate the safety and effectiveness of the Cordella PA Sensor System in NYHA Class III Heart Failure Patients compared to a Performance Goal (PG). |
| **Study Duration** | Study Follow-Up Period: Follow up visits will be scheduled at 1, 3, 6, 12, 18, and 24 months and year 3, 4 and 5 after the Cordella PA Sensor implant, or until study termination. |
| **Study Population** | Male and female subjects, ≥ 18 years of age with a diagnosis of NYHA Class III Heart Failure. |
| **Methods** | Screening/ Enrollment into this trial will continue until at least 450 are enrolled and successfully implanted with the Cordella PA (consisting of subjects from Cohort #2 and Cohort #3 below). These subjects will be the basis for the primary study analysis.<br>Additionally, up to 85 subjects (cross- over from former **Control Arm)** will continued to be followed in Cohort #1**.**<br>With this amendment to the protocol/CIP, subjects will be categorized into three (3) different cohorts:<br>1. Cohort #1- Previously enrolled **Control Arm** subjects<br>• Subjects in this cohort will be unblinded to their PAP measurements and informed about their previous group assignment and continue their Follow-up visit schedule<br>• Additionally, subjects will be asked, throughout the remaining Follow-up period, to complete a regular subject survey on their experience with PAP Measurements and PAP Values. |

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| | • Clinicians will be unblinded to their PAP measurements and start managing the patients to target PA pressures per protocol/ CIP and according to Guideline Directed Medical Therapy (GDMT)<br>• Additionally, the clinical site will be asked to contact the subject on a regular basis to discuss their PAP values<br>• Separate subgroup analysis (safety and effectiveness) will be performed<br><br>2. Cohort #2- Previously enrolled **Treatment Arm** subjects<br>• As of **month 12** subjects in this cohort will be able to see their own PAP measurements for the remaining duration of the study.<br>• Clinicians will continue to manage the patients to target PA pressures per protocol/CIP and according to GDMT<br>• All primary and secondary safety and effectiveness analyses will be performed<br><br>3. Cohort #3- Newly enrolled subjects<br>• Subjects will participate in the Screening/ Enrollment Visit<br>• Cordella PA Sensor Implant Visit, and Follow-Up Visits.<br>• Clinicians will manage the patients to target PA pressures per protocol/ CIP and according to GDMT<br>• As of **month 12** subjects in this cohort will be able to see their own PAP measurements for the remaining duration of the study.<br>• All primary and secondary safety and effectiveness analyses will be performed<br><br>The Cordella PA Sensor will be implanted in conjunction with a right heart catheterization (RHC) procedure. During this visit, the Cordella PA Sensor, which is pre-mounted on a catheter Delivery System, will be introduced via percutaneous venous access to the pulmonary artery.<br><br>Once deployed, the Sensor PAP will be calibrated using the Delivery System's fluid-filled catheter for independent reference measurements.<br><br>The calibration coefficients for that Sensor/Reader/ Subject will be stored in a database, allowing for consistent PAP calculations throughout the study duration.<br><br>Also, at the Screening Visit, eligible subjects will be provided with the commercially available Endotronix Cordella System to measure BP, HR, SpO2 and weight. |

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| | Subjects will be observed until stable and discharged home with instructions to take their PAP measurements daily in addition to their weight, BP, HR and SpO2, which will all be wirelessly transmitted to a secure website for review using the myCordella Patient Management Portal (part of Endotronix's commercially available Cordella System).<br><br>Visibility to patients' daily data trends will enable the clinician to proactively manage the patients to target PA pressures per protocol and according to GDMT.<br><br>The clinician will contact all subjects on a regular basis to discuss their health status and all patients will be treated according to GDMT.<br><br>All Subjects will return for follow up visits at 1, 6, 12, 18, 24 months, as well as at Year 3, 4 and 5, after the Cordella PA Sensor implant, or until study termination. The 3 month follow-up visit will be performed as remote/ virtual Telemonitoring visit.<br><br>At Month 6, the primary safety and efficacy endpoints will be assessed for subjects from Cohort #2 and #3. Additional monitoring of safety and efficacy assessments will be performed throughout the study duration, including evaluation of subject functional and health status, adverse events, Heart Failure (HF) related hospitalizations or equivalent (e.g., intravenous (IV) diuretics). |
| **Sites** | Up to 120 sites in the United States (US) and Europe |
| **Efficacy Endpoints** | **<u>Primary Efficacy Endpoint (through 6 months post- implant):</u>**<br><br>The primary efficacy endpoint will be the 6 month incidence of HF related Hospitalizations (HFH) or all- cause mortality.<br><br>**Secondary Efficacy Endpoints:**<br>1. Incidence of HF Hospitalizations or all-cause mortality at 12 months<br>2. Number of HF Hospitalizations at 6 and 12 months post-implant compared to the number of HF Hospitalizations in the 6 and 12 months prior to implant<br>3. Comparison of the number of HF Hospitalizations or Emergency Department/ Hospital Outpatient IV diuretic visits of Cohort #1 and Cohort #2 +#3 at 6 and 12 months post implant<br>4. Change of N-terminal pro B-type Natriuretic Peptide (NT-pro BNP) |

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| | from Baseline through 6 and 12 months<br>5. Combined outcome of<br>a. First and recurrent HF Hospitalizations<br>b. Emergency Department/ Hospital Outpatient IV diuretic visits<br>c. all-cause mortality<br>at 6 months, added together with equal weighting into a total number of events.<br>6. Heart failure hospitalization or Emergency Department / Hospital Outpatient IV diuretic visits at 6 and 12 months<br>7. Cardiac and all-cause mortality<br>8. Days Alive and Out of Hospital (DAOH)<br>9. Intravenous (IV) diuretic visits<br>10. Heart failure related Medication changes<br>11. Change in PAP:<br>a. From Baseline through 6 and 12 months in subjects with a baseline mPAP<br>i. above target range<br>ii. within or below target range<br>iii. Overall<br>b. Before and after 6-Minute Walk Test<br>12. Percentage of device success as documented by ability of the System to successfully transmit PAP data<br>13. Patient Outcome Measures, measured by KCCQ<br>14. Functional status improvement, as measured by NYHA and 6-Minute Walk Test<br>15. Health Economic Analysis |
| **Safety Endpoints** | **<u>Primary Safety endpoints:</u>**<br>1. Freedom from device/system related complication at 6 months<br>2. Freedom from pressure sensor failure at 6 months<br>**<u>Secondary safety endpoints:</u>**<br>1. Pressure sensor failure rate throughout the study |

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| | 2. Frequency of serious adverse events throughout the study<br>3. Frequency of implant procedure and procedure related adverse events and serious adverse events |
| **Sample Size Statistical Rationale** | **Primary Efficacy Endpoint (at 6 months post- implant):**<br>The primary endpoint will be the 6 month incidence of HF related Hospitalizations or all-cause mortality, compared to a performance goal (PG).<br>The statistical PG of 0.43 is derived from published results from clinically relevant, contemporary studies of NYHA class III HF subjects.<br>For study success, *the upper confidence bound of the observed event rate* for the planned study must be less than the $PG_6$. Additionally, we require the observed event rate to be less than 0.37.<br>Evaluating the upper bound of the confidence interval for the rate, ensures that 1) the observed rate will be comparable to prior studies of active treatment (highest observed value = 0.44), 2) the observed rate will be less than the mean rate from meta- analysis of prior studies of treatment and control, and 3) the observed rate will be less than the lowest rate observed in the control studies (GUIDE-HF). The added requirement for the observed rate to be less than 0.37 provides further assurance that results are comparable to studies of prior treatment.<br>Based on this, the study will implant 450 subjects (single arm cohorts) leading to an expected evaluable cohort of 406 subjects. With a PG of 0.43 and a one-sided 0.025 alpha level, the study will have greater than 80% power assuming a population treatment rate of 0.34. Calculations are based on a one-sample Poisson rate test and were performed with PASS 2021.<br>**Primary Safety Endpoints**<br>There are two primary safety endpoints.<br>Freedom from device or system related complications at 6 months will be tested against the null rate of 90%. Based on a one sample test of a proportion, a sample size of 450 patients provides greater than 95% power assuming a population rate of 95% based on a two-sided Type I error rate of 5%.<br>Similarly, Freedom from Pressure Sensor Failure at 6 months will be tested against the null rate of 95%. Based on a one sample test of a |

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| | proportion, a sample size of 450 patients provides greater than 95% power assuming a population rate of approximately 98.4% based on a two-sided Type I error rate of 5%. |
| **Inclusion Criteria** | 1. Subject has given written informed consent<br>2. Male or female, at least 18 years of age<br>3. Diagnosis and treatment of HF (regardless of left ventricular ejection fraction (LVEF)) for ≥ 3 months and NYHA Class III HF at time of Screening<br>4. Subjects should be on stable, optimally titrated medical therapy for at least 30 days, as recommended according to current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines as standard-of-care for HF therapy in the United States, or current European Society of Cardiology (ESC ) guidelines for HF treatment in Europe, with any intolerance documented.<br>5. HF related hospitalization, HF treatment in a hospital day-care setting, or urgent outpatient clinic HF visit for IV diuretics within 12 month (last hospitalization should be 30 days before Screening /Enrollment) **and/or** N-terminal pro B-type Natriuretic Peptide (NT-proBNP) at time of Screening/ Enrollment defined as:<br>a. Subjects with LVEF ≤ 50%: NT-proBNP ≥ 1500 pg/mL.<br>b. Subjects with LVEF > 50%: NT-proBNP ≥ 800 pg/mL .<br>Thresholds for NT-proBNP (for both LVEF ≤ 50% and LVEF > 50%) will be corrected for body mass index (BMI) using a 4% reduction per BMI unit over 25 kg/$m^2$<br>6. Subjects should be on diuretic therapy<br>7. Subjects who are physically able to hold the myCordella™ Patient Reader unit (approximate weight 1.3lb) against the ventral thoracic surface for up to 2 minutes per day while in a seated position, as well as dock and undock the myCordella™ Patient Reader<br>8. Subjects with sufficient eyesight, hearing, and mental capacity to respond to the myCordella™ Patient Reader's audio/visual cues and operate the myCordella™ Patient Reader<br>9. Subject has sufficient Cellular and/ or Wi- Fi Internet coverage at home<br>10. Subject agrees to return to the treating Investigator for all scheduled follow up visits and can return to the hospital for follow up |
| **Exclusion Criteria** | 1. Intolerance to all neuro-hormonal antagonists (i.e., intolerance to |

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| | angiotensin converting enzyme-inhibitors (ACE-I), angiotensin receptor blockers (ARB), angiotensin-neprilysin inhibitors (ARNI), and beta-blockers) due to hypotension or renal dysfunction<br>2. ACC/AHA Stage D refractory HF (including having received or currently receiving pharmacologic circulatory support with inotropes)<br>3. Subjects with history of recurrent pulmonary embolism ( ≥2 episodes within 5 years prior to Screening Visit) and/or deep vein thrombosis (< 3 month prior to Screening Visit)<br>4. Subjects who have had a major cardiovascular (CV) event (e.g., myocardial infarction, stroke) within 3 months of the Screening Visit<br>5. Unrepaired severe valvular disease<br>6. Subjects with significant congenital heart disease that has not been repaired and would prevent implantation of the Cordella PA Sensor or mechanical/tissue right heart valve(s)<br>7. Subjects with known coagulation disorders<br>8. Subjects with a hypersensitivity or allergy to platelet aggregation inhibitors including aspirin, clopidogrel, prasugrel, and ticagrelor; or patients unable to take dual antiplatelet or anticoagulants for one-month post implant<br>9. Known history of life threatening allergy to contrast dye<br>10. Subjects whereby RHC is contraindicated<br>11. Subjects with an active infection at the Cordella PA Sensor Implant Visit<br>12. Subjects with a Glomerular Filtration Rate (GFR) <25 ml/min or who are on chronic renal dialysis<br>13. Implanted with Cardiac Resynchronization Therapy (CRT)-Pacemaker (CRT-P) or CRT-Defibrillator (CRT-D) for less than 90 days prior to screening visit<br>14. Received or are likely to receive an advanced therapy (e.g., mechanical circulatory support or lung or heart transplant) in the next 12 months<br>15. Subjects who are pregnant or breastfeeding<br>16. Subjects who are unwilling or deemed by the Investigator to be unwilling to comply with the study protocol, or subjects with a history of non-compliance<br>17. Severe illness, other than heart disease, which would limit survival to |

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| | <1 year<br>18. Subjects whose clinical condition, in the opinion of the Investigator, makes them an unsuitable candidate for the study<br>19. Subjects enrolled in another investigational trial with an active treatment arm<br>20. Subject who is in custody by order of an authority or a court of law |

## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACC | American College of Cardiology |
| ACE-I | Angiotensin Converting Enzyme-Inhibitors |
| ADE | Adverse Device Event |
| AE | Adverse Event |
| AAHFN | American Association of Heart Failure Nurses |
| AHA | American Heart Association |
| ALT | Alanine Aminotransferase |
| ARB | Angiotensin Receptor Blockers |
| ARNI | Angiotensin-Neprilysin Inhibitors |
| AST | Aspartate Aminotransferase |
| AV | Atrioventricular Block |
| BARC | Bleeding Academic Research Consortium |
| BB | Beta Blocker |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| BUN | Blood Urea Nitrogen |
| CABG | Coronary Artery Bypass Grafting |
| CalEQ | Cordella™ Calibration Equipment |
| CEC | Clinical Events Committee |
| CDAP | CorPASS Data Analysis Platform |
| CFR | Code of Federal Regulations |
| Cordella System | Cordella™ Heart Failure System |
| CI | Cardiac Index |
| CIP | Clinical Investigational Plan |
| CK-MB | Creatinine Kinase-MB (isoenzymes CKM and CKB) |
| cm | Centimeters |
| CO | Cardiac Output |
| CorPASS | Cordella™ Pulmonary Artery Sensor System |
| CPX | Cardiopulmonary Exercise Testing |
| CRO | Contract Research Organization |
| CRP | C- Reactive Protein |
| CRT | Cardiac Resynchronization Therapy |
| CV | Cardiovascular |
| DAOH | Days Alive and Out of Hospital |
| DD | Device Deficiencies |
| dl | Deciliter |

| Abbreviation | Definition |
|---|---|
| DSRC | Device System Related Complication |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ED | Emergency Department |
| EDC | Electronic Data Capture |
| ESC | European Society of Cardiology |
| EU | European Union |
| FDA | Food and Drug Administration |
| FIH | First in Human |
| GCP | Good Clinical Practice |
| GDMT | Guideline Directed Medical Therapy |
| GFR | Glomerular Filtration Rate |
| HCP | Health Care Provider |
| HF | Heart Failure |
| HFH | Heart Failure Hospitalizations |
| HfpEF | Heart Failure with preserved Ejection Fraction |
| HfrEF | Heart Failure with reduced Ejection Fraction |
| HR | Heart Rate |
| ICD | Internal Cardiac Defibrillator |
| ICF | Informed Consent Form |
| ICH/GCP | International Committee for Harmonization for Good Clinical Practices |
| IEC | International Electrotechnical Commission |
| IEC | Independent Ethics Committee |
| IFU | Instructions for Use |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISO | International Organization of Standardization |
| ITT | Intent to Treat |
| IV | Intravenous |
| KCCQ | Kansas City Cardiomyopathy Questionnaire |
| kg | Kilogram |
| l | Liter |
| ITT | Intent To Treat |
| LBBB | Left Bundle Branch Block |
| LDH | Lactate Dehydrogenase |
| LVEDD | Left Ventricular End Diastolic Diameter |
| LVEF | Left Ventricular Ejection Fraction |

| Abbreviation | Definition |
|---|---|
| m | Meter |
| MDCG | Medical Device Coordination Group (Europe) |
| MDR | Medical Device Regulations (Europe) |
| MEMS | Microelectromechanical Systems |
| mg | Milligram |
| MI | Myocardial Infraction |
| mITT | modified Intent to Treat |
| mL | Milliliter |
| mmol | Millimole |
| MRA | Mineralocorticoid Receptor Antagonists |
| MRI | Magnetic Resonance Imaging |
| mRS | Modified Rankin Scale |
| NP | Nurse Practitioner |
| NT- Pro BNP | N-terminal pro B-type Natriuretic Peptide |
| NYHA | New York Heart Association |
| PA | Physician Assistant |
| PA | Pulmonary Artery |
| dPAP | Pulmonary Artery Pressure – Diastolic |
| mPAP | Pulmonary Artery Pressure – Mean |
| PAP | Pulmonary Artery Pressure |
| PAPGHFM | PAP Guided Heart Failure Management |
| sPAP | Pulmonary Artery Pressure – Systolic |
| PCI | Percutaneous Coronary Intervention |
| PCWP | Pulmonary Capillary Wedge Pressure |
| PG | Performance Goal |
| pH | Potential of Hydrogen |
| PMA | Pre -Market Approval |
| PMP | myCordella™ Patient Management Portal |
| PP | Per protocol |
| PTT | Partial Thromboplastin Time |
| RAP | Right Atrial Pressure |
| RBC | Red Blood Cell |
| RCT | Randomized Controlled Trial |
| RGA | Return Goods Authorization |
| RHC | Right Heart Catheterization |
| RIM | Reader Integration Module |
| RN | Registered Nurse |

| Abbreviation | Definition |
|---|---|
| RVP | Right Ventricular Pressure |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SEV | Site Evaluation Visit |
| SGOT | Serum Glutamic Oxaloacetic Transaminase |
| SGPT | Serum Glutamic Pyruvic Transaminase |
| SpO2 | Blood Oxygen Saturation |
| UADE | Unanticipated Adverse Device Effect |
| URL | Upper Range Limit |
| USADE | Unanticipated Serious Adverse Device Effect |
| US | United States |

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# 1 BACKGROUND INFORMATION

## 1.1 Introduction

Heart failure (HF) is a major public health problem that affects over 23 million people worldwide with approximately 2 million new cases diagnosed each year.[1] HF is a complex clinical syndrome in which the ventricle's ability to fill or eject blood is impaired, affecting delivery of oxygen- and nutrient-rich blood throughout the body.[2] The body's compensation mechanisms in the presence of HF include enlargement of the heart, a faster heart rate (HR), narrowing of blood vessels to maintain blood pressure (BP), and diversion of blood away from other vital tissues and organs. While these compensation mechanisms may decrease HF symptoms, their effects are only temporary and eventually, the heart fails to keep up with the body's demands. Heart failure is chronic, worsens over time, and is characterized by acute exacerbations.[1] These periodic exacerbations require treatment intensification most often in the hospital setting and are the single most frequent cause of hospitalization in persons aged ≥65 years.[1]

After the diagnosis of HF, survival estimates are 50% and 10% at 5 and 10 years, respectively,[3-5] and left ventricular dysfunction is associated with an increase in the risk of sudden death.[6] There is no cure for HF, but treatment plan options consist of lifestyle changes, medications, implantable cardiac devices, and surgical procedures including heart transplants. Treatment goals for HF include targeting the underlying cause of the condition, reducing clinical symptoms and improving the patient's quality of life, and preserving heart function.

HF is associated with significant mortality, morbidity, and healthcare expenditures affecting patients, their families, care providers, and payers. The incidence of HF is on the rise and healthcare systems are grappling with the persistent burden of HF. Nearly 1 million hospitalizations for HF occur each year,[1] and readmission rates are frequent.

In 2012, total cost for HF was estimated to be $30.7 billion. Of this total, 68% was attributable to direct medical costs.[9] Projections show that by 2030, the total cost of HF will increase almost 127% to $69.7 billion from 2012. This equals ≈$244 for every US adult.[10]

Entire economic systems are impacted due to the aging global population, high cost of care, and limitations of existing solutions for HF [8].

## 1.2 Pulmonary Artery Pressure (PAP)

Given the many challenges of HF, traditional HF management must be reevaluated to include continuous physiologic monitoring, proactive clinical decisions prior to development of symptoms, reduced hospital readmission rates, and improved quality of life. Hemodynamics, and PAP, have been shown to be critical measurements in determining early signs of worsening HF.[11] The precursor to clinically apparent congestion is an observed increase in PAP. In patients with HF, as the blood pressure inside the heart and lungs increases, Cardiac Output (CO) decreases. The decrease in CO results in less oxygenated blood being pumped throughout the body which induces compensatory mechanisms in the body. Long-term hypo perfusion ultimately creates damage to vital organs and further exacerbates the deterioration of heart function. Eventually, the high levels of heart and lung pressures result in a buildup of fluid in the heart or the lungs (hemodynamic and/or pulmonary congestion) as well as peripheral edema. The majority of HF patients are hospitalized with signs and symptoms of fluid overload and congestion.

Elevations in PAP as well as other hemodynamic measurements, which serve as surrogate indicators of PAP, are identified in the literature as associated with worse outcomes in HF patients and as predictors of adverse event outcomes (i.e., heart failure hospitalizations (HFH) and death). For example, pulmonary artery capacitance was found to be a strong independent predictor of mortality,[12] pulmonary artery diastolic pressure, independent of other covariates, was a significant predictor of mortality in chronic HF patients,[13] and a higher systolic PAP was independently associated with clinical status and outcomes of HF patients.[14]

Secondary pulmonary hypertension is common among HF patients. Studies have reported secondary pulmonary hypertension as an independent predictor of worse outcomes. A strong association between secondary pulmonary hypertension and an increased risk of mortality was found in several studies.[14-19] In addition, HF patients with severe secondary pulmonary hypertension were at an increased risk of recurrent HFHs.[15]

Direct PAP has been conventionally obtained via a RHC procedure in which a catheter inserted through a vein in the patient's neck or groin is advanced to the pulmonary artery under fluoroscopic guidance. The complications associated with this invasive procedure limit its use as a long-term monitoring tool in HF patients. In addition, there are discomforts to the patient associated with this procedure, and possible risks of a RHC include bruising and excessive bleeding at the catheter insertion site, blood clots, damage to the vein, and cardiac arrhythmias or embolisms.

Parallel to studies presenting the association between PAP and clinical outcomes, the evidence supporting the approach to patient treatment based on monitoring changes in PAP is also growing. Hemodynamic monitoring of HF patients utilizes PAP data obtained from implantable sensors.

The first PAP sensor, the CardioMEMS™ HF System, received CE Mark in 2010 followed by Premarket Approval by the U.S. Food and Drug Administration (FDA) in 2014. This system is an ambulatory PAP monitoring system in which a small PA sensor is permanently implanted in the pulmonary artery via a RHC procedure and provides PAP data on demand. This system allows for routine PAP monitoring and provides an alternative to repeated RHC procedures to monitor PAP.

With this recent technology, daily measurement of PAP is the key metric for managing patients with HF. PAP monitoring is a recommended HF management tool added to the European Society of Cardiology (ESC) guidelines since 2016. Additionally, just recently, the elevated importance and recommendation of PAP guided HF management was incorporated into the 2021 Update to the ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure with Reduced Ejection[48].

Longitudinal monitoring of PAP can allow for early detection of volume changes before the onset of fluid overload leads to deterioration of health status and decompensation. PAP awareness will allow for early detection of and rapid, proactive medical intervention to prevent worsening HF, ultimately leading to better patient outcomes. Long term results from the CardioMEMS™ CHAMPION-HF study demonstrated a 37% reduction in HF hospitalizations,[19] and a 58% reduction in all-cause 30-day readmissions. In addition, the treatment group in this trial had a lower risk of death.[20] These results were confirmed in real-world post market settings. Desai reported that the cumulative incidence of HFH was significantly lower in the period following device implantation (hazard ratio [HR]: 0.55; 95% confidence interval [CI]: 0.49 to 0.61; $p < 0.001$).[21] Furthermore, PAP guided therapy has been shown to significantly improve outcomes in HF patients with comorbidities compared to the control group.[22] In a recent presentation, there was demonstrated a 30% reduction of mortality for the CardioMEMS treatment group compared to a control group.[23] Lastly, results presented from a Post Approval Study with ambulatory HF patients showed at 1-year post-implant that HFH was reduced by 58%, compared to 1-year pre-implant and HFH/death was decreased by 44% at 1-year post-implant, compared to 1-year pre-implant.[42] These results are independent on geography as the results of the European post-market study (MEMS-HF) [46] also showed similar reduction of HFH rates.

The most contemporary randomized CardioMEMS study published, the GUIDE-HF study,[51] evaluated PAP guided HF management in NYHA class patients II-IV and included patients that had elevated NT-Pro-BNP/BNP and/or a recent HFH. Unfortunately, the study results were impacted by the COVID-19 pandemic (28.3% of follow up conducted during the pandemic). Consequently, the overall study endpoint (12 months HFH/mortality) was not met but the prespecified pre-COVID analysis showed a significant reduction (28%) in the treatment arm compared to the control arm for the combined endpoint of HFH/mortality. Importantly, NYHA class II and II combined, showed a significant reduction of 17% in HFH (0.525 tx vs. 0.633 ctl, p=0.050) in the overall analysis.

Abundant evidence correlates long-term elevations in PAP with worse clinical outcomes related to HF. Still more recent evidence demonstrates the immense value daily home PAP readings add to chronic HF management. The field will require increasingly advanced diagnostic systems to safely, reliably, and efficiently deliver PAP data to clinical managers of HF, laying the foundation for a new era in the treatment of this ubiquitous and deadly pathology.

The CorPASS is a second-generation PAP monitoring device and, as a part of the Cordella™ Heart Failure System, will allow for a well-rounded and proactive approach to improve HF patient management for the 21st century.

