| Medtronic<br>**Statistical Analysis Plan** | |
|---|---|
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## 1. Version History

| Version | Summary of Changes | Author(s)/Title |
|---|---|---|
| **1.0** | • Initial Release<br>Note: Version 1.0 of this document is equivalent to Version 2.0 in the Medtronic Trial Master File (RAD) | [redacted]<br>Principal Statistician |
| **2.0** | • Addition of Canada as a planned geography<br>• Clarified Primary Effectiveness Endpoint to include Echocardiography assessment should CMR not be available<br>• Addition of the definition of analysis cohort for outcome measure #7.<br>• Minor administrative changes to match the Clinical Investigative Plan Version 3.0.<br><br>*Note: Version 2.0 of this document may not align to the version of the document determined in the Medtronic Trial Master File (RAD)* | [redacted]<br>Principal Statistician |
| **3.0** | • Converted to the new version of template<br>• Addition of Japan as a planned geography<br>• Addition of TPV 25 and modified TPV 25 devices<br>• Inclusion of Roll-In cohort in the 40-subject primary cohort<br>• Clarified rescreened patients<br>• Updated the analysis cohort for all device-related adverse events<br>• Clarified analysis data for endpoints<br>• Clarified analysis method for the primary efficacy endpoint<br>• Inclusion of Native study cohort in the Harmony PMA submission | [redacted]<br>Senior Statistician |
| **4.0** | • Removed mixed effects model analysis for outcome measure #6: characterization of right ventricle remodeling | [redacted]<br>Senior Statistician |

| Version | Summary of Changes | Author(s)/Title |
|---|---|---|
| **5.0** | • Clarified the reason why the primary efficacy endpoint analysis for PMA excluded the mTPV 25 cohort.<br>• Clarified core lab echo after the 6-month time window opening will be used for primary efficacy endpoint when 6-month echo occurred prior to 6-month window opening or missed | [redacted]<br>Senior Statistician |
| **5.1** | • Administrative issue update for section 7.9.2.3<br>• Administrative issue update for revision number in header and page 1, changed from 3.0 to 5.1. | [redacted]<br>Senior Statistician |

## 2. List of Abbreviations and Definitions of Terms

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| AKI | Acute Kidney Injury |
| CEC | Clinical Events Committee |
| CIP | Clinical Investigation Plan |
| CMR | Cardiac Magnetic Resonance |
| CT | Computed Tomography |
| DMC | Data Monitoring Committee |
| FDA | Food and Drug Administration |
| HF | Heart Failure |
| IC | Informed Consent |
| ICF | Informed Consent Form |

| Abbreviation | Definition |
|---|---|
| IDE | Investigational Device Exemption |
| IRB | Institutional Review Board |
| LV | Left Ventricle |
| LVEDV | Left Ventricular End Diastolic Volume |
| LVEDVi | Left Ventricular End Diastolic Volume Index |
| LVEF | Left Ventricular Ejection Fraction |
| LVESV | Left Ventricular End Systolic Volume |
| mTPV 25 | Modified Transcatheter Pulmonary Valve 25 |
| PRF | Pulmonary Regurgitation Fraction |
| PVL | Paravalvular Leak |
| RV | Right Ventricle |
| RVEDV | Right Ventricular End Diastolic Volume |
| RVEDVi | Right Ventricular End Diastolic Volume Index |
| RVEF | Right Ventricular Ejection Fraction |
| RVESV | Right Ventricular End Systolic Volume |
| RVOT | Right Ventricular Outflow Tract |
| RVOTO | Right Ventricular Outflow Tract Obstruction |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SF-36 | RAND 36-Item Short Form Survey |

| Abbreviation | Definition |
|---|---|
| SOP | Standard Operating Procedure |
| SRDL | Substantial Radiation Dose Level |
| ToF | Tetralogy of Fallot |
| TPV | Transcatheter Pulmonary Valve |

## 3. Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of the Medtronic Coronary and Structural Heart (CSH) Harmony Transcatheter Pulmonary Valve (TPV) in patients who have congenital heart disease and are clinically indicated for pulmonary valve replacement. The purpose of this plan is to provide a framework which answers the study objectives in a statistically rigorous fashion, without bias or analytical deficiencies.