## 1.3 Trial Rationale

A PAP sensor is a diagnostic medical device with the sole purpose of providing real-time accurate pulmonary artery pressure (PAP) values when activated. A PAP sensor does not provide a direct therapeutic effect (as therapeutic medical devices do); however, the information it does provide, namely near real-time PAP, has important clinical implications. It is well established that increased PAP is a predictor for worse clinical outcomes in HF patients; thus, ongoing monitoring and consequently managing abnormal PAP is an important goal in guideline-directed medical therapy (GDMT). Increasing PAP is an early "warning sign" before any other clinical symptoms become apparent and if left untreated will likely lead to HF decompensation and rehospitalization. Rehospitalization in HF patients is a well-known clinical concern, and a large body of literature has described the HFH readmission rates and associated negative patient impact.

**Current landscape of Pulmonary Artery Pressure Guided HF management: Consistent, robust evidence of safety and effectiveness supports adoption in clinical practice**

Since PROACTIVE-HF IDE study (NCT04089059) submission and approval, evidence-based data supporting effectiveness of Pulmonary Artery Pressure (PAP) guided HF management has grown significantly and continues to build. To-date, more than 20,000 CardioMEMS devices have been implanted demonstrating an excellent safety profile for PA sensors and improving outcomes for patients.[19,21,24,44-47] The CardioMEMS post-approval studies, PAS[44] (N=1200) and MEMS-HF[46] (N=234), both published in 2020, further confirmed that PAP guided HF management was associated with low adverse events, lower PA pressures, and reduced rates of heart failure hospitalization (HFH) & all-cause hospitalization in HF patients with NYHA class III. To date, all published CardioMEMS studies (with more than 4,000 study subjects), have consistently demonstrated a clinically meaningful benefit for patients treated with PAP guided HF management. Of note, the observed clinical benefit following PA sensor implantation was sustained in more recent contemporary CardioMEMS studies,[44,46,47]despite leveraging newer HF drugs such as Angiotensin Receptor-Neprilysin Inhibitors (ARNi).

The publication of these study results has materially impacted clinical practice, as physicians have become significantly more convinced of the clinical benefits of PAP guided HF management over the last few years. The effect of the increasing physician acceptance of PAP guided HF management can be seen by the removal of negative coverage policies of Medicare Administrative Contractors Novitas and First Coast in July 2020 [50] resulting now in nation-wide Medicare reimbursement for PA sensor technology.

Further, the elevated importance and recommendation of PAP guided HF management was incorporated into the 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure with Reduced Ejection. [48] It was pointed out that in "*well-selected patients with recurrent congestion,*

*this highly specialized monitoring strategy may guide therapeutic decision making*" and ambulatory pulmonary artery pressure monitoring was incorporated in one of the guiding HF management principles: "*diligent measurement of volume status will reduce patient symptoms*".

The increasing acceptance of the clinical benefit of PAP guided HF management following the growing scientific evidence and acceptance by a variety of stakeholders has impacted enrollment in PROACTIVE-HF more than anticipated during the design of the study in late 2018. A randomized study design may still be possible from an academic standpoint, but in practice is growing exceedingly difficult and practically impossible. With increasing acceptance and utilization of PAP guided HF management, several clinicians have declined the study or refer some patients to commercial use of CardioMEMS, as they are hesitant to refer a patient to PROACTIVE-HF enrollment that may delay utilization of PAP guided HF management in the control arm when there is an approved PAP guided HF management (CardioMEMS) available to benefit the patient immediately outside of the study. This impact to enrollment has been further exacerbated by the COVID-19 pandemic, as clinicians and patients have been hesitant to accept the elevated risks of exposure to COVID-19 for a procedure that may not lead to benefit to a patient in the control arm for 12 months (at the time of cross-over to active treatment). A number of potential eligible study patients decided not to participate in PROACTIVE-HF as they were not willing to wait potentially for one year for therapy if the alternative commercial device is readily available. This issue may also lead to selection bias, as physicians may offer the study only to patients who they think can "wait" for PAP guided HF management, and therefore they are willing to randomize.

Taking the above-described recent advancements of PAP guided HF management into account and the subsequent negative impact on trial enrollment, an Open- Label Single Arm study design, will eliminate these concerns and allows all study subject prompt access to PAPGHFM treatment. A single arm study is well suited to show comparable effectiveness performance to the commercially available device and thus, will provide reasonable assurance that the device is effective for use in the intended population.

**Single arm PROACTIVE -HF rationale**

As for any (diagnostic) medical device, safety and effectiveness must be proven to attain PMA approval. In evaluating the potential for a single-arm study, Endotronix evaluated whether there was adequate data in the published literature for a sufficiently similar device and study population to support establishment of an appropriate performance goal. With respect to device similarity, both the CardioMEMS PA sensor and Cordella PA sensor are very similar in their diagnostic device properties. Both devices have the same mechanism of action, namely MEMS technology measuring pulmonary artery pressure, and both devices display PA pressure trends to the clinicians in a patient management portal. Both devices are implanted in the pulmonary artery during a right heart catheterization. Both devices target the same NYHA class III patient population to be treated. For

both devices, improved clinical outcomes (clinical effectiveness) relies heavily on the appropriate clinician's interpretation and consequently pharmacological treatment based on the displayed PA pressure values. Thus, the clinical outcomes reported from CardioMEMS studies are well suited to be used as a comparison group to establish a Performance Goal (PG) for the evaluation of the Cordella PA sensor effectiveness.

The safety profile of CardioMEMS and Cordella PA sensor [49] have been both excellent to date and there has not been any concern (with device or system related complications (DSRC) less than 2%)[19,24,44-47,49]. Nonetheless, safety will be evaluated in the single arm study as a primary endpoint.

### 1.4 Intended Use & Indications for Use

The Cordella PA Sensor System is intended to measure, record, and transmit pulmonary artery pressure data from NYHA Class III heart failure patients at home to clinicians for assessment and patient-centered heart failure management, with the goal of reducing heart failure hospitalizations.

# 2 INVESTIGATIONAL DEVICE: CORDELLA™ PA SENSOR SYSTEM

## 2.1 Generalized System Operation and Subsystem Description

The system consists of the following components:

- Cordella PA Sensor
- Cordella Delivery System
- myCordella Patient Reader and Dock
- Cordella Calibration Equipment (CalEQ)
- myCordella Tablet* (running the myCordella Patient App)
- Cordella Data Analysis Platform (CDAP)

The Cordella PA Sensor System, schematized in Figure 1 and described in the paragraphs that follow, comprises eight subsystems that operate together to take daily PA Pressure (PAP) readings at a patient's home and transmit the results to a care provider for evaluation.

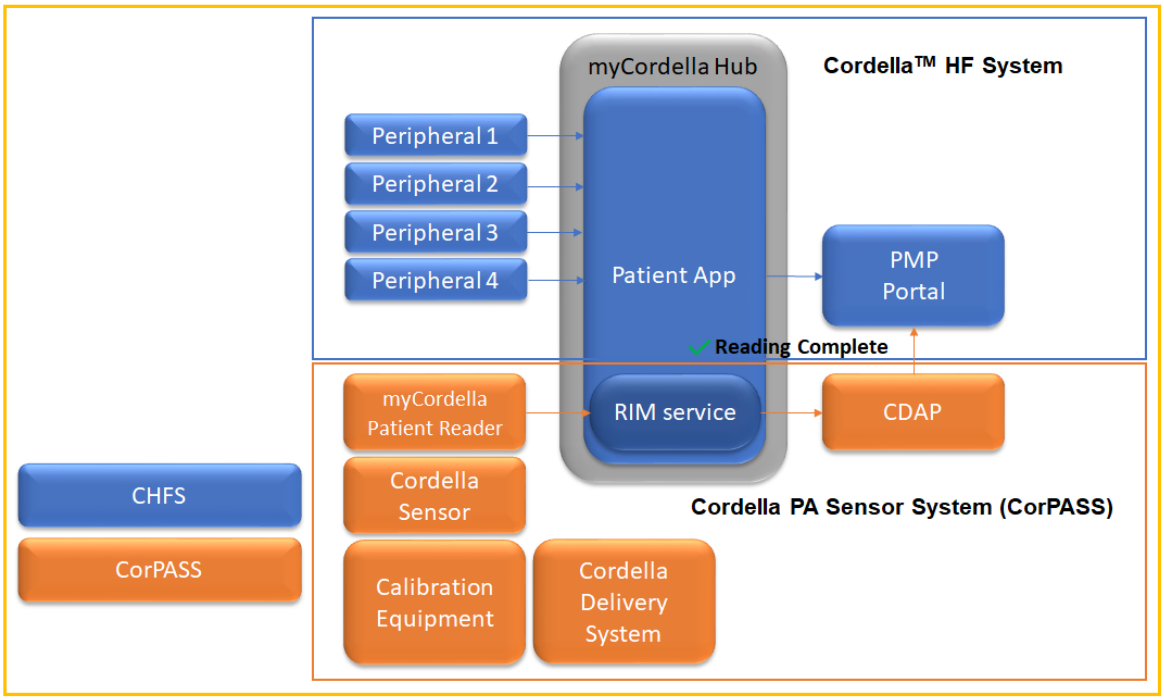


***Figure 1: Functional Block Diagram of the CorPASS***

The heart of the CorPASS is an active implantable medical device, the ***Cordella PA Sensor***, a permanent implant that resides inside a branch of the patient's pulmonary artery. The wireless Sensor, illustrated in Figure 2, has a glass body approximately 20 x 4 x 2 mm in size. Nitinol anchors extend from either end to hold the Sensor body in place against a wall of the PA, such that the sensitive surface of the Sensor body faces away from the vessel wall and into the bloodstream. The Sensor resonates electrically, changing its resonance frequency in proportion to the PAP. The Sensor is shipped sterile to a hospital pre-attached to the distal end of the ***Cordella Delivery System***, a custom catheter depicted in Figure 3. Attachment wires in the Catheter hold the Sensor's nitinol anchors flat during vascular ingress. A physician uses the Delivery Catheter to place the Sensor in a pre-defined location in the PA, via percutaneous venous access. Once placed, the physician uses the Delivery Catheter handle to retract the attachment wires and release the Sensor. At this point, the Sensor's nitinol anchors unfold and hold the device in place for the lifetime of the patient. The Delivery System is removed and discarded. The minimally invasive implant procedure is designed to resemble existing Right Heart Catheterization (RHC) procedures, and to be safe, simple, and brief.

***Figure 2: Cordella PA Sensor***


***Figure 3: Cordella Delivery System***

The ***myCordella Reader*** (Figure 4) is a handheld wireless device used for obtaining Sensor readings. Each day at home the patient acquires a PAP reading by holding their myCordella Reader against their chest. During the reading, the Reader powers the Sensor wirelessly and obtains the pressure reading by measuring the frequency transduced from the pressure on the Sensor. The Reader transmits data to the myCordella Tablet (part of Cordella System), where the RIM* service transmits the data to the ***Cordella Data Analysis Platform (CDAP)***, a web-based application that stores configuration and calibration data, processes raw data from the daily readings, and makes the final PA pressure data available to clinicians through the Cordella Patient Management Portal (PMP) (part of Cordella System). The myCordella Dock connects to a wall plug and recharges the Reader's battery. The entire home reading sequence is designed for patient convenience and is generally completed in less than one minute. The Reader remains docked at all other times, when the patIent is not actively taking a reading.


***Figure 4: Cordella Reader and Docking Station***

CDAP is a secure, cloud-based standalone app that collects and stores raw Reader data and processes it according to pre-defined algorithms to convert it into final-form PAP data. CDAP collects and stores data from the Reader's daily readings, Endotronix manufacturing (Sensor and Reader characterization data) and calibration equipment (CalEQ) (in-situ calibration coefficients measured at the time of implant, Reader serial number, Sensor serial number, and patient ID#). All data is fed into CDAP's processing engine to convert the Reader's raw data into final-form PAP data (systolic, diastolic, mean pressures and a waveform). CDAP sends the PAP data to the responsible care providers.

The ***Calibration Equipment (CalEq)*** supports the implantation procedure. CalEq facilitates the tracing of CorPASS component serial numbers to patient ID numbers, the calibration of the CorPASS to a reference pressure at the time of implantation, and the real time monitoring of PA Pressure.

The RIM* is a service within myCordella Patient App and has no user interface. The RIM service only transports the data. The myCordella Patient App is designed to operate on a commercially available tablet device running the Android operating system and connects to the internet via a cellular network and/or Wi-Fi.

The RIM service carries out the following functions:

- 'Listens' for Bluetooth messages from the Reader, indicating new raw data is ready for upload
- When requested by the Reader, receives the new raw data via Bluetooth
- Stores the raw data in local Tablet memory as a backup
- Uploads the new data to the Cordella Data Analysis Platform (CDAP), a secure, cloud-based standalone app that collects and stores raw Reader data, and processes it according to predefined algorithms to convert it into final-form PAP data
- Obtains an updated local date and time from the web server
- Transmits date and time to Reader, allowing it to update its internal Real Time Clock

* not a medical device

Figure 5 provides a functional illustration of the CDAP software. The blocks in this diagram represent CDAP functions, not necessarily architectural elements, data structures, or software modules. The arrows represent data flow between the functions. CDAP functionality can be partitioned into two major functional groups: a database, and a data processing computational engine. The database functions collect and store data from Readers. The processing function converts raw Reader data into final PAP data. Within each group, a number of interrelated subordinate functions exist.

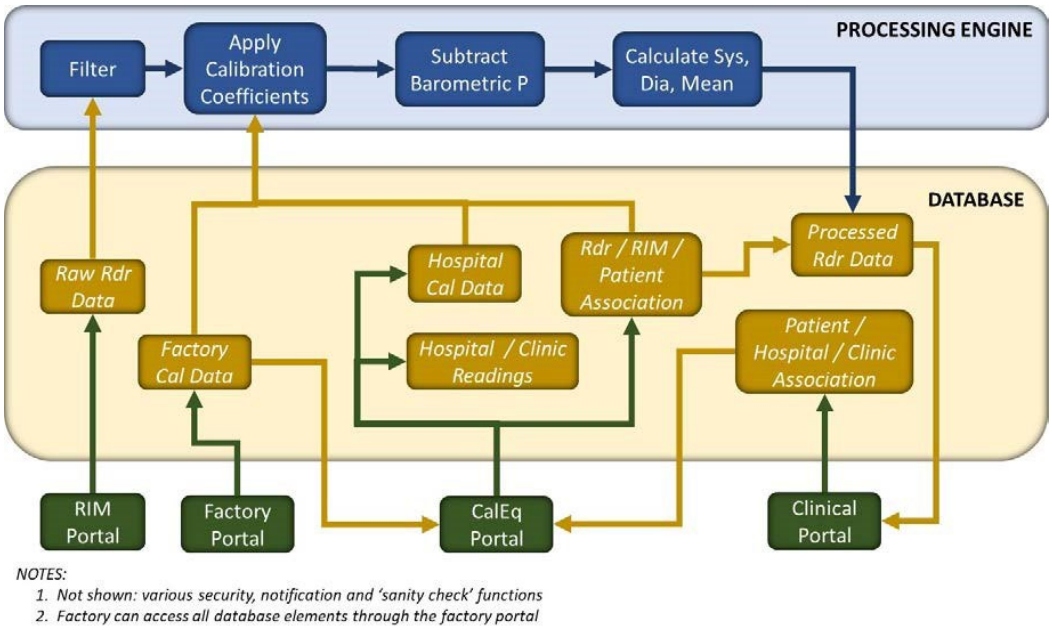


***Figure 5: Functional block diagram of the Cordella Data Analysis Platform (CDAP)***

Four (4) internet portals, shown in green at bottom, transfer data into and out of the CDAP:

1. The RIM portal (within CDAP) connects to all myCordella Patient Apps in the field, generally located in patients' homes. It receives raw data from daily readings. The database stores the raw data and transfers it to the algorithm for processing without performing an action on the data
2. The Factory portal connects to Endotronix's manufacturing facility, where authorized users (or automated test equipment) upload calibration data unique to each Reader and Implant. The CDAP database stores this data, which will be used in the processing algorithm to convert the raw data to calibrated PAP data. CDAP also downloads factory calibration data to the appropriate CalEq device for local processing
3. The CalEq portal communicates with all Calibration Equipment hardware in the field – generally located at implanting hospitals or care providers' clinics. CalEq uploads two types of data to the CDAP: readings taken at hospitals/clinics and final in-situ calibration coefficients measured at the time of implant. CalEq uploads the calibration coefficients it receives from its in-situ Cordella and reference readings. CalEq uploads the association between Reader serial number, Sensor serial number, and patient ID#, recorded at the time of implant, for storage. This association ensures that the correct factory and hospital coefficients are applied to the processing of each home reading
4. The Clinic Portal interfaces with the entity receiving the final processed output of each PAP reading – usually an app used by the patient's care provider (i.e., Cordella System Patient

Management Portal). Each reading contains an 18 second PAP waveform, as well as the systolic, diastolic, and mean values for that waveform. The Clinic portal connects to on-line apps accessible by staff at the clinics of care providers. These apps are clinical information systems which store and display the data, as well as allow for simple searches of past data. The Clinic portal's other function involves upload of patient / clinic / hospital association to a CDAP database.

The CDAP processing engine comprises five general steps:

1. Filtering raw data to reduce noise and outliers
2. Converting the raw frequency data to pressure data
3. Applying the factory and in-situ generated calibration coefficients
4. Subtracting the local ambient pressure (measured by an on-board sensor in the Reader at time of reading and uploaded via RIM)
5. Determine systolic, diastolic, and mean pressures for the reading

Not shown in Figure 6 are various functions supporting cybersecurity, patient privacy, diagnostics, and 'sanity checks' on incoming data. Additionally, CDAP may send notifications to the Clinical portal regarding missing readings, failed reader self-tests, end-of-life for reader, etc. CDAP may also record diagnostic Reader data for statistical analysis by Endotronix, to evaluate system performance.

The CorPASS and each of its subsystems only support diagnostic functions. Their purpose is to provide clinicians with accurate PAP data from patients' daily home readings. They do not recommend therapy or any other clinical action, nor do they draw conclusions from the data.

## 2.2 Use of CorPASS with the Commercially Available Endotronix Cordella Heart Failure System (Cordella System) Product

The CorPASS is a standalone system. For use in the proposed clinical trial, Endotronix intends to make it available to cardiologists in conjunction with Endotronix's Cordella System. The Cordella System collects, records, and transmits physiologic data and communications from the patient at home to clinician(s) for assessment, patient communication, and patient-centered heart failure management. The system consists of the following components:

- The **myCordella™ Patient Management Platform** (PMP) A clinic-facing, web-based database and communication portal, serving as an electronic patient record system for use by a clinician. The streamlined PMP enables clinicians to:
    - review the data generated from each patient's home use of the Cordella System Medical Devices

  - record notes and actions taken during the care of the patient
  - communicate with the patient and other clinicians regarding the patient's health status
  - access externally developed documentation (published referenced guides, etc.)

- The **myCordella™ Tablet** is a commercial, off-the-shelf mobile platform on which the myCordella Patient App resides. The Patient App (see below) uses general platform functions, such as Bluetooth connectivity, internet connectivity, a touchscreen, audio output, and an operating system. This is a tablet device running the Android operating system. The tablet hardware and software (operating system and standard drivers) are intended by their manufacturer for general purposes, and not specifically intended to be used for a medical purpose.

- **myCordella Patient App:** A standalone application that resides on the Tablet. This patient-facing app:
  - Reminds the patient at home, daily, to operate the Cordella System Medical Devices (see below)
  - Daily asks the patient several simple health-related questions using the Tablet's touchscreen
  - Receives wireless (Bluetooth) output data from the Medical Devices
  - Securely transmits the Medical Devices' generated data, and the patient's responses to the health-related questions, to the myCordella Patient Management Portal
  - Allows the patient to review his/her past data from the Medical Devices, as well as past question responses
  - Allows the patient to communicate with health care providers, for example by email, text, phone, or videophone
- **Three (3) Original Equipment Manufacturer (OEM) Medical Devices:** Commercially available medical devices that patients use at home to collect data (weight, BP, HR and SpO2). Each Medical Device is a standalone, approved device. Each retains its OEM labeling, packaging, and function. The Patient App prompts the patient to use each Device according to the Device's original Instruction for Use (IFU). After use, each Device uploads its output data to the myCordella Patient App via Bluetooth.

The CorPASS i' designed to operate with the Cordella System. The two systems "touch" one another at two points:

- The CorPASS Reader will interface with RIM service on the myCordella™ Tablet to send data from the Reader and the RIM service in turn will transport the data to CDAP.

- The CorPASS CDAP will transfer data to/from the myCordella™ Patient Management Portal, a cloud-based app that combines a simple database with a User Interface for use by clinicians. The connection point for the latter is the 'Clinic Portal' shown in Figure 6.

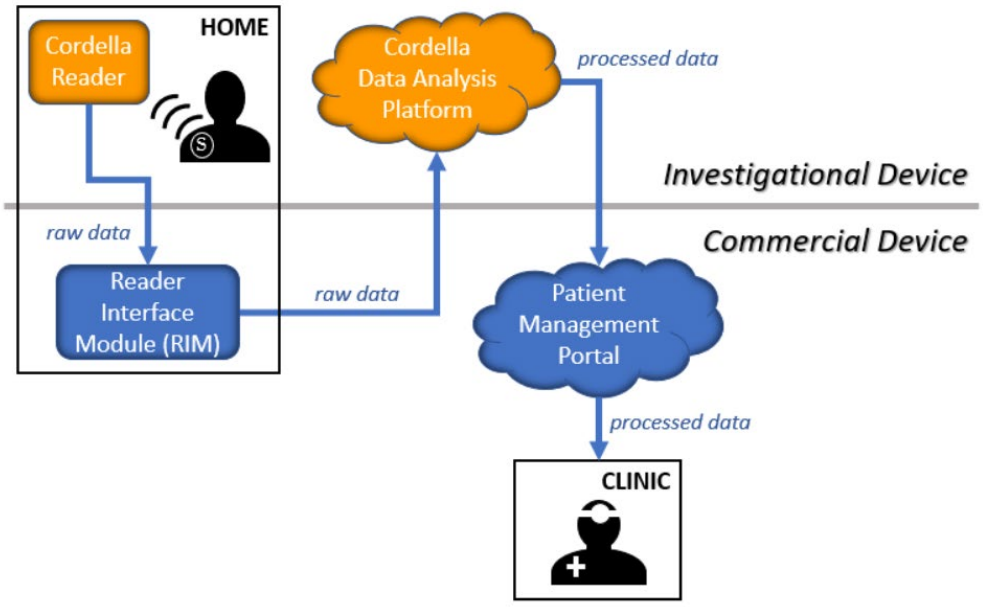


***Figure 6: Interaction between CorPASS and Cordella System***

## 2.3 Control Algorithm

The myCordella PMP will be able to calculate simple trends in the mean PA pressure (mPAP) of a patient and identify the time-points when treatment needs to be adjusted for each patient based on a defined ruleset (Appendix 14.5 Guidelines for managing HF using Pulmonary Artery Pressures). The goal for all the patients (HFrEF and HFpEF) is to adjust and maintain their mPAP within the normal range of 10-25 mmHg, adjusted for the seating position, which will be achieved at increments of 10mmHg until desired mPAP goal has been reached. After each patient receives the sensor their baseline pressure will be defined a few days after the implant procedure based on the initial home readings. The myCordella PMP will notify the physician to modify treatment based on the 7-day moving average trends and thresholds defined in the Guidelines in Appendix 14.5.

## 2.4 Device Accountability

The Cordella PA Sensor Systems are investigational devices. The Investigator is responsible for ensuring that only study participants utilize the device, and all Endotronix Cordella PA Sensor Systems must be stored in a location that is accessible only by authorized personnel. The disposition of all

Cordella PA Sensor System components must be maintained by serial number or lot number and must be accounted for in the Device Accountability Log. All unused product will be returned to Endotronix.

All components of the Cordella PA Sensor System must be kept by the Investigator for future Endotronix inspection including used catheter-based delivery systems after each Cordella PA Sensor implant procedure. Endotronix will provide the Investigator instructions to pack and ship the used delivery systems as biohazards.

# 3 PRECLINICAL AND CLINICAL STUDIES OF THE CORDELLA PA SENSOR SYSTEM

## 3.1 Pre-clinical Studies of the Cordella™ PA Sensor System

The Cordella PA Sensor System consisting of the Cordella™ Delivery System, Cordella PA Sensor, myCordella™ Patient Reader, CalEq and CDAP have been evaluated in bench, acute and chronic preclinical testing and found to meet performance specifications for clinical use. The below table outlines a summary of the Pre-Clinical Verification testing:

| **Pre-Clinical Verification Testing** | |
|---|---|
| **System Level Testing** | |
| Biocompatibility testing | Pass |
| In-vivo animal studies (Acute and Chronic) | Pass |
| Sterilization Validation | Pass |
| **Implantable Sensor** | |
| Sensor Bench Performance for overall safety<br>• Simulated Conditions<br>• Mechanical / Electrical Accelerated Lifecycle<br>• Structural Integrity and functionality | Pass |
| Magnet Resonance Imaging (MRI) Safety Evaluation and Performance | Pass |
| Ultrasound testing | Pass |
| Defibrillator-safe Testing | Pass |
| Safety testing per ISO 14708-1:2014 | Pass |
| **Delivery System** | |
| Visual and Dimensional Inspection | Pass |
| Simulated Use testing | Pass |
| Resistance to Torsional Forces | Pass |
| Pressure Leak Test | Pass |
| Tensile Strength | Pass |
| Compatibility with ISO 594 (Fluid-Communicating Port) | Pass |
| Corrosion resistance | Pass |

| | |
|---|---|
| **Reader and Docking Station** | |
| Essential Performance and Safety | Pass |
| Safety with Pacemaker / Internal Cardiac Defibrillator (ICD) | Pass |
| Safety in accordance with International Electrotechnical Commission (IEC) 60601-1 (General Safety) and IEC 60601-11 (Home Use) | Pass |
| Electromagnetic Compatibility per IEC 60601-1-2 | Pass |
| Shock and Vibration per ISTA-2A | Pass |
| Repeatability and Accuracy over time | Pass |
| Power and battery | Pass |
| Software Verification / Validation | Pass |
| **Calibration Equipment** | |
| Unit Level Testing | Pass |
| Integration testing | Pass |
| System Level Testing | Pass |
| Safety in accordance with IEC 60601-1 (General Safety) | Pass |
| **CDAP** | |
| Integration testing | Pass |
| System Level Testing | Pass |
| **Packaging** | |
| Pouch Integrity | Pass |

### 3.2 Device Set Up and Maintenance

The subjects will be trained at the clinical site by a trained Clinical Site Delegate or Endotronix representatives on the set up and use of the Cordella System during the Screening/ Enrollment Visit and for the Cordella PA Sensor System at the Implant Visit. Visits to the subject's home by an Endotronix Representative may be required throughout the study to provide troubleshooting, servicing, and maintenance of the system.

### 3.3 Clinical Studies of the Cordella PA Sensor System

In the US, no prior clinical studies have been performed to evaluate the Cordella™ Heart Failure system with the Cordella PA Sensor System.

In Europe, Endotronix has currently two studies ongoing: 1. SIRONA (NCT03375710), a First in Human (FIH) study and 2. SIRONA 2 (NCT04012944) study, our CE mark study.

1. SIRONA 1: The FIH study is ongoing at 2 centers in Europe. Overall, 15 patients have been implanted. The primary safety endpoint is freedom from adverse events associated with the use of the Cordella™ Heart Failure System through 30 days post index procedure. The primary efficacy endpoint is measurement of the correlation of Cordella PA Sensor pressure measurements compared with pressure measurements (Swan Ganz) obtained by standard RHC at 90-day post index procedure. In this FIH study, the patients use the Cordella PA Sensor System in combination with the Cordella™ HF System. All patients were successfully implanted with the Cordella PA Sensor without device system related complication or sensor failure. The primary efficacy endpoint of a mean PAP was met in all patients with a cohort difference of 2.7 mmHg (Cordella PA Sensor 22.5 mmHg +/-11.8, Swan-Ganz 25.2 mmHg +/8.5). Patient adherence to daily measurement and transmission of vital signs was 99% and Cordella PA Sensor readings compliance was 99% [45]. This study is ongoing and in long- term follow up, to date no safety or efficacy concerns have been reported.
2. SIRONA 2: This CE-Mark study is ongoing in 8 European centers in Europe (Belgium, Ireland, Germany). SIRONA 2 is a prospective, multi-center, open-label, single-arm CE-Mark trial to assess device safety and efficacy of the Cordella PA Sensor System in up to 85 NYHA Class III HF patients who received the Cordella PA Sensor implant. Enrollment is finalized and the PA sensor was successfully implanted in 70 patients. The primary efficacy endpoint was the accuracy of PA sensor mean PAP measurements, compared with fluid-filled catheter mean PAP measurements obtained by standard RHC at 90 days post-implant, assessed in all patients with a successful implant. The primary safety endpoint was freedom from adverse events associated with use of the Cordella PA Sensor System through 30 days post-implant, assessed in all patients who entered the Cath Lab for a PA sensor implant. Equivalence between the PA sensor and RHC for mean PA pressures was within the equivalence bounds of - 4.0 to 4.0 mmHg (mean PAP: 0.0 to 2.9 mmHg, P = 0.003), therefore the primary efficacy endpoint was met. The device safety profile was excellent with 98.6% freedom from Device System Related Complications, defined as invasive treatment, device explant or death and with no pressure sensor failures. This study is ongoing and in long- term follow up, to date no safety or efficacy concerns have been reported.

# 4 POTENTIAL RISKS AND BENEFITS

## 4.1 Potential Risks

There is extensive clinical experience with respect to right heart cardiac catheterization and interventional procedures, and it is expected that these acute procedural risks will not be significantly different with the Cordella PA Sensor System. Possible adverse events associated with cardiac catheterization and/or the implantation of the Cordella PA Sensor System may include, but are not limited to, the following:

- Allergic reaction
- Arrhythmias
- Bleeding complications (which may require transfusion)
- Cardiac arrest
- Chest pain
- Death
- Device embolization/migration
- Device explant
- Emergent or urgent cardiac, vascular, and/ or other surgery necessitated by the device or implant procedure (e.g., coronary sinus lead revision)
- Endocarditis or device infection
- Entry site complications (e.g., hematoma, dissection)
- Fracture of a component of the device/system that may or may not lead to serious injury or surgical intervention
- Gastrointestinal bleed (antiplatelet therapy)
- Hemoptysis
- Hypo or hypertension
- Infection or fever
- Peripheral embolism/thrombus
- Pulmonary embolism/pulmonary occlusion
- Pseudoaneurysm of the vein
- Radiation exposure
- Reaction to contrast media/ medication
- Renal insufficiency or failure
- Respiratory distress or failure (breathing problems)
- Sepsis
- Valvular injury (tricuspid and/or pulmonary)
- Vascular complications (e.g., venous dissection, perforation, rupture, arteriovenous fistula)
- Vessel trauma which may require surgical repair

- Worsening heart failure

When used in accordance with the clinical protocol, risks associated with commercially available Cordella System are considered low. To ensure proper use of the myCordella™ Tablet and Peripherals, subjects will be trained in accordance with the manufacturer's instructions for use. Potential risks of the commercially available Cordella System include the following:

- Temporary arm discomfort/pressure from the blood pressure cuff
- Skin irritation or petechia at the site of the blood pressure cuff placement
- Loss of balance while standing on scale
- Inaccurate measurements or measurement errors

In addition, there may be unknown or unforeseen adverse effects due to the CorPASS investigational device. All effort will be made to minimize these risks by selecting investigators who are experienced and skilled in catheterization procedures, conducting appropriate training on the use of the device, clearly defining Inclusion/Exclusion criteria to ensure that only appropriate patients are enrolled, and by ensuring that the treatment and follow-up of the patient are consistent with current medical practices.

## 4.2 Potential Benefits

It is hoped that the information collected will provide the clinicians with a better understanding of the Cordella PA Sensor System as a potential solution for proactive HF management, early detection of fluid overload, and ultimately prevention of worsening HF symptoms. Studies of other similar devices (Abbott's CardioMEMS) have shown the benefit of monitoring PAP as it relates to reduction of HF hospitalizations[19,20,42].

The Cordella PA Sensor System and the CardioMEMS™ systems are substantially equivalent in their intended use, technological characteristics, and risk profiles.

The Cordella PA Sensor System is a further refinement in remote PAP monitoring technology and combines clinical benefits of remote PAP management (i.e., proactive continuous PAP monitoring/ management over time without ongoing RHC risks, increased life span with improved quality of life) with its own system-specific benefits.

Benefits of the Cordella PA Sensor System over the CardioMEMS include an optimized system design for improved PA sensor positioning and anchoring within the vessel, reduced system components size resulting in better ease of use for the patient, and increased system versatility to provide a more comprehensive picture of the patient's overall health status.

In addition to collecting PAP, the Cordella PA Sensor System interacts with the commercially available Cordella™ HF System which has an interactive platform that incorporates collection of clinical information including weight, BP, HR, SpO2and patient feedback as part of the data communicated to clinicians. This platform also facilitates direct communications between the patient and their clinicians, which enhances the exchange of relevant clinical information and patient-clinician interactions that are important during the HF management process.

Despite their similarities, the Cordella PA Sensor System is differentiated from the Abbott CardioMEMS product by several advantageous features. These potential benefits include:

**Implantation.** Like CardioMEMS™, the Cordella PA Sensor provides a custom catheter assembly, pre-fitted with a sensor, as well as a dedicated hospital-use reader unit to facilitate the process of initial calibration against a reference reading. But unlike CardioMEMS™, Cordella PA Sensor's nitinol anchors are designed to hold the Sensor in the same anatomical PA target location for every patient. Anatomical features in the PA common to all patients facilitate quick and reliable mapping of the location with nonquantitative angiography. The Cordella PA Sensor anchors hold the Sensor's body in a known position against the vessel wall, eliminating errors due to the sensor surface contacting a wall. Cordella PA Sensor's standard location is proximal and more deterministic than that of CardioMEMS, reducing risks associated with going too distal into smaller branches, such as vessel obstruction, clotting, vessel damage, or Sensor migration after implant. The Cordella PA Sensor catheter features a softer tip to reduce vessel damage risk. Further, the catheter provides a built-in port for connecting a fluid-filled reference catheter for calibration and contrast dye injection for mapping of the pulmonary tree under fluoroscopy, requiring fewer intraprocedural catheter exchanges than the CardioMEMS™. The 'one location for all patients' design frees Cordella™ implanters from complicated and sometimes intractable rule sets involving vessel sizes, branches, and angles deep in the PA. Finally, doctors and nurses in the implantation environment will benefit from the efficient workflow afforded by CorPASS's 'Calibration Equipment' device. CardioMEMS' pencil-and-paper based calibration procedure is replaced by automated entry, data integrity checks, and secure cloud-based servers for recording, uploading, authenticating, and storing essential configuration and calibration data. Automation contributes to ease of use and allows catheter lab staff to calibrate Cordella PA Sensors efficiently. It also reduces potential for human error in data association, data entry, authentication, and cybersecurity.

**Home Readings**. Both the Cordella PA System and CardioMEMS ™ require the implanted patient to make bodily contact with a 'Reader' device to take a daily 18-second PAP reading and upload it to a secure website for clinician access. Patented Cordella™ technology sharply differentiates the two user experiences. CardioMEMS' reader requires the patient to lie supine on a bulky mattress-like electronics unit, which must plug into wall power. The CardioMEMS™ patient must remain in the supine position until data is uploaded, which can take up to several minutes. The Cordella™ Reader,

in contrast, is handheld and cordless. The patient undocks it, holds it against his chest with one hand for 18 seconds while seated, and re-docks in response to an audio cue.

The highly portable CorPASS hardware allows the patient to travel away from home and still receive uninterrupted HF management. Its physical size facilitates packing and transport in a small travel bag. The CardioMEMS™ device ships with its own full-sized roller bag and requires a dedicated bed or sofa at the destination to set the device up. Cordella™'s inherent portability also facilitates bringing Readers to and from the patient's cardiology clinic for any needed replacement, additional training, or troubleshooting.

Finally, the handheld reader allows caregivers to instruct patients to take PAP measurements before, after, or during exercise (e.g., 6-minute walk test), if desired.

**Data-Driven Management.** The CardioMEMS™ system processes reader data (filtering, signal strength analysis, application of calibration coefficients, etc.) locally in each of its Reader units, only uploading the final result to the remote database. It relies on human operators to set up initial calibration data and associations manually in the reader during the implant procedure. Cordella™ readers only upload raw, unprocessed pressure data, along with data indicative of signal strength for each reading. Cordella™ data processing is all carried out automatically with carefully maintained and monitored software on a secure cloud server. Besides enhancing cybersecurity, this arrangement allows Endotronix to update and improve algorithm accuracy, and more closely monitor the system for functionality and re-process raw data using different methods for new applications.

As a 21st Century digital health product, CorPASS's data management architecture emphasizes flexibility and interoperability with the myriad of third-party Electronic Medical Record (EMR) management systems in use by clinics today, without compromising availability, integrity, or confidentiality of data. Unlike CardioMEMS™, whose data interface is limited to St Jude's legacy Merlin system, CorPASS features a relatively simple data i/o stream that will be amenable to direct integration with current and future EMR products, by establishment of simple APIs with target EMR systems as needed.

Although CorPASS can function as a standalone system, it is typically most effective when used with Endotronix's Cordella System a separate commercial product. The Cordella System furnishes implanted or non-implanted HF patients with simple noninvasive devices: a BP cuff, weight scale, and pulse oximeter. It also provides each patient with a tablet for aggregating Bluetooth data from these devices and uploading it to the secure PMP database. The tablet also transfers secure, private communications between patient and caregiver. The PMP provides the cardiology staff with an easy-to-use yet powerful tool that ensures efficient workflow during the patient management process. Unlike the numerous other telehealth systems on the market, Cordella System focuses exclusively on heart failure, and was designed specifically to optimize productive workflow for cardiology

practices. With Cordella System, a cardiologist can manage all HF patients, from any NYHA class, and readily identify those that would benefit from the addition of a Cordella PA System Sensor (typically NYHA Class III). The new Reader PA data seamlessly integrates with the PMP data structures already established for the patient. In this trial, the new CorPASS patient and patient's cardiologist's staff will typically already have experience in use of the Cordella System for at approximately one week prior to getting the Cordella PA Sensor implant – adding the CorPASS measurement to the daily reading routine will be an incremental change in behavior for both patient and clinician.

A flexible, yet powerful and robust telehealth system that focuses exclusively on Heart Failure, while offering the option to obtain critical PAP data for specific patients, is unique in the market. It represents a major step away from legacy or fragmented 'all purpose' data systems, and towards efficient yet comprehensive management of HF. The table below demonstrates perceived advantages of the CorPASS compared to the CardioMEMS system.

| | Cordella™ HF System<br>Endotronix | CardioMEMS™ System<br>Abbott/St. Jude | Endotronix Advantage |
|---|---|---|---|
| SENSOR |  |  | • Stable positioning in proximal RPA<br>• Less lumen area obstructed<br>• More proximal positioning may reduce incidence of distal vessel injury |
| DELIVERY SYSTEM |  |  | • More control, fewer exchanges<br>• Intra-operative visualization and pressure measurements via side port<br>• Softer distal tip, more proximal |
| PATIENT READER |  |  | • Portable, handheld reader<br>• Enables simple daily measurements in seated position<br>• Supine, sitting, standing, exercise hemodynamics possible |
| PATIENT MANAGEMENT |  |  | • Comprehensive system with PAP, vitals, labs, meds, & communication<br>• Manages all advanced HF patients within existing clinic workflow<br>• Supports complex CCM reimbursement |

***Figure 7: Comparison CorPASS and CardioMEMS***

# 5 STUDY OBJECTIVES AND ENDPOINTS

The objective of this IDE study is to demonstrate the safety and effectiveness of the Cordella PA Sensor System.

Safety will be measured as described in Section 5.2. Efficacy will be measured by the primary and secondary endpoints as described in Section 5.1. In addition, subjects enrolled in this trial will be monitored for safety and adverse events, for device failures, Health Status and functional status improvement.

## 5.1 Efficacy Endpoints

**Primary Efficacy Endpoint through 6 months post- implant):**

The primary efficacy endpoint is the 6 month incidence of HF related Hospitalizations or all-cause mortality.

**Secondary Efficacy endpoints include:**

1. Incidence of HF Hospitalizations or all-cause mortality at 12 months
2. Number of HF Hospitalizations at 6 and 12 months post-implant compared to the number of HF Hospitalizations in the 6 and 12 months prior to implant
3. Comparison of the number of HF Hospitalizations or Emergency Department/ Hospital Outpatient IV diuretic visits of Cohort #1 and Cohort #2+#3 at 6 and 12 month post implant
4. Change of NT-proBNP from Baseline through 6 and 12 months
5. Combined outcome of:
   a. First and recurrent HF Hospitalizations
   b. Emergency Department/ Hospital Outpatient IV diuretic visits
   c. all-cause mortality

   at 6 months, added together with equal weighting into a total number of events.
6. Heart failure hospitalization or Emergency Department / Hospital Outpatient IV diuretic visits at 6 and 12 month
7. Cardiac and all-cause mortality
8. Days Alive and Out of Hospital (DAOH)
9. IV diuretic visits
10. Heart failure related Medication changes
11. Change in PAP:

a. From Baseline through 6 and 12 months in subjects with a baseline mPAP
    i. above target range
    ii. within or below target range
    iii. overall
b. Before and after 6-Minute Walk Test

12. Percentage of device success as documented by ability of the System to successfully transmit PAP data
13. Patient Outcome Measures, measured by KCCQ
14. Functional status improvement, as measured by NYHA and 6-Minute Walk Test
15. Health Economic Analysis

## 5.2 Safety Endpoints

**Primary Safety endpoints include:**

1. Freedom from device/system related complication at 6 months
2. Freedom from pressure sensor failure at 6 months

**Secondary Safety endpoints include:**

1. Pressure sensor failure rate throughout the study
2. Frequency of serious adverse events throughout the study
3. Frequency of implant procedure and procedure related adverse events and serious adverse events

# 6 STUDY DESIGN

This is a prospective, open-, single arm, multi-center clinical trial to evaluate the safety and effectiveness of the Cordella PA Sensor System in NYHA Class III Heart Failure Patients.

Subjects will be categorized into three (3) different cohorts, with subjects from Cohort #2 and Cohort #3 below serving as the basis for the primary study analysis:

1. Cohort #1- Previously enrolled **Control Arm** subjects
   - Subjects in this cohort will be unblinded to their PAP measurements and informed about their previous group assignment and continue their Follow-up visit schedule
   - Additionally, subjects will be asked, throughout the remaining Follow-up period, to complete a regular subject survey on their experience with PAP Measurements and PAP Values.
   - Clinicians will be unblinded to their PAP measurements and start managing the patients to target PA pressures per protocol/ CIP and according to GDMT
   - Additionally, the clinical site will be asked to contact the subject on a regular basis to discuss their PAP values
   - Separate subgroup analysis (efficacy and safety) will be performed
2. Cohort #2- Previously enrolled **Treatment Arm** subjects
   - As of **month 12** subjects in this cohort will be able to see their own PAP measurements for the remaining duration of the study.
   - Clinicians will continue to manage their patients to target PA pressures per protocol/ CIP and according to GDMT
   - All primary and secondary safety and effectiveness analyses will be performed
3. Cohort #3- **Newly enrolled** subjects
   - will participate in the Screening/ Enrollment Visit Cordella PA Sensor Implant Visit, and Follow-Up Visits
   - Clinicians will manage the patients to target PA pressures per protocol/CIP and according to GDMT
   - As of **month 12** subjects in this cohort will be able to see their own PAP measurements for the remaining duration of the study.
   - All primary and secondary safety and effectiveness analyses will be performed

All subjects will receive a Cordella PA Sensor Implant and will be followed for 6 month for the Primary Efficacy Endpoint, 6 months for the Safety Endpoints, and will be continued to be followed up to 5 years post implant.

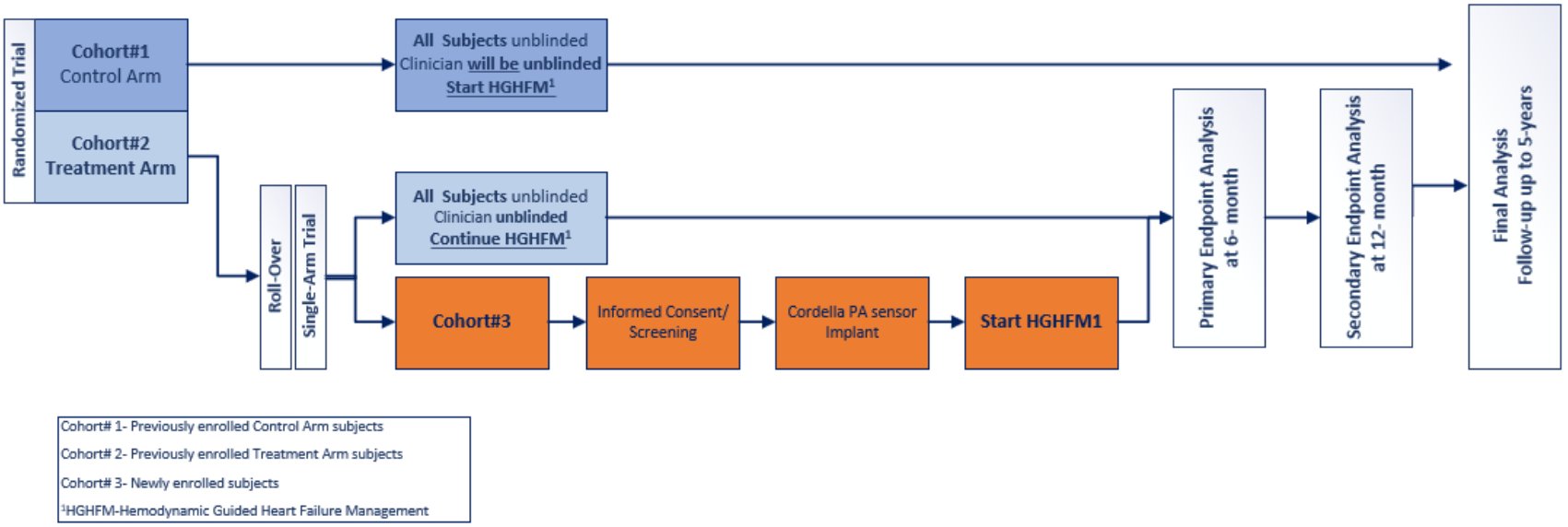


***Figure 8: Study Design***

## 6.1 Study Flow

The study will implant up to 535 subjects. Assuming a dropout rate of approximately 10% by 6 months, this study will implant a maximum of 450 patients in Cohort #2 and Cohort #3. This is to achieve at least 406 implanted patients with complete follow-up at 6 months. After completion of enrollment and as soon all 406 subjects reach their 6 month follow- up visit, the 6 month primary endpoint data will be used for Premarket Approval (PMA) submission. Up to 85 subjects (cross- over from former **Control Arm)** will continued to be followed in Cohort #1.

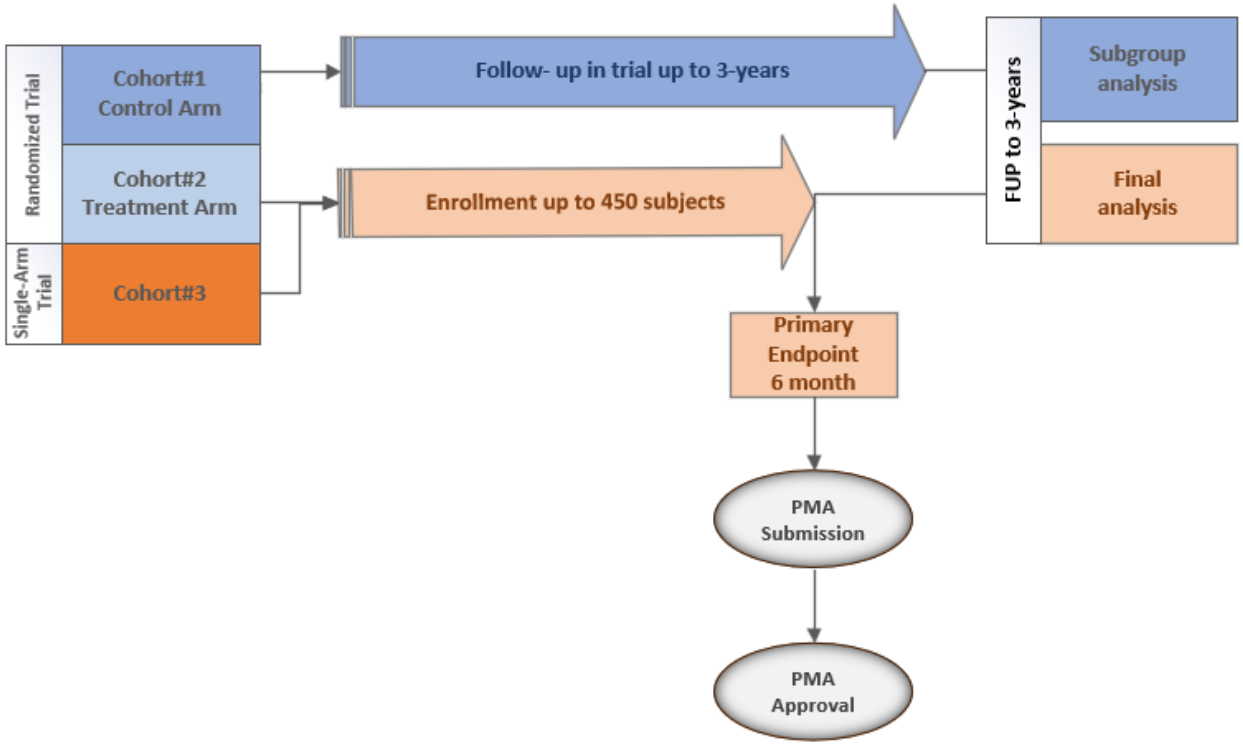


***Figure 9: Study Flow***

## 6.2 Number of Clinical Sites and Subjects

The trial will be conducted at up to hundred-twenty (120) sites in the US and Europe. Screening will continue until a maximum of 535 subjects are successfully implanted (all Cohorts).

Of these 535 subjects, up to 85 subjects (cross- over from former **Control Arm**) will continued to be followed in Cohort #1**.**

At least 50% of the total subjects will be enrolled in the US. No single clinical site will be allowed to enroll more of 20% of the total subjects into the study. In addition, clinical sites are not allowed to implant more than thirty (30) subjects into the study without prior written approval from Endotronix.

## 6.3 Subject Participation and Study Duration

Subjects will participate in the study for a total of 5 years.

The study started in the Fourth Quarter 2019 (First Implant) and enrollment (Last Implant) is estimated to be completed by First Quarter 2023.

## 6.4 Site Selection Criteria

The trial will be conducted at up to 120 clinical centers in the US and Europe (EU). A site evaluation visit (SEV) will be conducted to confirm that all participating centers meet the following criteria:

- Center having interventional cardiology (or access to) and Heart Failure teams and an established research group structure.
- Center needs to be Heart Failure Board Certified with at least 300 HF visits/ year
- American Association of HF Nurses (AAHFN) certified Nurse Practitioner (NP) & HF Nurses (US only)
- Each institution must have access to the necessary equipment and supplies that are needed to gather the data at baseline, implant and follow-up evaluations.
- Accredited laboratory or laboratories for the evaluation of blood chemistry and hematology.
- Clinical research study experience and resources that demonstrate good compliance with study requirements and timely, complete documentation of subject follow-up. Investigative teams must designate a study coordinator to manage the study.
- Ability to adhere to the standards of Good Clinical Practice (GCP).
- Agree to comply with data collection requirements and data input timelines.
- Centers will respond to queries from Endotronix in a timely fashion.
- Willingness to allow personnel from Endotronix (or its designate) access to the hospital records, investigator's study records, data and subject files as they pertain to the study.

## 6.5 Study Visits

Subjects will participate in the Screening/ Enrollment Visit, the Sensor Implant Visit, and Follow-Up Visits for a total study duration of up to 5 years.

At the Screening/ Enrollment Visit, subjects will review and sign the informed consent form prior to any study-related procedures performed. Based on Screening Visit results, the Investigator will confirm and document study eligibility for each subject. As part of the study screening process, all subjects will be trained on and instructed to use the commercially available Cordella System at home. As part of the study screening process, subjects will be scheduled for a RHC and PA Sensor Implant procedure.

At the Implant Visit, the Cordella PA Sensor, which is pre-mounted on a catheter Delivery System, will be delivered according to the system's Instructions for Use. Once deployed, the Sensor PAP readings will be calibrated using the system's fluid-filled catheter. The calibration coefficients for that Sensor/subject will be stored in a database, allowing for consistent PAP calculations throughout the study duration.

Subjects will be observed until stable, trained on and instructed to use the Cordella PA Sensor System and discharged home with instructions to take their PAP measurements daily (same time each morning) along with their weight, BP, HR and SpO2, which will all be wirelessly transmitted to a secure website. Subjects will also be given a Cordella™ PA Sensor System implant card, a Patient User's Manual, and a Technical Support number to contact Endotronix representatives with any questions.

Subjects will return for follow up visits at 1, 6, 12, 18, and 24 months and Year 3, 4 and 5 after the Cordella PA Sensor implant, or until study termination. The 3 month follow-up visit will be performed as remote/ virtual Telemonitoring visit.

When at least 406 implanted subjects (Cohort #2 and Cohort #3) completed their study visit 5 (Month 6) , the primary efficacy endpoint will be assessed to demonstrate durability of the treatment effect. Assessments to be performed at follow up visits include echocardiograms, physical examinations, cardiac medication assessment, clinical laboratory assessments, vital signs, review of Cordella PA Sensor PAP readings, NYHA Functional Classification, KCCQ, 6-Minute Walk and adverse events assessment.

# 7 STUDY POPULATION AND ENROLLMENT

## 7.1 Study Population

Subjects in this study will be male or female NYHA Class III heart failure patients at least 18 years of age. Subjects must be diagnosed with heart failure for a minimum of 3 months, are clinically stable, have an increase of NT-proBNP and a HF related hospitalization, HF treatment in a hospital day-care setting, or urgent outpatient clinic HF visit for IV diuretics within 12 month (last hospitalization should be 30 days before Screening /Enrollment). Subjects must also meet certain physical requirements necessary for the Cordella PA Sensor implant and functionality of the Cordella System as outlined in the study Inclusion/Exclusion Criteria.

## 7.2 Special Efforts to Ensure Optimal Inclusion of Women and Minorities

Discrepancies in HF management for women are apparent not only in clinical trials, but also in clinical practice. β-blockers, which have supportive data for men and women, are used less frequently in women with HF. In a European population-based study, women with HF and reduced ejection fraction were 25% less likely to receive Beta Blockers (BB) than men[27]. The CHARM study confirmed these findings, with women being 17% less likely than men to receive BBs[28]. Clinical practice also appears to vary in a gender-based fashion for ACE inhibitors. A British study found that women were 24% less likely to receive ACE inhibitors than men, while the National Heart Failure Project and the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) trial found that older women with HF were less likely to receive guideline-recommended treatments compared with men[29,30].

The recent published results from CHAMP-HF[31] showed that 99% of cardiologists are not following guidelines. In general, they are prescribing the right meds, but are being too conservative and under-medicating. Our system's constant feedback from the patient will enable them to titrate meds more confidently and thus better follow guidelines. This is especially true for women, since: (i) they tend to be smaller mass, and thus are more sensitive to overmedication and side effects; (ii) they may experience different side effects from men and thus the physician may not be as familiar with these side effects; (iii) they may be on different meds than men are typically (e.g. hormones) for other conditions, and so drug interactions may be different - physician will need extra feedback if these require special attention.

Major factors that might exclude women from receiving a Pulmonary Artery Sensor: 1) small PA size and 2) Inadequate social support for those women without a regular caregiver. Severe illness, other than heart disease, which would limit survival to < 3 years, could in theory limit the screening and enrollment of women with HF, who tend to be older and may have a larger burden of concomitant illnesses.
We believe that the proposed trial will recruit more women for several reasons:

- The Cordella PAP system is more suitable for smaller patients;
- Our anchoring system is a 'one size fits all' that depends on a universal anatomical feature
- Patients are expected to be older (mean > 65 years), where women with HF constitute a larger clinical population.

Endotronix believes that women should constitute ideally at least 35% of the population.

To ensure robust enrollment of women, we will (or already have):

1. Select sites that have Women's' Heart Clinics,
2. Make an appeal in all training materials and at investigator meetings for recruitment of women as subjects; and
3. Recruit leadership for the clinical trial and steering committee that includes women physicians.

In the CHAMPION HF trial [19] and GUIDE-HF trial [51], 73% of subjects and 81% respectively were White. The African-American population of the US is approximately 13%. According to American Heart Association statistics, the annual incidence of heart failure in whites is approximately 6 per 1,000 person-years, while in African Americans it is 9.1 per 1,000 person-years [33]. Endotronix believes the recruitment of African-American patients will be representative and will exceed 13% to approximately 20%. The location of many study sites in urban areas that serve larger African-American populations assumes adequate participation of this minority group. It is also expected that other minorities (e.g., Hispanics) will represent at least an additional 10%.

## 7.3 Optimal Heart Failure Medical Management

To be enrolled into the study, subjects must be receiving stable GDMT for HF per current AHA/ACC guidelines as standard-of-care for HF therapy in the United States and Europe, with any intolerance documented for at least 30 days. This will be verified by the trial specific PROACTIVE-HF Clinical Eligibility Committee. Throughout the study duration, all subjects will continue to receive appropriate medical management for their heart failure, including cardiac medication optimization as well as dietary and fluid restrictions. In addition, subjects will receive Treatment Optimization to target PA pressures, per the Project Specific Guidelines and GDMT considering daily PAP measurements and vital signs collected by Cordella System.

The clinician will contact all subjects on a regular basis to discuss their health status and all patients should be treated according to GDMT.

## 7.4 Inclusion Criteria

In order to be eligible to participate in this study, each subject must meet all of the following criteria:

1. Subject has given written informed consent

2. Male or female, at least 18 years of age
3. Diagnosis and treatment of HF (regardless of left ventricular ejection fraction (LVEF)) for ≥ 3 months and NYHA Class III HF at time of Screening
4. Subjects should be on stable, optimally titrated medical therapy for at least 30 days, as recommended according to current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines as standard-of-care for HF therapy in the United States, or current European Society of Cardiology (ESC ) guidelines for HF treatment in Europe, with any intolerance documented.
5. HF related hospitalization, HF treatment in a hospital day-care setting, or urgent outpatient clinic HF visit for IV diuretics within 12 month (last hospitalization should be 30 days before Screening /Enrollment) **and/or** N-terminal pro-Brain Natriuretic Peptide (NT-proBNP)) at time of Screening/ Enrollment defined as:
   a. Subjects with LVEF ≤ 50%: NT-proBNP ≥ 1500 pg/mL.
   b. Subjects with LVEF > 50%: NT-proBNP ≥ 800 pg/mL.

   Thresholds for NT-proBNP (for both LVEF ≤ 50% and LVEF > 50%) will be corrected for body mass index (BMI) using a 4% reduction per BMI unit over 25 $kg/m^2$
6. Subjects should be on diuretic therapy
7. Subjects who are physically able to hold the myCordella™ Patient Reader unit (approximate weight 1.3lb) against the ventral thoracic surface for up to 2 minutes per day while in a seated position, as well as dock and undock the myCordella™ Patient Reader
8. Subjects with sufficient eyesight, hearing, and mental capacity to respond to the myCordella™ Patient Reader's audio/visual cues and operate the myCordella™ Patient Reader
9. Subject has sufficient Cellular and/ or Wi- Fi Internet coverage at home
10. Subject agrees to return to the treating Investigator for all scheduled follow up visits and can return to the hospital for follow up

### 7.5 Exclusion Criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Intolerance to all neuro-hormonal antagonists (i.e., intolerance to ACE-I, ARB, ARNI, and beta-blockers) due to hypotension or renal dysfunction
2. ACC/AHA Stage D refractory HF (including having received or currently receiving pharmacologic circulatory support with inotropes)

3. Subjects with history of recurrent pulmonary embolism (≧ 2 episodes within 5 years prior to Screening Visit) and/or deep vein thrombosis within 3 months of the Screening Visit
4. Subjects who have had a major CV event (e.g., myocardial infarction, stroke) within 3 months of the Screening Visit
5. Unrepaired severe valvular disease
6. Subjects with significant congenital heart disease that has not been repaired and would prevent implantation of the Cordella PA Sensor or mechanical/tissue right heart valve(s)
7. Subjects with known coagulation disorders
8. Subjects with a hypersensitivity or allergy to platelet aggregation inhibitors including aspirin, clopidogrel, prasugrel, and ticagrelor; or patients unable to take dual antiplatelet or anticoagulants for one- month post implant
9. Known history of life threatening allergy to contrast dye.
10. Subjects whereby RHC is contraindicated
11. Subjects with an active infection at the Sensor Implant Visit
12. Subjects with a GFR <25 ml/min or who are on chronic renal dialysis
13. Implanted with CRT-P or CRT-D for less than 90 days prior to screening visit
14. Received or are likely to receive an advanced therapy (e.g., mechanical circulatory support or lung or heart transplant) in the next 12 months
15. Subjects who are pregnant or breastfeeding
16. Subjects who are unwilling or deemed by the Investigator to be unwilling to comply with the study protocol, or subjects with a history of non-compliance
17. Severe illness, other than heart disease, which would limit survival to <1 year
18. Subjects whose clinical condition, in the opinion of the Investigator, makes them an unsuitable candidate for the study
19. Subjects enrolled in another investigational trial with an active Treatment Arm
20. Subject who is in custody by order of an authority or a court of law

### 7.6 Strategies for Recruitment and Retention

A total of 535 subjects can be enrolled under this clinical protocol/CIP at up to 120 sites in the US and Europe. Potential subjects will be identified by the Investigator and research staff with the study Inclusion and Exclusion criteria in mind. At Screening, subjects will be fully informed on what to expect with study participation to maintain a high study participation retention rate. Subjects will

also undergo a training on the at-home use of the commercial Cordella System to ensure compliance with the web-based clinical care management component of the Cordella™ Heart Failure System, as part of their study screening/ enrollment visit. Throughout the study, subjects will continue to be followed closely to ensure study compliance as well as continued study participation.

## 7.7 Subject Withdrawal or Termination

### 7.7.1 Screening Failure and Documentation

Subjects who sign the Informed Consent, but do not meet the inclusion criteria or subjects who meet an exclusion criterion and are not enrolled into the study are considered screening failures. Information on screening failure subjects will be captured on a Screening Failure log and will include demographic information and the primary reasons for Screen Failures will not be recorded in the electronic Case Report Form (eCRF).

### 7.7.2 Reasons for Withdrawal or Termination

A subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary reason for termination must be recorded in the eCRF. In addition, efforts should be made to perform all procedures scheduled for the Month 6 visit if discontinuation is prior to that visit, or the year 5 visit if discontinuation is after year 4 but before year 5. Subjects who are withdrawn may be replaced with new subjects for evaluation upon Sponsor approval.

The primary reason for discontinuation or withdrawal of the subject from the study should be noted using the following categories:

- Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented
- Voluntary withdrawal. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF. NOTE: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded
- Principal Investigator withdrawal due to failure to comply with trial requirements or subject is uncooperative or refuses to continue in the trial
- Study termination. The sponsor, IRB/ IEC, or regulatory agency terminates the study
- Other (NOTE: The specific reasons should be recorded in the eCRF)

## 7.8 Subject Follow- up after trial completion or early termination

After completion of the last study visit, the subject will continue to participate in the site-specific Heart Failure Follow-up program.

# 8 STUDY PROCEDURES AND SCHEDULES

## 8.1 Study Procedures and Evaluations

The following sections describe the procedures to be completed throughout the conduct of the study. Subjects are to be assessed by the same Investigator or site personnel whenever possible. The Schedule of Study Procedures is described here in Section 8 and in Appendix 14.1. Every attempt should be made to perform evaluations at the designated time points. However, for visits conducted at Month 1 and 3 there is a window of +7 days, for visits at Month 6 there is a window of +14 days and after Month 6 (Month 12, 18, 24 and Year 3, 4 and 5) there is a window of +30 days.

### 8.1.1 Study Eligibility Review

Inclusion and exclusion criteria will be reviewed during the Screening period for all subjects to determine study participation eligibility using the following process:

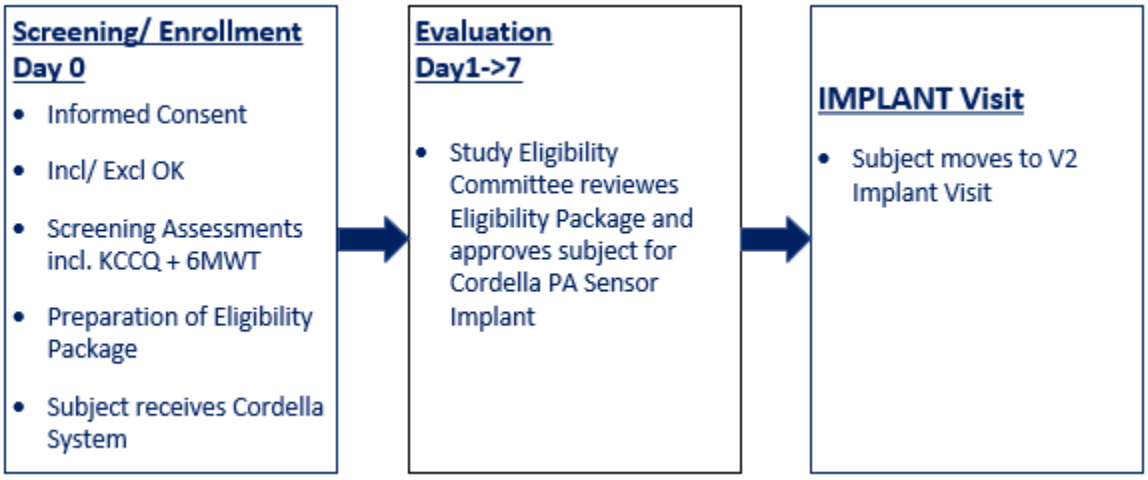


***Figure 10: Enrollment Process***

### 8.1.2 Informed Consent Procedure

Before enrolling the subject in the trial, i.e., before any trial-related examination is performed, a written Informed Consent Form (ICF) must be obtained. Each potential participant shall be informed of the aim of the trial and what participation entails. They shall be supplied with an Information Sheet summarizing the details of the trial. Ample time should be given to the subjects to consider their participation. Agreement to participate in the trial is to be confirmed by the subject and the Principal Investigator (or authorized designee) by signing and dating the consent form. Documentation of this procedure is required in the medical record.

Standard-of-care assessments obtained within the 30 days prior to consent for screening may be used: 1) to confirm eligibility; and 2) for screening measurements, if the subject meets eligibility criteria and signs the ICF. Echocardiograms obtained within 3 or 6 months prior to ICF may be used for screening measurements.

Vulnerable populations will not be included in this trial.

### 8.1.3 Point of Contact

A point of contact of where to obtain additional information on the trial, on the rights of the subject and whom to contact in the event of trial-related injury will be provided to each subject. This information will be specified in the ICF.

### 8.1.4 Informing the Subject's General Practitioner (EU only)

In certain applicable countries, and in cases where the subject is typically treated by a general practitioner or other equivalent Health Care Provider (HCP), then with the subject's agreement this HCP is to be informed of the subject's participation in the trial at enrollment. The provider should be informed of the title of the trial, date of enrollment into the trial, and the dates of the outstanding visits. The communication with the general practitioner should be documented in the subject's medical record.

### 8.1.5 Subject Demographics

Subject demographics will be collected and identified by a non-identifying number on the eCRF including sex, gender, year of birth, weight, height, race, and ethnicity. Subject BMI will also be recorded.

### 8.1.6 Cardiac/Medical and Surgical History

Medical and surgical history, including cardiac history, will be obtained at Screening and updated at the Cordella PA Sensor Implant Visit prior to the implant procedure as follows:

- General medical history
- Primary cardiac diagnosis (ischemic cardiomyopathy/ nonischemic cardiomyopathy)
- Previous cardiac history incl.:
  - Coronary Artery Bypass Grafting (CABG)
  - Percutaneous coronary intervention (PCI)
  - Hypertension
  - Ventricular Tachycardia
  - Atrial Fibrillation
  - ICD / CRT
- Duration of Heart Failure/ NYHA class
- Cardiopulmonary Exercise Testing (CPX) Results (if available)
- Number of hospitalizations in past year for cardiac reasons and HF
- Smoking, Alcohol, Drug Use

With co-morbidities to be identified as:

- Diabetes (diet, oral, insulin)
- COPD
- Chronic Kidney Disease
- Carotid artery disease, Peripheral vascular disease

### 8.1.7 Physical Examination and Vital Signs

A full physical examination including chest circumference* will be obtained at Screening. An abbreviated physical examination will be obtained at the Cordella PA Sensor Implant Visit prior to the implant procedure and at Month 1, 6, 12, 18, 24 and Year 3, 4 and 5. All physical examinations will be conducted by a licensed physician, NP, registered nurse (RN), or physician assistant (PA) in accordance with local laws and regulations.

Vital signs via Cordella System will be obtained at all study visits. BP, HR, arterial oxygen saturation ($SpO_2$) level, and weight. Height and BMI will be measured at Screening only.

*If chest circumference is above 55 inch/ 1400 mm please provide CT scan in Screening Package for PROACTIVE-HF Clinical Eligibility review. If a preexisting CT exists, which was taken within the last 12 months, the CT does not have to be repeated at the time of screening.

### 8.1.8 Electrocardiograms (ECG)

A 12-lead electrocardiogram (ECG) will be obtained at Screening, Month 6, 12, 24 and Year 3, 4 and 5. For all ECGs, the Investigator will write their findings on the ECG as either:

- “Normal ECG"
- "Abnormal ECG, Clinically Significant"
- "Abnormal ECG, Not Clinically Significant”

Subsequent ECGs may be obtained at the discretion of the Investigator. ECGs will be signed and dated by the Investigator. The original ECG tracing will be retained in the subject's records at the study site and a copy will be provided to the Sponsor if requested.

### 8.1.9 Clinical Laboratory Tests

Blood samples will be obtained for local clinical laboratory tests (hematology and serum chemistry) at Screening, Month 6, 12, 24 and Year 3, 4 and 5. Additionally, urine samples will be obtained for testing, including pregnancy tests for females at Screening. Appropriate accreditation for all laboratories as well as the reference ranges for each of the laboratory parameters measured with a description of the methods to be used in the study must be provided to Endotronix prior to initiation of the study. Changes in the reference ranges or in the methodology during the trial are to be communicated to Endotronix or representative.

| **Hematology** | **Biochemistry** | | **Urinalysis (Screening only)** |
|---|---|---|---|
| Hemoglobin | NT-pro BNP* | CRP | Glucose |
| Hematocrit | Sodium | SGOT (AST) | Protein |
| Leucocytes | Potassium | SGPT (ALT) | Specific gravity |
| Platelets | Creatinine | Cholesterol | pH |
| Lymphocytes | Total Bilirubin | Uric Acid | Ketones |
| aPTT** | Blood Urea Nitrogen (BUN)/ Urea | | Bilirubin |
| INR** | Total Protein | | Urobilinogen |
| | Albumin | | Nitrite |
| * also captured at Month 1, 3 and 18<br>** if indicated | | | Blood |
| | | | Leukocytes |
| | | | Urine Pregnancy Test (females) |

The results of laboratory tests will be returned to the investigator, who is responsible for filing and reviewing these results together with the data in the eCRF. The investigator is responsible for transcribing laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for each laboratory used.

The total amount of blood per subject for laboratory tests will be approximately 100 mL.

### 8.1.10 Echocardiogram

Echocardiograms will be performed at Screening, Month 12 and Year 3, 4 and 5.
Echocardiograms will determine the following parameters:

- LVEF
- Left ventricular mass
- Left ventricular volume
- Left Ventricular End Diastolic Diameter (LVEDD)
- Systolic pulmonary artery pressure (sPAP)
- Mean pulmonary artery pressure (mPAP)
- Diastolic pulmonary artery pressure (dPAP)
- Right atrial pressure (RAP)
- Left atrial size
- Left atrial volume
- Mitral regurgitation
- Tricuspid regurgitation

If an echocardiogram has been performed within 3 months of Screening, that LVEF may be acceptable to determine study eligibility. While an echocardiogram within 3 months of the screening visit date is preferable. In case this is not possible, Endotronix will accept an echocardiogram from within 6 months of Screening provided the patient does not have a standard of care indication for an echocardiogram during this interval.

### 8.1.11 NYHA Functional Classification

AHA/ACC and NYHA classification guidelines can be found in Appendix 14.2. The NYHA Functional classification categorizes the extent of HF by placing patients in one of four categories based on how much they are limited during physical activity and symptoms of shortness of breath and/or angina. Determination of NYHA classification will be performed by an independent assessor (defined as a physician or qualified PA, RN or NP not directly involved with this clinical trial).

NYHA Functional Classification will be obtained at all study visits and must be NYHA Class III for study entry.

### 8.1.12 Six (6) Minute Walk

Subjects will complete a six (6) minute walk test at Screening, Month 6, 12 and 24 as well as at Year 3, 4 and 5. In addition, PAP Measurements will be obtained before and after 6-minute walk test after unblinding at Month 12, 24 and Year 3, 4 and 5.

If the Subject is unable or unwilling to perform the 6-minute walk test, the distance recorded should be left blank. Instructions for the procedure are found in Appendix 14.3.

### 8.1.13 Quality of Life Questionnaire

The KCCQ are measures of health-related quality of life and can be found in Appendix 14.4 respectively. These questionnaires will be administered to subjects at screening visit as soon they receive the Cordella System and at all follow up visits. Subjects will be instructed to perform the KCCQ via the myCordella™ Patient App.

The KCCQ is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life related to HF.

### 8.1.14 Health Economic/ Operational Questionnaire

Subject related health economic or operational data may be collected throughout the study to provide an aggregated summary of case data to include, but not limited to Cordella Sensor procedural status (Inpatient/Outpatient), implant procedure complications, patient compliance to remote management schedule, readmissions during the study and care management experience feedback.

### 8.1.15 Subject Training & Use: Cordella PA Sensor and HF System

At the Screening/Enrollment Visit (Visit 1), subjects will be trained on the set up and use of the commercial Cordella System, on how to collect their weight, BP, HR and SpO2 and how to transmit their data daily for review.

During the Implant Visit (Visit 2), subjects will also be trained to use the Reader while seated at the same time each day (i.e., morning) and will be instructed to collect PAP information together with the other vital signs and transmit the data daily for review. This training will be performed prior to the subject's discharge from the implant visit hospitalization.

If the subject is unable to use the Reader to collect PAP data, an Endotronix representative will be available by phone or in person to assist. Subjects will be instructed to collect this information daily throughout the study. Subject compliance will be defined as at least 5 days of data collection/transmissions. The 5 days of data collection/transmissions do not have to be consecutive days.

### 8.1.16 Cordella PA Sensor Implant Procedure

At the Cordella PA Sensor Implant Visit, the Sensor, which is pre-mounted on a catheter Delivery System, will be delivered according to the system's IFU. Once deployed, the Sensor PAP will be calibrated using the systems fluid-filled catheter as part of an RHC. The calibration coefficients for that Sensor/subject will be recorded in the CalEQ and stored in the CDAP, allowing for consistent PAP calculations throughout the life of the Sensor.

Subjects will be observed until stable (per clinicians' discretion) and discharged home with post-RHC instructions and instructions to take their PAP measurements daily, which will be wirelessly transmitted to a secure website. Additional PAP measurements (seated and supine) will be performed within 24 hours of discharge. The study site should also instruct subjects to return for a catheter insertion site check per their standard-of-care. Before discharge, seated Cordella PA Sensor PAP will be measured via CalEQ.

### 8.1.17 Right Heart Catheter Procedure

A RHC procedure using percutaneous venous access will be performed at the Cordella PA Sensor Implant Visit, at Year 3 and as needed for Re-calibration purposes at the clinician's discretion. The RHC should be performed per the site's standard-of-care and subjects should also be asked by the site to return per their standard-of-care for a post-procedure catheter insertion site evaluation.

The following measurements will be obtained from the RHC:

- RAP
- Right ventricular pressure (RVP): systolic, diastolic, end diastolic
- PAP: systolic, diastolic, mean
- Pulmonary Capillary Wedge Pressure (PCWP)
- Heart Rate
- CO
- Cardiac Index (CI)

### 8.1.18 Cordella PA Sensor PAP Measurements

In addition, to daily PAP measurements transmitted by the subject, seated and supine PAP measurements are to be obtained at all Follow-up Visits* including systolic (sPAP), diastolic (dPAP), and mean (mPAP).

* PAP measurements can also be performed by the subject at home at the Follow- up visit day.

PAP readings from the Cordella PA Sensor will be accessible to the subjects and clinicians after the Cordella PA Sensor Implant Visit. PAP changes from baseline will be assessed and notification limits need to be set for the subjects so that out of range PAP readings are flagged for the Investigator's prompt review and appropriate HF management as per the guidelines in Appendix 14.5.

### 8.1.19 Cordella PA Sensor and HF System Data Transmission & Compliance

All subjects will be instructed to transmit their clinical data daily (PAP data and vital signs) using the myCordella™ Tablet during the study. Subjects will be asked to transmit their clinical data at approximately the same time each day (typically in the morning). Subjects will also be given a pre-set time window to make their daily transmission.

Use of the Cordella System and PAP Measurements will be monitored, and compliance will be measured by tracking the number of transmitted data occurrences. For study purposes, compliance will be defined as subjects transmitting at least 5 days of myCordella™ clinical data per week (does not need to be consecutive days). If a subject does not transmit at least 5 days per week, Endotronix will notify the study site on a regular basis on their subject's compliance.

Subjects will then be notified by the study site to review system use expectations and any other user issues will be addressed.

To help subjects with data transmission compliance during the study, the myCordella™ Tablet will be programmed with daily reminders to transmit data, successful transmission indicators, and flags to transmit data if a transmission is missed.

### 8.1.20 myCordella™ Patient Management Portal (PMP) Data Review and Contact

Following the Cordella PA Sensor implant, clinical data from the Cordella™ Heart Failure System including PAP sensor data will be continuously transmitted by all subjects and monitored by clinicians at the study site. Clinicians will be trained by an Endotronix representative on how to use the myCordella™ PMP to review data transmissions.

For all subjects' mandatory reviews and acknowledgements of all subject's vital signs is required as per the table below to assure optimal hemodynamic PAPGHFM in addition to GDMT HF management for all patients:

| **Data Review Schedule** | | **Comments** |
|---|---|---|
| Recommended Cordella System | At least 2 times per week | |
| Mandatory PAP Sensor Data | 2 times per week | *maximum of 4 days between data reviews* |

Regular review of the patient's data will allow proactive heart failure management. It is assumed that post sensor implant, more intense HF management is needed to optimize the patient's HF treatment for a period of 1-3 months, as the patient is treated to target pressures per the guidelines in Appendix 14.5 and GDMT. Data displayed at the myCordella™ PMP will enable clinicians to effectively adjust medication dosages (e.g., drug titration) during this "optimization" period. In the following "stabilization" phase, the clinician will be able to quickly assess the patient daily health status via the myCordella™ PMP and take action as needed. As it is the nature of this particular disease, even under optimal treatment, HF patients are likely to worsen again over time. Regular review of the patient PAP trends, in addition to other data provided by the Cordella System, will allow the clinician to proactively treat the patient before full decompensation and hospitalization.

When worsening occurs, the patient will undergo again the "optimization" phase, followed by the "stabilization" phase as per the guidelines in Appendix 14.5.

### 8.1.21 Subject Contact/ Subject Survey (Cohort #1 only)

**Subject Contact**

After unblinding subjects from Cohort #1 will be contacted by the clinical site as per the following schedule to discuss their PAP values:

| Time Point (Post unblinding) | Contact via scheduled Phone Call or Cordella® System Messaging |
|---|---|
| 1 month | X |
| Quarterly | X |

Additionally, a short optional site survey will be administered for those Cohort #1 subjects. This survey can be found in Appendix 14.8.

**Subject Survey**

A subject survey will be collected to evaluate the subjects experience on visibility of their PAP Measurements. This survey can be found in Appendix 14.9.

This survey is optional and will be administered to all Cohort #1 subjects after the first month and then on a quarterly basis after unblinding/ cross-over.

### 8.1.22 Concomitant Medications

Administration of beta blockers (BB), ACE-I, ARB, ARNI, mineralocorticoid receptor antagonists, (MRA), nitrates, hydralazine, inotropes, anticoagulants, anti-arrhythmics, antiplatelet medications, antibiotics, diuretics and antihypertensive medications, and any other cardiac medications at all study visits between screening and year 5 will be recorded.

Information collected at time of visit will include:

- Drug
- Dose
- Route of administration

**Adverse Events**

Any Concomitant Medications taken prior, up to onset and to treat an Adverse Event will be collected at the time of each event.

**Anticoagulation**

For subjects who are not being treated with chronic anticoagulant therapy, it is recommended to use dual antiplatelet therapy with aspirin and clopidogrel, (or prasugrel, ticagrelor) for 30 days post implant.

Subjects who are currently on anticoagulant therapy, or those in which chronic anticoagulant therapy is indicated for HF treatment should discontinue use of anticoagulant therapy 1-2 days prior to the Cordella Sensor implant and restart treatment post- implant. An INR of <1.5 is recommended prior to sensor implant for subjects who were previously on anticoagulant therapy. The standard of care as bridge therapy to Cordella Sensor placement should be used in patients who were on anticoagulant therapy.

Post 30 days, continuous single antiplatelet therapy with aspirin indefinitely is recommended.

It is important to resume or initiate antiplatelet or anticoagulant therapy post-implant to reduce the likelihood of thrombotic events.

## 8.2 Device Explant

In the event that the Cordella PA sensor is explanted (i.e., death or intervention to explant) the Cordella PA sensor should be returned to Endotronix for analysis. Endotronix will provide an Explant Kit that is designed for transportation of used health care products. Explant, packaging and shipping instructions will be included in each Explant Kit. In addition, a Return Goods Authorization (RGA) number must be obtained from Endotronix prior to shipment of the Cordella PA Sensor and associated components.

## 8.3 Schedule of Observations and Procedures

### 8.3.1 Study Visit 1 (Screening/ Enrollment Visit)

Subjects will be screened against entry criteria, and if confirmed to meet all requirements for enrollment and sign/date the current IRB approved consent, will be eligible for implant and enrollment into the study. The screening log will be maintained per Section 8.3.2

Written ICF must be provided by the subject prior to any study procedures being conducted, including screening labs or tests of any kind. Subjects will be screened against the inclusion and exclusion criteria and, if confirmed to meet all requirements, will then be enrolled into the study.

The following study procedures will be performed during this visit:

- Informed Consent
- Subject Demographics

- Study Eligibility Review
- Cardiac/Medical & Surgical History
- Physical Examination
- Height, Weight and BMI
- Vital Signs: BP, HR, SpO2
- 12-Lead ECG
- Safety Labs (Chemistry & Hematology & Urinalysis)
- Urine Pregnancy Test (female), if applicable
- Serum NT-pro BNP
- aPTT/INR (if indicated)
- Echocardiogram (may be obtained within 3 months of Screening)*
- NYHA Functional Classification (may be obtained within the 30 day Study Visit 1 window)
- 6-Minute Walk Test
- KCCQ Quality of Life Questionnaires
- Concurrent/Cardiac Medications
- Set Up/Subject Training: Cordella™ HF System (myCordella™ Tablet & Peripherals)*

*While an echocardiogram within 3 months of the screening visit date is preferable. In case this is not possible, Endotronix will accept an echocardiogram from within 6 months of Screening provided the patient does not have a standard of care indication for an echocardiogram during this interval.

After the subject has been approved by the PROACTIVE-HF Clinical Eligibility Committee, they will be enrolled into the study and can be scheduled for Study Visit 2 (Implant Visit).

In case a subject will be implanted >30 days after Study Visit 1, the following study procedures will need to be repeated and results obtained prior to implant:

- Reconfirm Study Eligibility Review
- Any changes in Health Status
- Any changes in concomitant medications
- Repeat selected Safety Labs

| **Hematology** | **Biochemistry** | **Urinalysis** | |
|---|---|---|---|
| Hemoglobin | Sodium | Glucose | Nitrite |
| Hematocrit | Potassium | Protein | Blood |
| Leucocytes | Creatinine | Specific gravity | Leukocytes |
| Platelets | BUN | pH | |
| Lymphocytes | SGOT (AST) | Ketones | |
| aPTT/ INR | SGPT (ALT) | Bilirubin | |
| INR | GFR | Urine Pregnancy Test (females) | |

* Subject training on and distribution of the commercial Cordella™ System (

### 8.3.2 Study Visit 2 (Cordella PA Sensor Implant Visit: Admission & Implant)

Before the subjects return for the Cordella PA Sensor Implant Visit, they will be instructed by the Investigator to discontinue use of anticoagulation therapy 1-2 days prior to the procedure. The investigator should consider utilizing another anticoagulant per the site's standard-of-care as bridge therapy to Cordella PA Sensor placement in subjects who were on anticoagulation therapy.

Implant procedures for the Cordella PA Sensor are described in detail in section 6 of the IFU, which will be provided to each site at study start.

Implants may be performed via RHC using percutaneous venous access.

In case the Cordella PA Sensor Implant is attempted but not completed, subjects will be followed through 30 days for safety purposes.

It is critical that accountability of the device is maintained for research records. Federal regulations require that the lots / ID number of the device are appropriately noted and tracked (please also see Section 2.4).

The following study procedures will be performed during this visit:

- Cordella PA Sensor implant
- RHC PAP: diastolic, systolic, mean, HR, RAP, Pulmonary Capillary Wedge Pressure (PCWP), CO, Cardiac Index (CI), RVP: diastolic, systolic, end diastolic
- Cordella PA Sensor PAP: diastolic, systolic, mean, pulse (via CalEQ):
    - after calibration
    - seated and supine before discharge or at home (within 24 hours)
- Set Up/Subject Training: Cordella™ HF System (myCordella™ Tablet & Peripherals)
- Subject Training/Subject Use: CorPASS (myCordella ™ Patient Reader and Dock)
- Abbreviated Physical Examination
- Concurrent/Cardiac Medications
- Adverse Event

### 8.3.3 Study Visit 3 (Month 1, ±7 days)

The following study procedures will be performed prior/ during this visit:

- Abbreviated Physical Examination
- Vital Signs: weight, BP, HR and SpO2 (via myCordella™ Patient App)
- Serum NT-pro BNP
- Cordella PA Sensor PAP (seated and supine): diastolic, systolic, mean, pulse (via myCordella™ Patient App)
- Subject Status
- NYHA Functional Classification
- KCCQ Quality of Life Questionnaire

- Concurrent/Cardiac Medications
- Adverse Event

### 8.3.4 Study Visit 4 (Month 3, ±7 days)

This visit should be performed as remote/ virtual Telemonitoring Visit and the following study procedures will be performed prior/during this visit:

- Vital Signs: weight, BP, HR and SpO2 (via myCordella™ Patient App)
- Serum NT-pro BNP (if available)
- Cordella PA Sensor PAP (seated and supine): diastolic, systolic, mean, pulse (via myCordella™ Patient App)
- Subject Status
- NYHA Functional Classification
- KCCQ Quality of Life Questionnaire
- Concurrent/Cardiac Medications
- Adverse Event

### 8.3.5 Study Visit 5 (Month 6, ±14 days)

The following study procedures will be performed prior/ during this visit:

- Abbreviated Physical Examination
- Vital Signs: weight, BP, HR and SpO2 (via myCordella™ Patient App)
- 12-Lead ECG
- Safety Labs (Chemistry & Hematology)
- Serum NT-pro BNP
- Cordella PA Sensor PAP (seated and supine): diastolic, systolic, mean, pulse (via myCordella™ Patient App)
- Subject Status* including question on assigned treatment
- 6-Minute Walk Test
- NYHA Functional Classification
- KCCQ Quality of Life Questionnaire
- Concurrent/Cardiac Medications
- Adverse Event

### 8.3.6 Study Visit 6 (Month 12 ±30 days)

The following study procedures will be performed prior/ during this visit:

- Abbreviated Physical Examination
- Vital Signs: weight, BP, HR and SpO2 (via myCordella™ Patient App)
- 12-Lead ECG
- Safety Labs (Chemistry & Hematology)

- Serum NT-pro BNP
- Cordella PA Sensor PAP (seated and supine): diastolic, systolic, mean, pulse (via myCordella™ Patient App )
- Echocardiogram
- Subject Status* including question on assigned treatment
- 6-Minute Walk Test (additional PAP Measurements will be obtained before and after 6-minute walk test via myCordella™ Patient App)
- NYHA Functional Classification
- KCCQ Quality of Life Questionnaire
- Concurrent/Cardiac Medications
- Adverse Event

### 8.3.7 Study Visit 7 to 8 (Month 18, 24, ±30 days)

The following study procedures will be performed prior/ during this visit:

- Abbreviated Physical Examination
- Vital Signs: weight, BP, HR andSpO2 (via myCordella™ Patient App)
- 12-Lead ECG (Visit 8 only)
- Safety Labs (Chemistry & Hematology) (Visit 8 only)
- Serum NT-pro BNP
- Cordella PA Sensor PAP (seated and supine): diastolic, systolic, mean, pulse (via myCordella™ Patient App)
- Subject Status
- 6-Minute Walk Test (additional PAP Measurements will be obtained before and after 6-minute walk test via myCordella™ Patient App) (Visit 8 only)
- NYHA Functional Classification
- KCCQ Quality of Life Questionnaire
- Concurrent/Cardiac Medications
- Adverse Event
- Health Economic Questionnaire/Cost-Effectiveness Analysis (Visit 8 only)

### 8.3.8 Study Visits 9 to 11 (Years 3, 4, 5 ±30 days)

The following study procedures will be performed prior/during these visits:

- Abbreviated Physical Examination
- Vital Signs: weight, BP, HR and SpO2(via myCordella™ Patient App)
- 12-Lead ECG
- Safety Labs (Chemistry & Hematology)
- Serum NT-pro BNP

- RHC PAP: diastolic, systolic, mean, HR, RAP, Pulmonary Capillary Wedge Pressure (PCWP), CO, Cardiac Index (CI), RVP: diastolic, systolic, end diastolic *
- Cordella PA Sensor PAP (seated and supine): diastolic, systolic, mean, pulse (via myCordella™ Patient App)
- Echocardiogram
- Subject Status
- 6-Minute Walk Test (additional PAP Measurements will be obtained before and after 6-minute walk test via myCordella™ Patient App)
- NYHA Functional Classification
- KCCQ Quality of Life Questionnaire
- Concurrent/Cardiac Medications
- Adverse Event

*Visit 9/ Year 3 only

### 8.3.9 Early Termination Visit

The following study procedures will be performed prior/during this visit:

- Abbreviated Physical Examination
- Vital Signs: weight, BP, HR andSpO2 (via myCordella™ Patient App)
- 12-Lead ECG
- Safety Labs (Chemistry & Hematology)
- Serum NT-pro BNP
- Cordella PA Sensor PAP (seated and supine): diastolic, systolic, mean, pulse
- Subject Status
- 6-Minute Walk Test
- NYHA Functional Classification
- KCCQ Quality of Life Questionnaire
- Concurrent/Cardiac Medications
- Adverse Event

# 9 ADVERSE EVENTS

From the time of enrollment, at each evaluation of a subject enrolled in the trial, the investigator or site staff determines whether any adverse events (AE) have occurred and determines their relationship to the study devices or procedures. All adverse events, study device malfunctions and other product issues must be recorded in the appropriate eCRF section(s).

Safety will be assessed throughout the study by the frequency of Adverse Events (AEs), pressure sensor failure rate, and device/system-related complications by relationship to the device and severity. Additional emphasis on safety for the primary safety endpoint will be placed through 6 month following the Cordella PA Sensor Implant procedure to capture any adverse events associated with use of the Cordella PA Sensor.

Adverse events may be volunteered spontaneously by the subject, or discovered as a result of general, non-leading questioning. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE page of the eCRF, in accordance with the guidelines that accompany it. The investigator must submit to sponsor (or designee) any UADEs, and SAEs occurring during the study within 24 hours after being notified of the event and provides additional information, if required by Endotronix.

All AEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained or is judged by the investigator to be no longer clinically significant, or until the subject is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations necessary to elucidate as completely as practical the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Investigators are not obligated to actively seek AEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product or study participation, the investigator should promptly notify Endotronix.

All AEs will be collected until a subject's participation in the trial is considered complete.

## 9.1 Definition and Documentation of Adverse Events

Adverse Event definitions specific to the EU sites can be found in Appendix 14.7.

### 9.1.1 Adverse Events (AE)

An adverse event is any undesirable clinical occurrence in a subject whether it is considered to be device related or not.

### 9.1.2 Serious Adverse Event (SAE):

The event is serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability or permanent change
- Congenital Anomaly/Birth Defect
- Required Intervention to Prevent Permanent Impairment or Damage
- Other Serious (Important Medical Events)

A planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

### 9.1.3 Device or Procedure-Related Adverse Events

#### 9.1.3.1 Device deficiency (DD)

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error, and inadequate labeling.

#### 9.1.3.2 Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health or safety, any life threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21CFR812.3).

### 9.1.4 Anticipated/ Expected Adverse Events:

An anticipated/expected event by its nature, incidence, severity or outcome has been previously identified in the risk analysis report and is included into the table below.

Anticipated Adverse Events include those that are reasonably expected to occur in association with the use of any RHC and the use of the result of implanting an investigational medical device. The anticipated/ expected adverse events that will be collected are:

| Potential Event | Overall Incidence % overall |
|---|---|
| Allergic reaction [33] | 3% |
| Arrhythmias [34-36] | < 1% |
| Bleeding complications which may require transfusion | < 1% |
| Cardiac arrest [34] | < 1% |
| Chest pain [34,36] | < 1% |
| Death [34,36] | < 1% |
| Device embolization/migration | Not Available |
| Device explant | < 1% |
| Emergent or urgent cardiac, vascular, and/or other surgery necessitated by the device or implant procedure | Not Available |
| Endocarditis or device infection [36] | < 1% |
| Entry site complications (e.g., hematoma, dissection) [34,36] | < 1% |
| Fracture of a component of the device/system that may or may not lead to serious injury or surgical intervention | Not Available |
| Gastrointestinal bleed [36] | 3% |
| Hemoptysis[24,43] | < 1% |
| Hypo or hypertension [34,36] | 6% |
| Infection [36,37] | < 1% |
| Peripheral embolism/thrombus | Not Available |
| Pulmonary embolism/pulmonary occlusion [36] | < 1% |
| Pseudoaneurysm of the vein [38-40] | < 2% |
| Radiation exposure | Not Available |
| Reaction to contrast media/ medication [33] | 3% |
| Renal insufficiency or failure [41] | 10% |
| Respiratory distress or failure (breathing problems) | Not Available |
| Sepsis | < 1% |
| Valvular injury (tricuspid and/or pulmonary) | Not Available |
| Vascular complications (e.g., venous dissection, perforation, rupture, arteriovenous fistula) [35] | < 1% |
| Vessel Trauma which may require surgical repair [35,36] | < 1% |
| Worsening heart failure | < 30%[36] |

## 9.2 Assessment of Causality

The likely relationship of each adverse event to the investigational medical device will be assessed according to the definitions below:

### 9.2.1 Not related

Is defined as an AE which is not related to the use of the investigational medical device.

### 9.2.2 Unlikely related

The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

### 9.2.3 Possibly related

Is defined as an AE which might be due to the use of the investigational device. An alternative explanation (e.g., concomitant drug(s), concomitant disease(s)) is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

### 9.2.4 Probably related

The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

### 9.2.5 Related

Data demonstrating clear evidence for a causal relationship (i.e., a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the investigational medical device, which cannot be explained by concurrent disease or other factors.)

## 9.3 Adverse Event Reporting Requirements

### 9.3.1 Investigator Reporting Requirements

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and in the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to Endotronix instructions.

All events will be classified per Adverse Event definitions as documented in Appendix 14.7. Additionally, the date of the event, seriousness criteria and outcome should also be recorded.

Laboratory and clinical parameters will be followed to evaluate the safety and performance of the Cordella PA Sensor System; these include adverse event reporting and monitoring, routine clinical laboratory tests (hematology, biochemistry, and urinalysis), vital signs, review of concomitant medications and echocardiogram.

It is the responsibility of the investigators to inform their IRB/IEC of adverse events as required by their local IRB procedures.

Investigators must notify Endotronix (or designee) within 24 hours of discovering any Unanticipated Adverse Device Effects (UADE)/ Unanticipated Serious Adverse Device Effect (USADE). Investigators are required to submit a report of a UADE/ USADE to the reviewing IRB/ IEC as soon as possible, but in no event later than 10 working days after the investigator first learns of the event. UADEs/USADEs must be documented on the appropriate eCRF.

### 9.3.2 Regulatory Reporting Requirements

**UADE/ USADE:**

Endotronix's evaluation of the UADE/ USADE must be reported to the FDA/CAs, all reviewing IRBs/IECs, and participating investigators within 10 working days of knowledge of the event by Endotronix. All UADE/ USADEs will be reported to the FDA/CAs according to regulatory reporting requirements found in CFR 812.46 (US) and MDCG 2020-10/1 under Directive Regulation 2017/ 745 on Medical Device Regulations (MDR) (EU). Contacts for SAE/ UADE/ USADE receipt can be found on the Endotronix/Medical Monitor Contact Information page in the Site File.

**AEs/ DDs**

Endotronix Inc. is required to expedite to worldwide regulatory authorities reports of AEs and DDs as applicable for each region and in line with the relevant legislation including Safety 21CFR 812.3, CFR 812.46 (US) as well as in MDCG 2020-10/1 under Directive Regulation 2017/745 on MDR (EU).

All investigators will receive a safety letter notifying them of relevant reports. In accordance with the applicable national regulations, Endotronix or designee will notify the relevant IRBs/ IECs of applicable reports as individual notifications or through a periodic line listing as defined in the region's applicable Safety Plan.

Endotronix or its designee will submit to the regulatory authorities all safety updates and periodic reports, as required by applicable regulatory requirements.

Endotronix authorized a CRO to perform the processing (receipt/triage/reporting) of SAEs within this clinical trial. The responsible vigilance contact person is:

Iva Penava, Safety Projects Manager,
Syneos Health
Email: safetyreporting@syneoshealth.com

Details and Instructions on the procedures for the documentation, evaluation and reporting of SAEs occurring in this clinical trial to the German Federal Institute for Drugs and Medical Devices (BfArM) can be found on www.bfarm.de and in the study specific Safety Management Plan.

### 9.3.3 Contacting Endotronix Regarding Safety

Contacts for SAE/ USADE receipt can be found on the Sponsor/Medical Monitor Contact Information page in the Site File.

## 9.4 Device/System-Related Complication (DSRC)

Any suspected Cordella PA Sensor System malfunction will be reported to Endotronix and recorded on the eCRF. Any potentially affected component(s) will be returned to Endotronix for evaluation upon request by Endotronix. A DSRC is defined as an adverse event that is, or is possibly, related to the device/system (Cordella PA Sensor System or electronic components) and is either treated invasively (other than intramuscular medication or diagnostic RHC) or results in patient death or explant of the device.

Pressure Sensor Failure is assumed when the sensor malfunctions and no readings can be obtained.

All attempts to troubleshoot (including recalibration) should be exhausted including ruling out any problems with the electronic components, prior to determining that a Pressure Sensor Failure has occurred.

## 9.5 Study Implant Card

As the subjects are not under 24-hour supervision of the Investigator or site staff, they must be provided with a "study/implant card" indicating the following:

- Investigational device name/model
- Investigational device identifiers (serial numbers, etc.…)
- Study number
- Investigator's name
- 24-hour emergency contact number

- Warnings or precautions
- Expected lifetime of the investigational device
- Any other information to ensure safe use of the investigational device

# 10 STATISTICAL CONSIDERATIONS

## 10.1 General Statistical Considerations

All data collected in this study will be documented using summary tables and subject data listings. For categorical variables, frequencies and percentages will be presented. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented.

Demographic data, including sex, gender, race, age, weight, height, race, ethnicity, BMI, and screening assessments (e.g., primary cardiac diagnosis, previous cardiac history, duration of HF, number of hospitalizations in past year for cardiac) will be summarized using frequencies and percentages, or descriptive statistics, as applicable.

Any deviations from the planned statistical analyses will be reported with proper justification as a protocol deviation.

Statistical analysis will be performed using SAS version 9.3 or higher.

## 10.2 Analysis Population

The focus of analyses will be on treated subjects from Cohort #2 and #3 (previously enrolled **Treatment Arm** subjects and Newly Enrolled subjects). Unless otherwise specified, the sets defined below are based only on these two treated cohorts.

### 10.2.1 Enrolled Set

The Enrolled Set will include all subjects enrolled from Cohort #2 and #3. Screen failures are not entered into the database and are therefore not included in this set.

### 10.2.2 Intent-to- Treat Population (ITT)

The Intent-to-Treat Population (ITT) will include all enrolled subjects intended to receive the Cordella PA Sensor who entered the Cath Lab, including those in whom Implant Procedure is not attempted for whatever reason (e.g., Cordella PA Sensor Implant cannot be performed due to anatomical reasons) from Cohort #2 and #3. Subjects in this population in whom the Cordella PA Sensor Implant is not attempted will be followed through 30 days for safety purposes. The ITT will be used for all analyses of safety endpoints. Effectiveness analysis will not be performed on the ITT population.

### 10.2.3 Modified Intent-to-Treat Population (mITT)

The Modified Intent-to-Treat Population (mITT) will include all implanted subjects form Cohort #2 and Cohort #3. All primary and secondary effectiveness analyses will be performed on the mITT.

### 10.2.4 Per Protocol Population (PP)

The Per Protocol Population (PP) will include all mITT subjects without any major protocol deviations. All primary and secondary safety and effectiveness analyses will be performed in addition on PP population. If PP and mITT populations will be identical, analysis will be performed based on mITT only.

### 10.2.5 Cohort #1- Previously enrolled Control Arm subjects- Population

This subgroup will include all Cohort #1 (previously enrolled Control Arm) subjects and will be reported separately for all endpoints.

## 10.3 Primary Efficacy Endpoint and Hypotheses

To meet the objectives of the study, observed event rates in the single arm PROACTIVE-HF should be similar to observed event rates in the treatment arm of CardioMEMS studies. Furthermore, observed event rates in the single arm PROACTIVE-HF should be lower than observed event rates in the control arm of CardioMEMS studies.

Thus, we set the performance goal (PG) as the LOWER of 1) the meta-analysis upper bound confidence interval of CardioMEMS treated patients, and 2) the meta-analysis estimate of CardioMEMS control patients, further adjusted down by potential impact of SGLT2i.

Furthermore, we also require that the single arm PROACTIVE-HF observed event rate is LOWER than both 1) the meta-analysis estimate of CardioMEMS treatment patients, and 2) the lowest observed event rates of CardioMEMS control patients, further adjusted down by potential impact of SGLT2i.

The primary endpoint will be the 6 month incidence of HF related Hospitalizations (HFH) or all-cause mortality compared to a PG.

Meta-analysis of treatment and control event rates were considered in determining the Primary Endpoint PG. Meta-analyses were based on a random effects meta-analysis for the log-transformed

incidence rate fit via restricted maximum likelihood. Results are back transformed to the rate scale. Calculations were performed in R version 3.6.3 with the "metafor" package.

The mean 6 month event rate from the meta-analysis of prior control studies is 0.46, or 0.43 on an adjusted basis to account for SGLT2i inclusion in the guidelines[a]. A 6 month event rate of 0.43 also represents a value just below both the highest event rate observed across the CardioMEMS treatment studies (0.44 in MEMS-HF) and the upper bound of the overall meta-analytic treatment estimate (0.44). Taking the totality of results from the meta-analysis of active treatment trials, individual results of active treatment trials, as well as the meta-analysis of control trials, we set the primary endpoint performance goal ($PG_6$) at 0.43.

Furthermore, the mean 6 month event rate from the meta-analysis of prior treatment studies is 0.38, with both the CHAMPION (0.37) and GUIDE-HF (0.31, NYHA class III) treatment groups with event rates lower than the mean. The lowest 6 month event rate across CardioMEMS control studies of 0.39 occurred in GUIDE-HF (NYHA class III), where modest use of SGLT2i occurred during the trial. We conservatively adjust this lowest observed control event rate down to 0.37 to account for increased SGLT2i utilization.

The table below outlines the data sources used to derive a PG for this endpoint.

Since patient level data was not available and summary data was limited in scope, analysis was based on the numbers of events reported from each study and the number of enrolled subjects was for denominator, assuming all subjects were followed for the corresponding time period. Accordingly, the estimates are likely conservative underestimates of true rates since complete follow-up on all subjects was unlikely.

For studies reporting only 12 month rates, estimates of 6 month rates were estimated via an exponential distribution. For example, for a study with a reported 12 month rate, $r_{12}$, we calculated the 6 month rate, $r_6$, as:

$$r_6 = 1\text{-}\exp(\log_n(1- r_{12})/2)$$

where the division by two (2) accounts for a calculation of the rate for half the follow-up time (i.e. a linearized rate). When possible, events of each type (HF related hospitalization and death) were

[a] Adjustment applied assuming 50% use of SGLT2i at the average hazard ratio observed across EMPEROR Preserved, EMPEROR REDUCED, DAPA-HF for NYHA III subjects.

calculated separately and summed to produce the composite event counts and the corresponding composite rate. Rates are calculated as numbers of events over numbers of subjects.

**Active Treatment - updated 6 Month Rates with calculation details**

| Study/Publication | Number of Subjects[1] | Events | Rate[2] | Details |
|---|---|---|---|---|
| CHAMPION[19] | 270 | 99 | 0.37 | - 6 month HFH rate reported as 0.31, yielding approx. 84 events<br>- 15 deaths reported<br>- Adding calculated 6 month HFH events and deaths yields 99 events |
| MEMS PAS[44] | 1200 | 493 | 0.41 | - 6 month rate calculated via reported 12 month rate of 0.54<br>- Calculated 6 month HFH rate of 0.32, yielding 386 events<br>- 107 deaths reported<br>- Adding calculated 6<br>- month HFH events and deaths yields 493 events |
| MEMS-HF [46] | 234 | 102 | 0.44 | - 6 month HFH calculated via reported 12 month rate of 0.60<br>- Calculated 6 month HFH rate of 0.37, yielding 86 events<br>- 16 deaths reported<br>- Adding calculated 6 month HFH and deaths yields 102 events |
| GUIDE-HF [52] – NYHA class III only | 322 | 100 | 0.31 | - Reported 12 month rate of 0.431/0.089 for HFH/D, for composite of 0.52.<br>- Assuming exponential rate, calculated 6 month rate (events) is 0.31 (100)<br>- Events calculated as 322 subjects x 0.31 |
| Estimate (CI) | | | 0.38 (0.33, 0.44) | |

[1] Numbers of subjects are those treated subjects estimated to be followed for 6 month events.
[2] Estimates for events are based on either reported results or are estimated from published figures. For studies reporting 12 month results, 6 month rates were estimated based on exponential rates.

Altogether, for study success, *the upper confidence bound of the observed event rate* for the planned study must be less than the $PG_6$ (0.43) and the observed event rate must be less than 0.37. Evaluating the upper bound of the confidence interval for the rate ensures that 1) the observed rate will be comparable to prior studies of active treatment (highest observed value = 0.44), 2) the observed rate will be less than the meta-analytic value derived from prior studies of treatment and control, and 3) the observed rate will be less than the lowest rate observed in the control studies (GUIDE HF). The added requirement for the observed event rate to be less than 0.37 provides further assurance that results are comparable to studies of prior CardioMEMS treatment.

The assumed PROACTIVE-HF population event rate is expected to be 0.34. This assumed event rate is lower than all prior active CardioMEMS treatment rates except for GUIDE-HF. While the

contemporary GUIDE-HF study observed an event rate of 0.31 (NYHA Class III), PROACTIVE-HF has higher NTproBNP thresholds than the GUIDE-HF cohort and we expect subjects with higher NTproBNP levels to more closely align with subjects with a recent hospitalization, which have higher event rates.

The mathematical statement of the null and alternative hypothesis is as follows:

$H_O$: $r_6 \geq PG_6$
$H_A$: $r_6 < PG_6$

where $r_6$ is the 6 month rate of primary endpoint events and $PG_6$ is the performance goal. A value of 0.43 will be used for the goal. The null hypothesis will be rejected if the upper confidence bound for the rate is less than the performance goal, or equivalently, that the corresponding p-value from the hypothesis test is less than 0.025. An observed rate of less than 0.37 and rejection of the null hypothesis indicate that the observed rate is statistically less than the performance goal, indicating clinically acceptable results and study success. Analysis will be based on a Poisson regression approach for the number of events, with the log follow-up time as an offset term. Sensitivity analyses using a negative binomial approach to capture within-subject correlation will be performed.

The study will implant 450 subjects (combined in Cohort #2 and Cohort #3) leading to an expected evaluable cohort of 406 subjects. With a goal of 0.43 and a one-sided 0.025 alpha level, the study will have greater than 80% power assuming a population treatment rate of 0.34. Calculations are based on a one-sample Poisson rate test and were performed with PASS 2021.

### 10.4 Additional Secondary Efficacy Endpoints

The first secondary efficacy endpoint is incidence of HF Hospitalizations or all-cause mortality at 12 months compared to a PG.

The mean 12 month event rate from the meta-analysis of prior control studies is 0.75, or 0.70 on an adjusted basis to account for SGLT-2i inclusion in the guidelines[b]. A 12 month event rate of 0.70 represents a value just below the highest event rate observed across the CardioMEMS treatment studies (0.73 in MEMS-HF) and the upper bound of the overall meta-analytic treatment estimate (0.74). Taking the totality of results from the meta-analysis of active treatment trials, individual

[b] Adjustment applied assuming 50% use of SGLT2i at the average hazard ratio observed across EMPEROR Preserved, EMPEROR REDUCED, DAPA-HF for NYHA III subjects.

results of active treatment trials, as well as the meta-analysis of control trials, we set the secondary endpoint performance goal ($PG_{12}$) at 0.70.

Furthermore, the mean 12 month event rate from the meta-analysis of prior treatment studies is 0.64, with both the CHAMPION (0.6) and GUIDE-HF (0.52, NYHA class III) treatment groups with event rates lower than the mean. The lowest 12 month event rate across CardioMEMS control studies of 0.63 occurred in GUIDE-HF (NYHA class III only), where modest use of SGLT2i occurred during the trial. We conservatively adjust this lowest observed control event rate down to 0.59 to account for increased SGLT2i utilization.

The table below outlines the data sources used to derive a PG for this endpoint.

**Active Treatment - updated 12 Month Rates with calculation details**

| Study/Publication | Number of Subjects[1] | Events | Rate[2] | Details |
|---|---|---|---|---|
| CHAMPION[53] | 270 | 162 | 0.60 | - HFH rate of 0.46, yielding approx. 124 events<br>- Mortality rate of 0.14, yielding approx. 38 events<br>- Total events = 124 + 38 |
| MEMS PAS[44] | 1200 | 840 | 0.70 | - HFH rate of 0.54, yielding 648 events<br>- Mortality rate of 0.16, yielding 192 events<br>- Total events = 648 + 192 |
| MEMS-HF [46] | 234 | 171 | 0.73 | - HFH rate of 0.60, yielding 140 events<br>- Mortality rate of 0.13, yielding approx. 30 events<br>- Total events = 140 + 31 |
| GUIDE-HF [51] – NYHA class III only | 322 | 167 | 0.52 | -<br>- HFH rate of 0.431 + plus death rate of 0.0897<br>- Composite rate = 0.52<br>- Total events = 322 subjects x 0.52 |
| Estimate CI | | | 0.64 (0.55, 074) | |

Altogether, for study success, *the upper confidence bound of the observed event rate* for the planned study must be less than the $PG_{12}$ (0.70) and the observed event rate must be less than 0.59. Evaluating the upper bound of the confidence interval for the rate ensures that 1) the observed rate will be comparable to prior studies of active treatment (highest observed value = 0.74), 2) the observed rate will be less than the meta-analytic value derived from prior studies of treatment and control, and 3) the observed rate will be less than the lowest rate observed in the

control studies (GUIDE HF). The added requirement for the observed rate to be less than 0.59 provides further assurance that results are comparable to studies of prior treatment.

The assumed PROACTIVE-HF population event rate is expected to be 0.55. This assumed event rate is lower than all prior active CardioMEMS treatment rates except for GUIDE-HF. While the contemporary GUIDE-HF study (NYHA class III only) observed an event rate of 0.52, PROACTIVE-HF has higher NTproBNP thresholds than the GUIDE-HF cohort and we expect subjects with higher NTproBNP levels to more closely align with subjects with a recent hospitalization, which have higher event rates. The mathematical statement of the null and alternative hypothesis for the first secondary efficacy is as follows:

$H_O$: $r_{12} \geq PG_{12}$
$H_A$: $r_{12} < PG_{12}$

where $r_{12}$ is the 12 month rate of secondary endpoint events and $PG_{12}$ is the performance goal. A value of 0.70 will be used for the goal. The null hypothesis will be rejected if the upper confidence bound for the rate is less than the performance goal, or equivalently, that the corresponding p-value from the hypothesis test is less than 0.025. An observed value of less than 0.59 and rejection of the null will indicate that the observed rate is statistically less than the performance goal, indicating clinically acceptable results. Analysis will be based on a Poisson regression approach for the number of events, with the log follow-up time as an offset term. Sensitivity analyses using a negative binomial approach to capture within-subject correlation will be performed.

Sample size calculations for the first secondary endpoint were performed in PASS 2021 and based on an assumed population event rate of 0.55, the sample size of 450 subjects would provide approximately 95% power for the secondary endpoint based on a one-sided 0.025 alpha level. If 406 subjects are followed for 12 months, approximately 95% power will be provided, so that the planned sample size is sufficient in light of potential attrition.

Formal hypothesis testing for the purposes of labeling claims for the first secondary efficacy endpoint will only be performed if the null hypothesis for the primary efficacy endpoint is successfully rejected.

This gatekeeping approach preserves the overall type I error rate. Any other calculated P-values and confidence intervals for secondary endpoints will be nominal, without adjustment for multiple comparisons.

The remaining secondary efficacy endpoints are as follows:

1. Number of HF Hospitalizations at 6 and 12 months post-implant compared to the number of HF Hospitalizations in the 6 and 12 months prior to implant

2. Comparison of the number of HF Hospitalizations or Emergency Department/ Hospital Outpatient IV diuretic visits of Cohort #1 and Cohort #2+#3 at 6 and 12 month post implant
3. Change of NT-pro BNP from Baseline through 6 and 12 months
4. Combined outcome of:
    a. First and recurrent HF Hospitalizations
    b. Emergency Department/ Hospital Outpatient IV diuretic visits
    c. all-cause mortality

    at 6 months, added together with equal weighting into a total number of events
5. Heart failure hospitalization or Emergency Department / Hospital Outpatient IV diuretic visits at 6 and 12 months
6. Cardiac and all-cause mortality
7. Days Alive and Out of Hospital (DAOH)
8. IV diuretic visits
9. Heart failure related Medication changes
10. Change in PAP:
    a. From Baseline through 6 and 12 months in subjects with a baseline mPAP
        i. above target range
        ii. within or below target range
        iii. Overall
    b. Before and after 6-Minute Walk Test
11. Percentage of device success as documented by ability of the System to successfully transmit PAP data
12. Patient Outcome Measures, measured by KCCQ
13. Functional status improvement, as measured by NYHA and 6-Minute Walk Test
14. Health Economic Analysis

### 10.5 Safety Endpoints

There are two primary safety endpoints, Freedom from device/system related complication at 6 months and Freedom from pressure sensor failure at 6 months. Freedom from device or system related complications at 6 months will be tested against the null rate of 90%. Freedom from Pressure Sensor Failure at 6 months will be tested against the null rate of 95%.

Mathematical statements of the null and alternative hypothesis for each test are as follows:

$H_O$: S1 ≤ $PG_{S1}$

$H_A$: S1 > $PG_{S1}$

and

$H_O$: S2 ≤ $PG_{S2}$

$H_A$: S2 > $PG_{S2}$

where S1 and S2 represent the freedom-from-event rates for device/system related complication at 6 months, and pressure sensor failure at 6 months respectively, and $PG_{S1}$ and $PG_{S2}$ represent the corresponding performance goals with values expressed as a proportion of 0.90 and 0.95 respectively.

Each of these will be assessed within among all patients who underwent a device implant by estimating freedom from the event of interest at 6 months by the Kaplan-Meier method. The proportion event free at 6 months and the corresponding two-sided 95% confidence interval will be compared to the null rate. We use a one-sample test of binomial proportions with a two-sided Type I error rate of 5% to estimate the power available for these analyses.

A sample size of 450 patients provides greater than 95% power assuming a population rate of 95% for the freedom-from-event rates for device/system related complication at 6 months. Power would still be maintained at this level for an evaluable sample size of 406.

Similarly, a sample size of 450 patients provides approximately greater than 95% power assuming a population rate of approximately 98.4%, for the pressure sensor failure at 6 months endpoint. Power would still be maintained at this level for an evaluable sample size of 406.

Primary Safety Endpoints:

1. Freedom from device/system related complication at 6 months
2. Freedom from pressure sensor failure at 6 months

In addition to the two (2) primary safety endpoints with hypothesis tests, the following secondary safety endpoints will be summarized.

Secondary Safety Endpoints:

1. Pressure sensor failure rate throughout the study
2. Frequency of serious adverse events throughout the study
3. Frequency of implant procedure and procedure related adverse events and serious adverse events

### 10.6 Analysis sites

The study will be conducted such that: 1) the same protocol will be used at each study site; 2) site investigators and personnel will receive uniform training; and 3) central data management, and

monitoring will be applied with equal rigor at all sites. The diversity of hospital and clinical practice settings will add to the scientific validity and generalizability of the findings.

Subjects will be pooled across sites for analysis of study endpoints.

Sites with at least 20 subjects will retain their identities. Smaller sites will be ranked in decreasing order of size (site identification numbers, smallest first, will be used to break ties) and cumulatively pooled until pooled sites of no less than 10 subjects are achieved. After this pooling process, we will test for homogeneity in the treatment effects across site with a likelihood ratio test of the hypothesis that all sites have the same rate. The homogeneity test will be conducted at the 0.15 level based on Fisher's exact test.

### 10.7 Adverse Events and Other Safety Analyses

Adverse events and other safety analyses will also be assessed. No formal statistical hypothesis tests will be conducted. Analyses will involve Kaplan-Meier curves for time to event outcomes, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for quantitative outcomes, and count and frequency results for categorical outcomes.

### 10.8 Study Retention and Handling of Missing and Incomplete Data

Every effort will be made to collect all data points in the study. Endotronix plans to minimize the amount of missing data by appropriate management of the prospective clinical trial, proper screening of study subjects, and training of participating investigators, monitors and study coordinators. The primary efficacy analysis will be based on the mITT population and the primary safety analyses will be based on the population of patients who underwent a device implant. The primary analysis methods naturally handle missing data by censoring patients who have dropped out. Sensitivity analyses to missing data will be conducted. For the primary safety analyses, the endpoints can be considered as dichotomous and the extreme cases as well as a tipping point analysis can be presented. Reasons for missing data (e.g., patient withdrawal of consent, death, etc.) will be captured and summarized.

# 11 ETHICAL ASPECTS

## 11.1 Ethical Considerations

This trial is to be conducted according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ISO 14155:2020, ICH GCP and applicable regulatory requirement(s) including the Code of Federal Regulations (CFR) 21CFR Part 812, 21CFR Part 54 and 21CFR Part 56.

The Investigator is responsible for ensuring that the clinical trial is performed in accordance with the protocol/ CIP, current ISO 14155:2020, ICH guidelines on GCP, and applicable regulatory requirements.

Good Clinical Practice is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of the trial subjects are protected.

The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician. Each individual involved in conducting the trial should be qualified by education, training and experience to perform his or her respective task(s).

The trial can only start at the Investigator's site when the relevant IRBs/ IECs have given signed and dated approval of the protocol/CIP, written ICFs and other written information to be provided to the subjects (e.g., questionnaires).

## 11.2 Subject Information and Consent

All subjects will be informed that participation is voluntary and that they can cease participation at any time without necessarily giving a reason and without any penalty or loss of benefits to which they are entitled. However, the Investigator should try to exclude an adverse event as the reason for withdrawing voluntarily.

With the help of the Information Sheet, the subject will be informed about the device and anticipated effects, and the reason, design and implication of the trial. The subject must give consent to participate prior to enrollment in the trial. This consent must be given in writing or orally in the subject's native non-technical language that is understandable to the subject if witnessed by a third party due to the subject's condition if allowed for by local legislation. The witness must sign the consent form. The person who conducted the ICF discussion must also sign. With consent, the

subject will confirm that his participation is voluntary and that they will follow the instructions of the Investigator and answer the questions asked. Signatures must be personally dated.

Prior to participation in the trial, the subject, should receive a copy of the signed and dated written ICF and any other pertinent written information.

The ICF and Information Sheet must include all elements required by law, local regulations and ICH GCP guidelines, and CA requirements as well as trial specific items.

The subject must be informed that it may be necessary for the analysis of certain data that their name will remain visible whilst the analysis is performed. The results of the analysis will be processed so that the confidentiality of the subject is maintained.

Neither the Investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in the trial. The Investigator should not include themselves, their relatives, and members of their clinical team or their relatives in the trial. Ample time must be allowed for the subject to make his or her decision, and to make further enquiries about the trial.

The signed and dated consent form will be kept by the Investigator.

Should new information become available during the course of the trial that may be relevant to the subject's consent, the Information Sheet will be revised. The revised version will be submitted for IRB/IEC approval before use. The subject must be informed as soon as possible if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented. The subject should receive a copy of any updates to the signed and dated written ICF or other pertinent written information.

### 11.3 Institutional Review Board (IRB)/Independent Ethic Committee (IEC)

An Institutional Review Board (IRB)/ Independent Ethic Committee (IEC) will safeguard the rights, safety, and well-being of all trial subjects. This study will be undertaken only after full approval of the protocol addenda, and ICFs have been obtained from an IRB/ IEC and a copy of this approval has been received by Endotronix.

The IRB/ IEC must be informed of all subsequent protocol amendments issued by Endotronix.

Reports on, and reviews of, the study and its progress will be submitted to the IRB/ IEC by the investigator at intervals stipulated in their guidelines.

At study termination, a Final Report must be submitted by the Investigator to their respective IRB/ IEC.

Copies of all submissions to and correspondence (approvals and disapprovals) from the IRB must be maintained on file at the study site.

### 11.3.1 Investigator Reports

Investigators are required to prepare and submit the following complete, accurate and timely reports on this investigation to Endotronix Clinical Operations or designee.

Responsibilities for Preparing and/or Submitting Reports

| Type of Report | Submit to | Time of Notification to Endotronix | Time of Notification to IRB/ IEC |
|---|---|---|---|
| Suspected Device Malfunction or problem | Endotronix, IRB, IEC | Within 5 working days of knowledge | As required |
| Device Failure | Endotronix, IRB, IEC | Within 72 hours of knowledge | As required |
| Unanticipated Adverse Device Event | Endotronix, IRB, IEC | Within 24 hours of knowledge | Within 10 days |
| Subject death during study | Endotronix, IRB, IEC | Within 24 hours of knowledge | As required |
| Subject withdrawal | Endotronix, IRB, IEC | Within 72 hours of knowledge | As required |
| Withdrawal of IRB approval | Endotronix, IRB, IEC | Within 72 hours of knowledge | Not Applicable |
| Serious deviations from the protocol/CIP | Endotronix, IRB, IEC | Within 5 working days | As required |
| ICF not obtained | Endotronix, IRB, IEC | Within 5 working days | As required |
| Progress Reports | Endotronix, IRB, IEC | At least annually | At least annually |
| Final summary report | Endotronix, IRB, IEC | ≤6 months of study completion | ≤6 months of study completion |
| Other information as requested by Endotronix, IRB and/or regulatory bodies | As appropriate | As requested | As requested |

## 11.4 Annual Report

Endotronix will provide the FDA/ CAs with an Annual Progress Report, where applicable. Investigators must provide their annual progress reports to Endotronix in a timely fashion to allow compliance with this requirement. Individual IRBs/ IEC will be provided with copies of the annual progress reports, where applicable.

## 11.5 Insurance

Insurance for the subjects participating in this trial which will provide compensation to subjects for clinical investigation related injuries will be arranged by Endotronix.

A copy of the insurance certificate will be held in the central or the country specific parts of the Trial Master File at Endotronix.

The insurance regulations will be handed over to the subjects upon request.

## 11.6 Regulatory Affairs

This trial will be carried out in compliance with legal regulations. Before initiating the trial Endotronix and/or the Investigator, if required by the applicable regulatory requirement(s), will submit any required application(s) to the appropriate authorities for review, acceptance, and/or permission to begin the trial. A copy of the submission will be held in the central files.

The Investigator will be informed by Endotronix when new information about the Device and adverse events due to the Device becomes available.

## 11.7 Investigators and Trial Administrative Structure

### 11.7.1 Investigator

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, Declaration of Helsinki, ISO 14155:2020, ICH GCP Guidelines, and 21CFR Part 812, 21CFR Part 54 and 21CFR Part 56, and any country laws, as applicable.

If the trial is conducted by a team of individuals at the trial site, the Investigator is the responsible leader of the team and may be called the Principal Investigator.

A Sub-Investigator (e.g., associates, residents, research fellows) is any individual member of the clinical trial team designated and supervised by the Principal Investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions.

The Investigator must maintain a signed list of appropriately qualified persons to whom they have delegated significant trial-related duties which must be specified. A copy is held in the site files at Endotronix and the Contract Research Organization (CRO).

Trial-related medical decisions are the responsibility of a qualified physician (the Investigator or delegate).

Curricula vitae and/or other relevant documents confirming the qualifications of the Investigator and Sub-Investigators are required by Endotronix/the CRO. Any previous training in the principles of GCP or experience obtained from work with clinical trials and subject care should be described in the curriculum vitae. When personnel changes are made, the relevant documentation must be updated before a new member of the team can perform critical and/or significant trial-related activities.

The Investigator has to comply with the local legal requirements concerning reporting of information relevant for the trial conduct. The standard requirements for IRB review, ICF, subject data protection, investigator agreements and financial disclosures will apply.

#### 11.7.1.1 Investigator Agreement

Prior to study initiation, the Investigator must sign an Investigator Agreement (Endotronix to provide Investigator Agreement template to sites). The Investigator Agreement identifies the Investigator's legal and ethical commitments with respect to the conduct of the clinical study as defined in Practice 21 CFR Part 812, Part 56, Part 50, and Part 54 and ISO 14155:2020.

In addition, responsibility for insurance or indemnity to cover any liability of the Investigator which may arise directly or indirectly from his participation in the trial will be specified in a contract between the Investigator and / or Institution and Endotronix.

#### 11.7.1.2 Financial Disclosure

A Financial Disclosure Form must be reviewed and signed by the Investigator and sub-investigator(s) prior to study initiation. Endotronix or designee will provide Financial Disclosure Form to sites. Updates to financial disclosure will be made during the course of the study and for 1 year following completion of the study (21 CFR Part 54).

The Financial Disclosure form is required to record the Investigator's and Sub-Investigator's financial interests in Endotronix which may be a potential source of bias in the outcome of the clinical study.

#### 11.7.1.3 Protocol/ CIP Deviations and Medical Emergencies

The Investigator will not deviate from the protocol without the prior written approval of Endotronix except in medical emergencies or in unforeseen, isolated instances where

minor changes are made that will not increase the subject's risk or affect the validity of the study. In addition, Endotronix will not allow any deviations/waiver from the Inclusion and Exclusion Criteria.

In medical emergencies, prior written approval for protocol deviations will not be required, but Endotronix personnel must be notified via telephone within 24 hours of occurrence.

If there are any circumstances during the clinical trial which can affect the safety of the subjects, users or third person, Endotronix and the investigator will take all necessary security measures immediately to protect the subjects, users and third persons against direct or indirect risk. Endotronix and the investigator must inform FDA/CA and the responsible IRB/IEC immediately about these new circumstances and the measures taken.

However, in case of any deviation for a scheduled assessment e.g., out of window assessment, missing laboratory sample, and prior approval from Endotronix is required in advance for changes in or deviations from the protocol.

### 11.7.2 Endotronix (Sponsor)

Endotronix accepts the responsibilities of the Sponsor.

### 11.7.3 Contract Research Organization

A CRO (Syneos Health) has been employed by Endotronix to perform 1 or more of its trial-related duties and functions. The extent of the delegation must be specified in a contract between the involved parties. The CRO should implement quality assurance and quality control but Endotronix will have the right to supervise the implementation of the methods for quality assurance and quality control.

### 11.7.4 Endotronix (Device Support)

Endotronix Device Support involved in many trial-related duties and functions in cooperation with Endotronix Clinical Operations. Their tasks include but are not limited to:

- Training the Investigator and site staff in the use of the Cordella™ Heart Failure System including CorPASS
- Ongoing education
- Implant support
- On-Call clinical and technical support
- Assist with subject training
- Device inventory and replacement
- Complaints (Cordella System only)
- Device Deficiencies (DD)

This will be specified case by case before actions for the trial are taken and documented in the trial documentation.

# 12 DOCUMENTATION OF TRIAL DATA

## 12.1 Case Report Forms

An Electronic Data Capture (EDC) system will be utilized to collect all subject data during the course of the study. Data must be entered into eCRFs in English. The eCRFs are to be completed within 72 hours of the subject's visit, with the exception of results from tests performed outside the investigator's office, so that they always reflect the latest observations on the subjects participating in the study. This includes all medication changes in between study visits. A predetermined/designated individual(s) will be responsible for completion of the Electronic Case Report Forms (eCRFs). The PI will ultimately be responsible for the review, completion and accuracy of data entered into the eCRF.

Completed eCRFs will be verified by a Sponsor monitor at the site at regular intervals throughout the study. The Investigator will allow the monitor and the regulatory bodies (Competent Authorities (CAs)) to review the study files, subject eCRFs, medical records and other study-related documents.

## 12.2 Data Management

### 12.2.1 Data Management

Data Management will be coordinated by Endotronix or their assigned designee.

### 12.2.2 eCRFs

During data entry in the eCRF, queries will be directly issued to clarify missing data, inconsistencies and incorrect values. After completion of the eCRF, further queries will be issued to the Investigator to clarify (e.g., inconsistencies resulting out of the medical and manual review). Resolutions of queries will be made by the Investigator or the trial site's designated persons. The query is answered directly in the eCRF system and the original value is changed, if necessary.

### 12.2.3 Coding

Medication names will be coded using the World Health Organization Drug Dictionary. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The version most currently implemented when the first subject is enrolled will be used through the study. Coding will be reviewed by an Endotronix Medical Monitor.

### 12.2.4 Source data

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents which comprise clinical documentation, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments and data and records arising from other departments such as the pharmacy, laboratory and medico-technical departments).

Clinical documentation relevant to the trial includes all records in any form including, but not limited to:

- Medical history/physical condition of the subject before enrollment sufficient to verify
- Protocol entry criteria
- Dated and signed notes for specific results of procedures and exams
- Laboratory reports
- Concomitant Medications incl. changes
- Information related to adverse events
- Notes on subject's condition with device implanted and when explanted
- Quality of Life studies
- Discharge Summaries/Procedure reports
- Autopsy reports

All clinical documentation and data arising from the trial are to be kept by the Investigator who must provide direct access for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

In certain circumstances, data may only be recorded in the trial specific eCRF and not in other documents. When this occurs, the eCRF is considered to be the source document.

At the end of the trial, the Investigator will receive a certified copy of all data captured for their subjects, in human readable form, on a read-only CD-ROM. Data captured of all subjects will be sent to the sponsor in human readable form, on a read-only CD-ROM for archiving.

## 12.3 Data Review

All eCRFs will be reviewed for completeness and clarity. Missing data will be investigated by the monitor and clarified by study personnel as necessary. Endotronix may request additional documentation such as physician procedure notes or written summaries relating to adverse events or procedures. Endotronix will be responsible for the quality control of the database and confirming the overall integrity of the data.

### 12.4 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol/ CIP procedures with the investigator and associated personnel prior to the study and periodic monitoring visits by the sponsor. eCRFs will be reviewed for accuracy and completeness by the sponsor during on-site monitoring visits and after their return to Endotronix and any discrepancies will be resolved with the investigator or designees, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

### 12.5 Database lock

When all data are received, all data checks and quality control checks have been performed, and a final data review meeting has been held, the trial database is considered clean and can be locked.

# 13 ADMINISTRATIVE REQUIREMENTS

## 13.1 Monitoring of the Study

Endotronix contracted a CRO who will perform on-site monitoring visits as frequently as necessary. Visits are usually made at intervals of at least four to twelve weeks. The dates of the visits will be recorded by the monitor in a study center visit log to be kept at the site. The first post initiation visit will usually be made as soon as possible after enrollment has begun. At these visits the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). At a minimum, source documentation must be available to substantiate proper ICF procedures, adherence to protocol/ CIP procedures, adequate reporting and follow-up of AEs, administration of concomitant medication and device receipt/ return records. Specific items required as source documents will be reviewed with the investigator prior to the study. Findings from this review of eCRFs and source documents will be discussed with the investigator. The sponsor expects that, during monitoring visits, the investigator (and as appropriate the study coordinator) will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents.

## 13.2 Independent Data Review and Event Adjudication

To meet the trial's ethical responsibility to its subjects, results will be monitored by two independent groups that have no formal involvement with the subjects or the investigation, as follows:

1. DSMB- Data Safety Monitoring Board.
2. CEC- Clinical Events Committee.

The members of these committees shall function independently of Endotronix and the CRO.

### 13.2.1 DSMB and CEC Composition

These two committees will include a Data Safety Monitoring Board (DSMB) and Clinical Events Committee (CEC). Each committee will be composed of at least three or more members (at least two physicians from the fields of HF cardiology and Interventional Cardiology) who are not directly involved in the conduct of the trial. A semi-annual report will be provided to the FDA, which will include the names of each DSMB and CEC member.

### 13.2.2 DSMB

The DSMB will review the study at key points during the conduct.

The first DSMB safety review will take place after the first 50 subjects which have been implanted with the Cordella PA Sensor reached their Month 3 follow-up. The next DSMB

safety will then take place after the first 100 implanted subjects reached their 30-day follow-up.

Periodic safety review of study data every six months from the date of the first Cordella PA Sensor implant. Members will be provided data summaries (listings) from the clinical study in a blinded fashion without site or physician identification. Based on the safety data, the DSMB may recommend that the trial be modified or stopped. No formal statistical rule will be defined for stopping the trial for safety reasons.

The DSMB process (including their ability to stop an ongoing study due to safety concerns) is documented in the study specific DSMB Charter.

### 13.2.3 CEC

The CEC will adjudicate all events including device malfunctions dynamically. Each event will be adjudicated by an independent CEC committee (at least 3 reviewers) with the final adjudicated result being a consensus of the committee.

The CEC process is documented in the study specific CEC Charter.

## 13.3 Quality System, Audit and Inspection

### 13.3.1 Quality system

Endotronix is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures. Endotronix/the CRO is responsible for ensuring that all parties involved with the trial agree to direct access to all trial-related sites, source data and documents, and reports for the purposes of monitoring and auditing by Endotronix/the CRO, and inspection by domestic and foreign regulatory authorities.

The documentation of the trial should be adequate for reconstruction of the course of events (audit trail).

### 13.3.2 Audit

An audit is the systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data recorded, analyzed and accurately reported according to the protocol/ CIP, Endotronix /the CRO's Standard Operating Procedures, GCP and applicable regulatory requirements.

The Investigator will permit an appointed person by the Quality Assurance Unit of Endotronix/the CRO to audit the facilities and documentation at agreed times. Auditors are independent of the clinical trial and its performance.

#### 13.3.3 Inspection

Inspection is the act by regulatory authorities of conducting an official review of the documents, facilities, records and other resources that are deemed by the authorities to be related to the clinical trial and that may be located at the trial site, at Endotronix, at the CRO, or at other facilities deemed appropriate by the regulatory authorities. The Investigator is obliged to cooperate with any inspection.

### 13.4 Maintenance of Study Documentation

The Investigator must maintain the following documents throughout the study:

- Protocol/ CIP
- IRB/ IEC Approvals and Correspondence
- IRB/ IEC Approved ICF
- Correspondence with Endotronix
- Electronic Signature Authorization Form Device Accountability
- Investigator Agreements
- Curriculum Vitae
- Financial Disclosure Forms
- Telephone Logs
- Screening Logs
- eCRFs
- Monitoring Visit Log
- Laboratory Accreditation and Normal Values
- Site Delegation and Responsibility log
- Source Documents supporting information on eCRFs
- Any other study specific documents

### 13.5 Subject Data Protection

Subjects will be identified on the eCRF by a subject identification number. The investigator will maintain a confidential subject identification list separate from investigational files to link medical records and subject identification numbers.

All information and data sent to Endotronix or their authorized representative, concerning subjects or their participation in this study, will be considered confidential. All data used in analysis and

reports will be used without identifiable reference to the subject. At all times throughout the study, confidentiality shall be observed by all parties involved. All data shall be secured against unauthorized access.

All subjects consented for this study will be informed and must agree to the use and disclosure of their study information by the institution and investigators to Endotronix, their agents and representatives, the Competent Authorities (CAs) or other government agencies or review boards.

## 13.6 Protocol/ CIP Modifications

Changes to the protocol/ CIP during the trial will be documented as amendments. The amended protocol will be signed by the relevant personnel at Endotronix, and by the Investigator(s).

Depending on the contents of the amendment and local legal requirements, the amendment will be submitted to the relevant IRBs/ IECs and, where necessary, to the FDA/ national CAs of the participating EU member states.

The Investigator should not implement any deviation from, or changes to the protocol, without agreement by Endotronix and the CRO and prior review and documented approval/favorable opinion of the appropriate IRB/ IEC and, if legally required, the FDA/ CA, except where necessary to eliminate an immediate hazard to the subjects, or when the change(s) involve only logistical or administrative aspects of the trial.

If an amendment substantially alters the trial design, increases the potential risk to the subjects or affects the treatment of the subject, then the Information Sheet must be revised and submitted to the relevant IRB/ IEC and, where necessary, to the FDA/ national CAs of the participating EU member states, for review and approval. When a subject is currently undergoing trial procedures and is affected by the amendment, then the subject must be asked to consent again using the new Information Sheet. The new Information Sheet must be used to obtain consent from new subjects before enrollment.

In general, any substantial amendment to the CIP will be approved by the relevant IRB/IEC and, where necessary, by the FDA / national CAs of the participating EU member states before it can be implemented.

## 13.7 Compliance/ Investigational Site Termination

### 13.7.1 Compliance

Compliance is the adherence to all trial-related requirements, to Good Clinical Practice (GCP) and to regulatory rules and regulations.

### 13.7.2 Investigational Site Termination

An initiative for center closure or study termination can be taken at any time either by the sponsor or by the investigator, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Endotronix reserves the right to terminate an investigational site from the study for any of the following reasons:

- Repeated failure to complete case report forms
- Failure to obtain ICF
- Failure to report SAEs and UADEs/ USADEs
- Loss of or unaccountable investigational device inventory
- Repeated protocol/ CIP violations
- Failure of investigator to comply with training or Instructions for Use
- Failure to screen and/or enroll an adequate number of subjects
- Insufficient subject and caregiver/Companion training

## 13.8 Record Retention

Endotronix and all participating Investigators must establish and maintain records and reports. The Investigator must maintain the signed ICFs, eCRFs, study documentation (listed above) and source documents for at least 15 years from the date of the manufacture of the last product in agreement with the local regulations. Endotronix should be contacted if the Principal Investigator plans to leave or otherwise absent themselves from the investigational site.

In the event of an FDA/ CA audit, the Investigator must allow FDA/ CA access to the study records for inspection and copying. The Investigator must inform Endotronix of any FDA/ CA audit and provide Endotronix with a copy of Form FDA 483/ List of Observations, if issued.

The trial master file, the eCRFs, and other material supplied for the performance will be retained by Endotronix according to applicable regulations and laws.

## 13.9 Site Training

Sites will be trained by Endotronix on the device usage and on implant technique as appropriate. Training on GCP, protocol required procedures and data collection will be provided by the vendor(s).

## 13.10 Confidentiality of trial results

The results of this trial are confidential and are not to be transmitted to a third party in any form or fashion. All persons involved in the trial are bound by this confidentiality clause.

### 13.11 Publication policy

The results of the trial will be published as soon as the data for the primary endpoint is available, initially as a poster/presentation at a congress, and then as a full publication in an international cardiology/heart failure journal. Draft manuscripts of publications will be prepared in co-operation between Endotronix and the Coordinating Investigator/Investigator(s). Joint publications are only possible if all parties agree. All editorial decisions will be made jointly by Endotronix and the Coordinating Investigator/Investigator(s).

Endotronix reserves the right to review any publication pertaining to the trial before it is submitted for publication. Neither party has the right to prohibit publication unless publication can be shown to affect possible patent rights or regulatory submission requirements.

In case of discrepancies with other contracts, the provisions of the protocol shall prevail.

### 13.12 End of Investigation /Premature Termination /Suspension

For EU only: In accordance with the Article 77(1) the end of this trial or, if applicable, a temporary halt or early termination of the trial will be reported to the national CAs of the participating European member states within the timelines stipulated in Article 77(3 and 4) of the MDR (Regulation (EU) 2017/745).

### 13.13 Final report

A final report, integrating medical and statistical aspects, will be prepared. This will be authorized by the relevant personnel of Endotronix, and the Investigators. The Investigator(s) will be provided with a copy of the summary of the final report. Endotronix will provide the FDA/ CAs and IRBs/ IECs with the complete clinical trial report within 1 year after the end of the trial or on request, where required.

### 13.14 Organization/ Site personnel

It may be necessary to define additional site personnel (e.g., doctors, nurses, technicians) who have a special responsibility for the performance of portions of the trial at a site under the auspices of the Investigator. The information regarding all site personnel taking part in the trial will be documented and stored in the Investigator's site file.

# 14 APPENDICES

## 14.1 Time and Event Schedule

| Assessment | V1: Screening/ Enrollment (30 days)[15] | V2: Cordella PA Sensor Implant Visit | V3: Month 1 (±7 days) | V4 [11]: Month 3 (±7 days) | V5: Month 6 (±14 days) | V6: Month 12 (±30 days) | V7 to V8: Months 18, 24 (±30 days) | V9 to V11 Year 3, 4, 5 (±30 days) |
|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | |
| Subject Demographics | X | | | | | | | |
| Study Eligibility Review and Committee Approval | X | | | | | | | |
| Cardiac/Medical & Surgical History | X | | | | | | | |
| Physical Exam, height, weight, and vital signs [1, 5] | X | X | X[12] | | X | X | X | X |
| 12-Lead ECG with Interpretation | X | | | | X | X | X[4] | X |
| Urinalysis [2] | X | | | | | | | |
| Safety Labs (Chemistry/Hematology/ aPTT/ INR) | X | | | | X | X | X[4] | X |
| Serum NT-pro BNP | X | | X | X[12] | X | X | X | X |
| aPTT/ INR (if indicated) | | | | | | | | |
| Echocardiogram [3] | X | | | | | X | | X |
| Subject Training: Cordella™ HF System [14] | X | | | | | | | |
| Subject Training: CorPASS | | X | | | | | | |
| Cordella™ PA Sensor Implant | | X | | | | | | |
| Cordella System Use (daily) | X | X | X | X | X | X | X | X |
| Cordella™ PAP – dia/sys/mean/pulse | | X[9] | X[5,6] | X[5,6] | X[5,6] | X[5,6] | X[5,6] | X[6] |
| RHC PAP / RAP/ PCWP/ CO/ CI/ RVP[8] | | X | | | | | | X[17] |
| Subject Status | X | | X | X | X[10] | X[10] | X | X |
| 6- Minute Walk Test | X | | | | X | X[7] | X[4,7] | X[7] |
| NYHA Functional Classification | X[16] | | X | X | X | X | X | X |
| KCCQ Quality of Life Questionnaires [5] | X | | X | X | X | X | X | X |
| Concurrent/Cardiac Medications | X | X | X | X | X | X | X | X |
| Adverse Events | X | X | X | X | X | X | X | X |
| Health Economic Questionnaire | | | | | | | X[4] | |
| Subject Survey (optional)/ **Cohort #1 only[13]** | 1. Month 1 after Unblinding<br>2. Quarterly until V11 / Year 5 | | | | | | | |
| Site Survey (optional)/ **Cohort #1 only[13]** | 1. Month 1 after Unblinding<br>2. Quarterly until V11 / Year 5 | | | | | | | |

| | |
|---|---|
| 1. Full Physical Examination and Height performed at Screening Visit only<br>2. Urine (V1) pregnancy test for females<br>3. Echo may be obtained within 3 or 6 months of Screening details are in section 8.1.10<br>4. At Month 24 only<br>5. via myCordella™ Patient App at home prior to visit. Baseline KCCQ will be completed on myCordella tablet following Cordella System distribution at Screening Visit<br>6. via myCordella™ Patient App seated and supine<br>7. Additional PAP Measurements will be obtained before and after 6-minute walk test<br>8. Additional RHC as needed for Re-calibration purposes at the clinician's discretion | 9. Via CalEQ<br>10. Incl. question on assigned treatment at Visit 5 and 6<br>11. Visit should be completed remote/ virtually<br>12. If available<br>13. After subject gets unblinded to PAP Pressures at V6 or cross-over whatever comes first<br>14. Subject training on and distribution of the commercial Cordella™ System (should occur at Screening Visit (Visit 1).<br>15. Some study procedures need to be repeated in case a subject is implanted >30 days after Visit 1, details are in section 8.3.1.<br>16. may be obtained within the 30 day Study Visit 1 window<br>17. At V9/ Year 3 only |

### 14.2 New York Heart Association (NYHA) Functional Classification

The subject's functional status will be assessed by a qualified individual at the institution (who is not associated with the trial) by utilizing the NHYA functional classification below:

**ACC/AHA vs. NYHA Classification of Heart Failure**

| **ACC/AHA Stage** | | **NYHA Functional Class** | |
|---|---|---|---|
| **Stage** | **Description** | **Class** | **Description** |
| **A** | Patients at high risk of developing HF because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF. | **No comparable functional class** | NA |
| **B** | Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF. | **I (Mild)** | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea. |
| **C** | Patients who have current or prior symptoms of HF associated with underlying structural heart disease. | **II (Mild)** | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea. |
| | | **III (Moderate)** | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. |
| **D** | Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions. | **IV (Severe)** | Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased. |

ACC/AHA = American College of Cardiology/American Heart Association; HF = heart failure; NYHA = New York Heart Association

### 14.3 Procedure for 6 Minute Walk Test

**Location**

The 6-minute Walk test (6MWT) should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The distance should be reported in meters walked. The walking course must be 30 meters in length. A 35-meter hallway is required. The length of the corridor should be marked every 3 meters. The turnaround point should be marked with a cone (such as an orange traffic cone). A starting line which marks the beginning and end of each 60-meter lap should be marked on the floor using brightly colored tape.

**Patient Preparation**

1. Comfortable clothing should be worn
2. Appropriate shoes for walking should be worn
3. Patients should use their usual walking aids during the test (cane, walker, etc.)
4. The patients' usual medical regimen should be continued
5. A light meal is acceptable before early morning or early afternoon tests
6. Patients should not have exercised vigorously within 2 hours of beginning the test

**Measurements**

1. Repeat testing should be performed at about the same time of day to minimize intraday variability.
2. A warm up period before the test should not be performed.
3. The patient should sit at rest in a chair located near the starting position for at least 10 minutes before the test starts. During this time, check for contraindication, measure pulse and blood pressure, and make sure clothing is appropriate.
4. At the Month 12, 24 and Year 3, 4 and 5 visits, perform a PAP Measurement with the myCordella™ Reader and Tablet before start of the test.
5. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, worksheet) and move to the starting point.
6. Instruct the patient as follows: "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around the cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now or whenever you are ready:

1. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
2. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once. Let the participant see you do it.
3. After the first minute, tell the patient the following (in even tones): "You are doing well. You have five minutes to go." Repeat after each minute.

   When the timer is 15 seconds from completion say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are, and I will come to you."

   When the timer rings, say this: "Stop!" Walk over to the patient. Consider taking a chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or piece of tape on the floor.
4. At the Month 12, 24 and Year 3, 4 and 5 visit, perform a PAP Measurement with the myCordella™ Reader and Tablet right after the patient finished the test.
5. Record the number of laps from the counter.
6. Record the additional distance covered using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter and record it on the worksheet.
7. Congratulate the patient on good effort and offer a drink of water.

***Excerpted from the American Thoracic Society, ATS Statement: Guidelines for the Six-Minute Walk Test, March 2002.**

## 14.4 Kansas City Cardiomyopathy Questionnaire

**THE KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE:**

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an X in one box on each line

| Activity | Extremely Limited | Quite a bit Limited | Moderately Limited | Slightly Limited | Not at all Limited | Limited for other reasons or did not do the activity |
|---|---|---|---|---|---|---|
| Dressing yourself | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Showering/Bathing | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Walking 1 block on level ground | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Doing yardwork, housework or carrying groceries | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Climbing a flight of stairs without stopping | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Hurrying or jogging (as if to catch a bus) | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue or ankle swelling) changed?
My symptoms of **heart failure** have become . . .

| Much worse | Slightly worse | Not changed | Slightly better | Much better | I've had no symptoms over the last 2 weeks |
|---|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

| Every morning | 3 or more times a week, but not every day | 1–2 times a week | Less than once a week | Never over the past 2 weeks |
|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ |

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?
It has been . . .

| **Extremely** bothersome | **Quite a bit** bothersome | **Moderately** bothersome | **Slightly** bothersome | **Not at all** bothersome | I've had **no swelling** |
|---|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

| All of the time | Several times per day | At least once a day | 3 or more times per week but not every day | 1–2 times per week | Less than once a week | Never over the past 2 weeks |
|---|---|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |

6. Over the past 2 weeks, how much has your **fatigue** bothered you?
It has been . . .

| **Extremely** bothersome | **Quite a bit** bothersome | **Moderately** bothersome | **Slightly** bothersome | **Not at all** bothersome | I've had **no fatigue** |
|---|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

| All of the time | Several times per day | At least once a day | 3 or more times per week but not every day | 1–2 times per week | Less than once a week | Never over the past 2 weeks |
|---|---|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?
It has been . . .

| **Extremely** bothersome | **Quite a bit** bothersome | **Moderately** bothersome | **Slightly** bothersome | **Not at all** bothersome | I've had **no shortness of breath** |
|---|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

| Every night | 3 or more times a week, but not every day | 1–2 times a week | Less than once a week | Never over the past 2 weeks |
|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ |

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

| **Not at all** sure | **Not very** sure | **Somewhat** sure | **Mostly** sure | **Completely** sure |
|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ |

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet, etc.)

| Do not understand at all | Do not understand very well | Somewhat understand | Mostly understand | Completely understand |
|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ |

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

| It has **extremely** limited my enjoyment of life | It has limited my enjoyment of life **quite a bit** | It has **moderately** limited my enjoyment of life | It has **slightly** limited my enjoyment of life | It has **not limited** my enjoyment of life at all |
|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ |

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

| Not at all satisfied | Mostly dissatisfied | Somewhat satisfied | Mostly satisfied | Completely satisfied |
|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ |

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

| I felt that way **all of the time** | I felt that way **most of the time** | I **occasionally** felt that way | I **rarely** felt that way | I **never** felt that way |
|---|---|---|---|---|
| ❑ | ❑ | ❑ | ❑ | ❑ |

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

| **Activity** | **Severely** limited | Limited **quite a bit** | **Moderately** limited | **Slightly** limited | **Did not** limit at all | Does not apply or did not do for other reasons |
|---|---|---|---|---|---|---|
| Hobbies, recreational activities | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Working or doing household chores | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Visiting family or friends out of your home | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |
| Intimate relationships with loved ones | ❑ | ❑ | ❑ | ❑ | ❑ | ❑ |

### 14.5 Guidelines for managing HF using Pulmonary Artery Pressures

These guidelines are required for clinicians for managing HF to allow for proactive heart failure management, if clinically tolerated by patient. It is **mandatory** to use them for all patients in Cohort #2 and Cohort #3 after the implant of the Cordella PA Sensor and for subjects in Cohort #1 as soon they have been unblinded.

Deviations from the Treatment Guidelines have to be justified.

In addition, Data and Reminders will be provided by the myCordella™ PMP to support the clinician and team to facilitate following these guidelines.

## Cordella PA Sensor Treatment Guidelines for PROACTIVE-HF

**Mean Pulmonary Artery Pressure (mPAP)**
as used in these treatment guidelines is defined as a 7-day moving average of daily mean PA pressure readings.
When less than 7 days of daily readings are available, **mPAP** is the average of all mean PA pressure readings.

**Target Range for mPAP is 5-20mmHg**

**Post Cordella PA Sensor Implant, after 7 days of home reading assess Baseline mPAP**

→ if mPAP **in target range**, continue current treatment.

if mPAP **out of target range**, continue current treatment.

### mPAP below target

- Address precipitating factors: medication/ dietary non compliance, use of harmful medications (e.g. NSAIDS), new or poorly controlled arrhythmia, hypertensive emergency, active coronary ischemia, iron deficiency/ anemia, infection
- Consider stopping thiazide diuretic
- If loop diuretic equivalent > 40 mg daily Furosemide, then decrease by half
- If loop diuretic equivalent < 40 mg daily Furosemide, then stop diuretic
- Check chemistry panel within 1-3 days

**After 3 days**

**mPAP below target**

- Evaluate for precipitating factors: diarrhea, infection
- Reduce loop diuretic further
- Ensure adequate oral

**mPAP 5-20mmHg**

- Resume half dose diuretic
- Repeat chemistry panel within 3-4 days

**Optimize GDMT (ACE/ ARB/ ARNI, BB, MRA and/or SGLT2 for HFrEF; MRA and/or SGLT2 for HFpEF)**

### mPAP above target

- Address precipitating factors: medication/ dietary non compliance, use of harmful medications (e.g. NSAIDS), new or poorly controlled arrhythmia, hypertensive emergency, active coronary ischemia, iron deficiency/ anemia, infection
- Assess weight changes and if weight gain of > 5 lbs over previous 3 days, treat fluid overload with diuretics:
  - Consider doubling loop diuretic dose
  - If loop diuretic equivalent > 240 mg daily Furosemide, add thiazide diuretic[1] for 1-2 days
  - If already on a loop and thiazide diuretic, then double dose of thiazide diuretic for 1-2 days or switch to more bioavailable, longer acting loop diuretics (torsemide/ bumetanide)
  - Add high dose spironolactone (50-100 mg daily) if GFR > 40 and K < 4.5
  - Check chemistry panel in 3-4 days
- If weight increase < 5 lbs over previous 3 days, consider adding nitrates/ hydralazine if ACE/ARB/ARNI[2] already optimized

**After 3 days**

**mPAP at target**

- Stop thiazide diuretic
- Resume baseline loop diuretic dose
- Repeat chemistry panel within 3-4 days

**mPAP > target**

- If there is no weight decrease > 5 lbs over the previous 3 days, consider double thiazide diuretic dose for 1-2 days
- Repeat chemistry panel within 3-4 days
- If there is a weight decrease > 5 lbs, over previous 3 days consider adding or increasing nitrates/ hydralazine

**Optimize GDMT (ACE/ ARB/ ARNI, BB, MRA and/or SGLT2 for HFrEF; MRA and/or SGLT2 for HFpEF)**

### mPAP > 10mmHg above target

- Address precipitating factors: medication/ dietary non compliance, use of harmful medications (e.g. NSAIDS), new or poorly controlled arrhythmia, hypertensive emergency, active coronary ischemia, iron deficiency/ anemia, infection
- Assess weight changes and if weight gain of > 5 lbs over previous 3 days, treat fluid overload with diuretics:
  - Consider doubling loop diuretic and/or increase to max dose and/ or switch to more bioavailable, longer acting loop diuretics (torsemide/ bumetanide)
  - Consider adding thiazide diuretic twice daily
  - If already on thiazide diuretic, then double dose
  - Add high dose spironolactone (50-100 mg daily) if GFR > 40 and K < 4.5
  - Check chemistry panel in 3-4 days
- If weight increase < 5 lbs over previous 3 days, consider adding hydralazine/ nitrates if ACE/ARB/ARNI[2] already optimized

**After 3 days**

**mPAP at target**

- Stop thiazide diuretic
- Resume baseline loop diuretic dose
- Repeat chemistry panel within 3-4 days

**mPAP > target**

- If there is no weight decrease > 5 lbs over previous 3 days, consider maximizing oral loop and thiazide diuretic doses
- Repeat chemistry panel within 1-2 days
- Consider outpatient IV diuretics if no improvement in 48 hrs
- If there is a weight decrease > 5 lbs over previous 3 days, consider adding/ maximizing doses of nitrates/ hydralazine

**Optimize GDMT (ACE/ ARB/ ARNI, BB, MRA and/or SGLT2 for HFrEF; MRA and/or SGLT2 for HFpEF)**

[1] Thiazides: If GFR <30, use Metolazone 5 mg or Diuril 500 mg; If GFR >30, use Metolazone 2.5 or Diuril 250 mg

[2] ARNI indicated only for HFrEF

***Clinicians always have the ability and responsibility to overrule these Treatment Guidelines if clinically indicated.***

***The Clinician may override the suggested Treatment Guidelines based on clinical judgement. A note entry in Patient Management Portal during acknowledgement is required in this event to avoid a protocol deviation.***

### 14.6 Adverse Event Definitions

Adverse event definitions continue to evolve. The adverse event definitions below may be revised according to the published adverse event definitions as determined by following references.

**References:**

Kappetein et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document,
*European Heart Journal (2012) 33, 2403-2418*

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**ACUTE KIDNEY INJURY (AKIN CLASSIFICATION [a])**

**Stage 1:** Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dl (≥26.4 mmol/l) OR Urine output <0.5 ml/kg/h for >6 but <12 h.

**Stage 2:** Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) OR Urine output <0.5 ml/kg/h for >12 but <24 h

**Stage 3b[b]:** Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l) OR Urine output <0.3 ml/kg/h for ≥24 h OR Anuria for ≥12 h

The increase in creatinine must occur within 48 h.

[a] Metha et all; Acute Kidney Injury N. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11: R31.
[b] Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.

**BLEEDING**

**Life-threatening or disabling bleeding**

- Fatal bleeding (BARC type 5)

OR

- Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating peri cardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c).

OR

Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b).

OR

- Overt source of bleeding with drop in hemoglobin ≥5 g/dl or whole blood or packed red blood cells (RBCs) transfusion ≥4 units [a] (BARC type 3b).

**Major bleeding (BARC type 3a)**

- Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of two (2) or three (3) units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery.

AND

- Does not meet criteria of life-threatening or disabling bleeding

**Minor bleeding (BARC type 2 or 3a, depending on the severity)**

- Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling, or major

[a] Given that one unit of packed RBC typically will raise the hemoglobin concentration by 1 g/dl, an estimated decrease in hemoglobin will be calculated.

*BARC: Bleeding Academic Research Consortium

**CONDUCTION DISTURBANCES AND ARRHYTHMIAS**

Data elements to be collected should include

- Baseline conduction abnormalities, paroxysmal or permanent atrial fibrillation (or flutter), and the presence of permanent pacemaker[a].
- Implant-related new or worsened cardiac conduction disturbance (new or worsened first-degree atrioventricular (AV) block, second-degree AV block (Mobitz I or Mobitz II), third-degree AV block, incomplete right bundle branch block, right bundle branch block, intraventricular conduction delay, left bundle branch block, left anterior fascicular block, or left posterior fascicular block, including block requiring a permanent pacemaker implant.
- Persistent or transient high-degree AV block. High-grade AV block is persistent if it is present every time the underlying rhythm is checked.
- New permanent pacemaker implantation, with precision of the indication and the number of days post-implant of the placement of new permanent pacemaker.
- New-onset atrial fibrillation (or flutter)[b]
- Any new arrhythmia resulting in hemodynamic instability or requiring therapy[c].

[a] Type of permanent pacemaker should be recorded (e.g. defibrillator, single vs. dual chamber, biventricular).

[b] New-onset atrial fibrillation (or flutter) is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of atrial fibrillation (or flutter) and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 s on a rhythm strip.

[c] Therapy includes electrical/medical cardioversion or initiation of a new medication (oral anticoagulation, rhythm, or rate controlling therapy).

**DEATH**

**Cardiovascular (CV) death**

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to HF, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes.

**Non-cardiovascular death**

Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide).

**DEVICE / SYSTEM-RELATED COMPLICATION**

A Device /system related complication is an adverse event that is, or is possibly, related to the system (wireless pressure sensor or external electronics) and at least one the following:

- is treated with invasive means (other than intramuscular medication or a right heart catheterization with a Swan-Ganz measurement which is used for diagnostic purposes)
- results in the death of the subject
- results in the explant of the device

**HEART FAILURE (HF)**

A HF Event includes hospitalization for HF and may include urgent, unscheduled outpatient office/practice or Emergency Department (ED) visits.

- A HF Hospitalization is defined as an event in which the patient is admitted to the hospital with a primary diagnosis of HF, the length of stay is at least 24 h, the patient exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for HF.
- An Urgent HF Visit is defined as an event in which the patient has an urgent, unscheduled office/practice or ED visit for a primary diagnosis of HF but is not admitted to the hospital and exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for HF. Note that changes to oral diuretic therapy do not qualify as initiation or intensification of treatment.

**HEMOPTYSIS**

Spitting up blood or blood-tinged sputum from the respiratory tract. Hemoptysis occurs when tiny blood vessels that line the lung airways are broken.

**MYOCARDIAL INFARCTION (MI)**

**Peri-procedural MI (≤72 h after the index procedure)**

- New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening HF, new ST-segment changes, hemodynamic instability, new pathological Q-waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality).

AND

- Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15× as the upper reference limit for troponin or 5× for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase in at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.

**Spontaneous MI (>72 h after the index procedure)**

Any one of the following criteria:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with the evidence of myocardial ischemia with at least one of the following:
    - Symptoms of ischemia
    - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)].
    - New pathological Q-waves in at least two contiguous leads
    - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality.
    - Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
    - Pathological findings of an acute myocardial infarction.

**PRESSURE SENSOR FAILURE**

A pressure sensor failure occurs when the sensor malfunctions to the point that no readings can be obtained from it after all attempts are exhausted including troubleshooting the system to rule out any problems with the electronic components.

NOTE: Recalibration of CorPASS via RHC will be performed as deemed necessary by Sponsor.

**PULMONARY EMBOLISM**

Pulmonary embolism (PE) is a sudden blockage of an artery in the lungs. The blockage usually is caused by a blood clot that travels to the lung from a vein in the leg.

A PE assessment requires the diagnosis of a PE. Subjects will be assessed for signs and symptoms of PE – including, but not limited to any sudden onset of dyspnea, tachypnea,

worsening hypoxemia, unexplained tachycardia or sustained hypotension, chest pain, syncope, or shock.

If signs or symptoms are present, unless an alternative diagnosis is suspected, assess the results of AT LEAST ONE of the following diagnostic examination to confirm or rule out the presence of a PE:

1. Spiral multi-detector CT (MDCT) scan
2. Pulmonary angiogram
3. Ventilation perfusion (V/Q) scan
4. A cardiac ECHO will be considered as a diagnostic option only in study subjects with clinical diagnosis of PE who:
   Are considered at High Risk of Mortality or Massive PE
   Are hypotensive and/or in shock

Diagnosis of PE is confirmed when:

1. An intraluminal filling defect in multiple (>1) segmental or more proximal branches on spiral multi-detector CT (MDCT) scan AND not seen in previous spiral MDCT.
2. An intraluminal filling defect or an extension of an existing defect or a new sudden cutoff of multiple (>1) segmental or more proximal branches on the pulmonary angiogram **AND** not seen in a previous pulmonary angiogram.
3. A perfusion defect of at least multiple (>1) segment with a local normal ventilation result (high-probability) **AND** not seen in a previous ventilation perfusion scan.
4. There is evidence of right ventricular dysfunction AND visualization of a mobile thrombi in the right heart cavities and/or in the pulmonary arteries with the ECHO images.

**PULMONARY OCCLUSION**

A blockage of an artery in the lung causing hemodynamic compromise.

**RENAL DYSFUNCTION**

Two categories of renal dysfunction will be identified:

**Acute Renal Dysfunction**

Abnormal kidney function requiring dialysis (including hemofiltration) in patients who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL sustained for over 48 hours.

**Chronic Renal Dysfunction**

An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.

**STROKE AND TRANS ISCHEMIC ATTACK (TIA)**

**Diagnostic criteria:** Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke.

**Stroke:** duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death.

**TIA:** duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct.

No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist[a].

Confirmation of the diagnosis by at least one of the following:

- Neurologist or neurosurgical specialist.
- Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone.

**Stroke classification:**

- **Ischemic:** an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue.
- **Hemorrhagic:** an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic.

**Stroke definitions [b]:**

- **Disabling stroke:** a modified Rankin Scale (mRS) score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline.
- **Non-disabling stroke:** an mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline.

[a] Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction-based upon neuroimaging studies (CT scan or brain MRI).

[b] mRS assessments should be made by qualified individuals according to a certification process.

**VASCULAR ACCESS SITE AND ACCESS-RELATED COMPLICATIONS**

**Major vascular complications**

- Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm

OR

- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudo aneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment

OR

- Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage

OR

- The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment

OR

- Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR
- Surgery for access site-related nerve injury

OR

- Permanent access site-related nerve injury

**Minor vascular complications**

- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudo aneurysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding [a], visceral ischemia, or neurological impairment.

OR

- Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage.

OR

- Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication.

OR

- Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft).

[a] as per Bleeding definition

**VESSEL TRAUMA**

Any injury to a blood vessel – an artery, which carries blood to an extremity of an organ, or a vein, which returns blood to the heart. Causes for this type of trauma are: 1. blunt or 2. penetrating injury.

1. A blunt injury can occur when a blood vessel is crushed or stretched.
2. A penetrating injury can occur when a blood vessel is punctured, torn or severed.

Either type of vascular trauma can cause the blood vessel to clot (thrombosis) and interrupt blood flow to an organ or extremity, or cause bleeding which can lead to life-threatening hemorrhage.

**OTHER**

An event that causes clinically relevant changes in the patient's health (e.g. cancer).

## 14.7 Definition, Documentation and Reporting of Adverse Events specific for EU sites

### 14.7.1 Definitions

**Adverse Events (AE)**

An adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether it is considered to be device related or not.

**Serious Adverse Event (SAE):**

Any adverse event that led to any of the following:

- Death
- Serious deterioration in the health of the subject, that resulted in any of the following:
    - life-threatening illness or injury
    - permanent impairment of a body structure or a body function
    - hospitalization or prolongation of patient hospitalization
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
    - chronic disease
    - fetal distress, fetal death or a congenital physical or mental impairment or birth defect

**Adverse Device Effect (ADE)**

Adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional misuse.

**Serious Adverse Device Effect (SADE)**

A SADE is one that has resulted in any of the consequences characteristic of a serious adverse event.

**Unanticipated Serious Adverse Device Effect (USADE)**

A USADE which by its nature, incidence, severity or outcome has not been identified in the current Risk Management section of the Investigator's Brochure (IB) and IFU.

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with the Cordella PA Sensor System, that was not previously identified in nature, severity, or degree of incidence in the CIP, IB or IFU or any other unanticipated serious problem associated with the study device that relates to the rights, safety, or welfare of subjects.

An unanticipated event is one where the nature or intensity is not consistent with the information in the current Risk Management section of the CIP, IB and IFU.

Furthermore, reports which add significant information on specificity or severity of a known, already documented adverse effect constitute unanticipated events. For example, an event more specific or more severe than described in the IB would be considered 'unexpected'.

### 14.7.2 Causality Assessment

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized as follows:

- **Not related**

  Relationship to the device, comparator or procedures can be excluded when:
  - the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
  - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible
  - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
  - the event involves a body-site or an organ that cannot be affected by the device or procedure;
  - the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
  - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

  In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

- **Possible**

The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

- **Probably related**

  The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

- **Causal Relationship**

  the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
  - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has a temporal relationship with investigational device use/application or procedures;
  - the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
  - the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
  - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
  - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
  - harm to the subject is due to error in use;
  - the event depends on a false result given by the investigational device used for diagnosis10, when applicable;

### 14.7.3 Safety Reporting

**Regulations**

Safety reporting will be performed in line with the requirements of the Regulation (EU) 2017/745 –Medical Device Regulation (MDR) Article 80(2) and MDCG 2020-10-1.

The sponsor will report, without delay to all Member States in which the clinical investigation is being conducted, all of the following (reportable events):

a) any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
c) any new findings in relation to any event referred to in points a) and b)

All causality assessments will be made as described in the section 9.2.2 of the CIP. Only causality level 1 (i.e. “not related”) is excluded from reporting. If either the sponsor or the investigator has assigned a higher causality level than "not related", the event should be reported.

Safety reporting-Investigator:

As indicated in the section 9 of the CIP, the investigator must submit to sponsor (or designee) any UADEs and SAEs occurring during the study within 24 hours after being notified of the event and provide additional information, if required by Endotronix. In addition, any new finding regarding such events must be reported to the sponsor within the same time window (24 hours).

Germany: The reporting timelines for the investigator or principal investigator are in accordance with the requirements of Section 63 of the German Medical Device Law Implementation Act (MPDG).

For further information regarding the safety reporting by investigators please refer to the sections 9 and 11.3.1 of the CIP.

Reporting method:

A template for the Summary Reporting Form will be used for the safety reporting (please refer to the Appendix of MDCG 2020-10-01)

Report to whom

Reportable events must be reported all at the same time to all national competent authorities where the clinical investigation is authorized to start or has commenced.

Reportable events occurring in the USA

Reportable events occurring in the USA will be reported to the NCA(s) of the participating EU member states.

- The NCA will start receiving the reportable events occurring in the USA as soon as the clinical investigation is authorized to start in the participating EU Member State
- Events occurring in the USA after the participating European sites have closed will continue to be reported

## Country Specific reporting timelines requirements

| Country / Authority | Specific requirement to be met | Process to meet this requirement |
|---|---|---|
| **Ireland/ Belgium** | For all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.<br>Any other reportable events or a new finding/update to it: Immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.<br>The safety reports will be sent to:<br>Belgium: ct.rd@fagg-afmps.be Ireland: mailto:devices@hpra.ie | All reportable SAEs will be processed in 2- day timeline (for SAEs which indicates an imminent risk of death, serious injury, or serious illness) and 7-day timeline for all other SAEs |

| Country / Authority | Specific requirement to be met | | | Process to meet this requirement |
|---|---|---|---|---|
| **Germany** | A causal relationship between the SAEs and the investigational medical device, a comparator device, diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial conduct **cannot be excluded**<br><br>**To be reported** *immediately* | Germany | German SAE Report Form to: MPSAE@bfarm.de | All reportable SAEs will be processed in 2 day timeline (for SAEs which indicates an imminent risk of death, serious injury, or serious illness requiring immediate corrective action) and 7 day timeline for all other SAEs.<br><br>New findings regarding an event will be reported within the original ridge requirement for that event. |
| | | All other countries where the clinical trial is performed | -Summary table<br><br>-Clinical Investigation Summary Safety Reporting form | |
| | A causal relationship between the SAE and the investigational medical device, a comparator device, diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial conduct **can be excluded**<br><br>**To be reported quarterly** | All countries where the clinical trial is performed | -Summary table<br><br>-Clinical Investigation Summary Safety Reporting form | SAE summary evaluation and cumulative Clinical Investigation Summary Safety Reporting form will be sent on a quarterly basis on predefined intervals |
| | All SAEs | All countries where the clinical trial is performed | -SAE summary evaluation<br><br>-Annex 3.1 complication rate | |
| Further guidance as well as a link to the aforementioned reporting forms can be found under the following link: https://www.bfarm.de/EN/Medical-devices/Applications-and-reports/SAE-report/_node.html | | | | |

## 14.8 PROACTIVE-HF Site Survey (V1.0/ 09 Nov 2021)

ENDOTRONIX

**ETX-HFS-PA-03 (PROACTIVE- HF)**
**Site Survey**

**Site #:** **Patient #:**

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At Unblinding Date /____/____/_____/
Day Month Year

Month 1 after Unblinding /____/____/_____/
Day Month Year

Quarterly

Month _ after Unblinding /____/____/_____/
Day Month Year

Thank you for participating in this short survey which will take less than 10mins.

The following questions refer to your review of the PAP and vital signs of the trial subjects in the former Control Group.

Please read the following 5 questions and mark the answer that best applies to you. There are no right or wrong answers.

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| # | Question | Answers |
|---|---|---|
| 1 | For this patient, are you using PAP Guided Heart Failure Management as per study guidelines? | ☐ Yes<br>☐ No Reason_____ |
| 2 | How often do you review PAP trends and vital signs in the Patient Management Portal? | ☐ 2 times per week as per protocol<br>☐ 2-4 times per week<br>☐ Daily<br>☐ once per week |
| 3 | How often do you use PAP trends to adapt medication treatment? | ☐ on a regular basis<br>☐ on somewhat regular basis<br>☐ Rarely<br>☐ Never |
| 4 | How do you discuss Treatment changes with the patient? | ☐ via phone<br>☐ during on-site visit<br>☐ via messaging using PMP<br>☐ Other_____ |
| 5 | Do you feel that having a combination of PAP and peripheral vital sign values help you to better manage and treat the patient's condition? | ☐ I strongly agree<br>☐ I agree<br>☐ I somewhat agree<br>☐ I disagree<br>☐ I strongly disagree |

## 14.9 PROACTIVE-HF Subject Survey (V2.0/ 11 Feb 2022)

ENDOTRONIX

**ETX-HFS-PA-03 (PROACTIVE- HF)**
**Subject Survey**

**Site #:** **Patient #:**

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Month 1 after Unblinding /____/____/_____/
Day Month Year

Quarterly

Month _ after Unblinding /____/____/_____/
Day Month Year

Thank you for participating in this short survey which will take less than 10mins.

The following questions refer to your daily Pulmonary Artery Pressure (PAP) measurements.

Please read the following 9 questions and mark the answer that best applies to you. There are no right or wrong answers.

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ENDOTRONIX

| # | Question | Answers |
|---|---|---|
| 1 | Do you understand what Pulmonary Artery Pressure (PAP) is and why it is important to measure/monitor this parameter on a frequent basis? | ☐ Yes ☐ No |
| 2 | In general, how would you describe ease of use of taking daily Pulmonary Artery Pressure (PAP) readings using the Cordella system? | ☐ Poor ☐ Fair ☐ Good ☐ Very Good ☐ Excellent |
| 3 | How long does a reading session take for you? | ☐ < 2 min ☐ 2- 5 min ☐ >5 min |
| 4 | How confident are you in using the myCordella tablet in finding PAP trends? | ☐ Extremely ☐ Slightly ☐ Moderately<br>☐ Very |
| 5 | Do you take notice and monitor your PAP trends in the "My Info"" section of the myCordella tablet? | ☐ No, I leave that to my doctor/nurse<br>☐ I know what my normal trend range is and would know if it was higher or lower than normal |
| 6 | How often do you check your Pulmonary Artery Pressure (PAP) trends in the "My Info" section of your myCordella tablet? | ☐ Never<br>☐ Not Often (1-2 times every few months)<br>☐ Often (1-2 times per month)<br>☐ Very Often (at least 1-2 times per week) |
| 7 | Do you make changes to your lifestyle based on the Pulmonary Artery Pressure (PAP) trends you see?<br>Lifestyle changes would include changes to diet, exercise, and smoking cessation among others. | ☐ No, I only make lifestyle changes at the direction of my doctor/nurse<br>☐ I sometimes make lifestyle changes on my own<br>☐ I regularly use my daily measurements to make lifestyle changes on my own |
| 8 | How often are you communicating with your physician/nurse about your PAP trends and related Heart Failure medication(s)? | ☐ Never<br>☐ Not Often (1-2 times every few months)<br>☐ Often (1-2 times per month)<br>☐ Very Often (at least 1-2 times per week) |
| 9 | Overall how would you rate the impact Pulmonary Artery Pressure (PAP) readings and resulting clinician care have had on your health? | ☐ Poor ☐ Fair ☐ Good ☐ Very Good ☐ Excellent |

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