Specifically, this Statistical Analysis Plan (SAP) has the following purpose: to prospectively (a priori) outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of statistical analysis in the medical device industry.

The primary analysis for safety and effectiveness will be performed when the first 40 implanted subjects (including Roll-in TPV 25 subjects) have completed their 6-month follow-up. While the primary safety endpoint is measured at 30 days, primary objective analysis will be completed upon completion of the primary efficacy endpoint, which is measured at 6 months. Following the completion of the 40 pivotal cohort of the TPV 22 and TPV 25, the TPV 25 was modified and is referred to as modified TPV 25 (mTPV 25). A supplemental analysis will be performed when the 10 US implants of modified TPV 25 (mTPV 25) cohort have completed their 1-month follow-up for both safety and efficacy. Both cohorts will be pooled for additional analysis out to 5 years after the previously mentioned analyses are completed. Hence the primary efficacy endpoint analysis for PMA will not include the mTPV 25 cohort due to those subjects not being eligible for their 6-month visit at the time of PMA snapshot. Once all subjects from both cohorts finish their 6-month visit, the endpoint analysis will be repeated on all subjects.

The analysis population for the Harmony PMA will include subjects from the Harmony Pivotal Study in combination with the data from the Native Outflow Tract Transcatheter Pulmonary Valve Research Clinical Study (IDE #G120175). Note the Native study only includes TPV22 implants.

Results obtained from the analyses outlined in this document will be the basis of the Clinical Study Reports for this study. This plan does not limit the analyses in reports, and additional analyses of the study data beyond this plan are expected.

## 4. Study Objectives

The primary objective of this study is to demonstrate the safety and effectiveness of the Harmony™ TPV system as measured by freedom from procedure or device-related mortality at 30 days and percentage of subjects with acceptable hemodynamic function at 6 months.

## 5. Investigation Plan

This is a prospective, non-randomized, multi-center study, with each center following a common protocol. Up to 40 subjects will be implanted at up to 15 centers in the United States, Canada, and Japan. It is anticipated that more than 40 subjects will be enrolled (i.e. consented) to meet the target of up to 40 implants as not all subjects will be suitable for implantation. No site shall implant more than 10 subjects., excluding roll-in subjects. Subjects who discontinue participation prematurely following implant will be included in the analysis of results (as appropriate) and will not be replaced in the enrollment of total study subjects implanted. All implanted subjects will receive the Harmony™ TPV, either size 22 or 25. Each implanted subject will be followed for five years or until the subject's Harmony™ TPV is explanted. Subjects who failed the first screen for the TPV 22 device before the second device size TPV 25 were introduced, will either exit from the study or rescreen for the second device size later when TPV 25 device is available. All subjects who are rescreening for the new valve size TPV 25 will have all baseline assessments performed for TPV 25.

The addition of the second device size (Harmony TPV 25) is intended to expand the number of patients anatomically suitable for implantation and will include a Roll-In cohort of Harmony TPV 25 subjects. A minimum of five and up to eight qualifying subjects will be implanted with the Harmony™ TPV 25 at up to four Study Proctor sites. Each Study Proctor site can implant up to three subjects. The Roll-In phase is described in Section 8.4 Harmony TPV 25 Roll-In Phase in Clinical Investigation Plant (CIP) version 6. If Roll-in phase outcome measures are met and no concerns are raised by the DMC, Steering Committee or Medtronic, the Harmony™ TPV 25 will be made available to all participating Harmony™ TPV study sites. All subjects in Roll-In phase and all subjects after Roll-In phase will be included in the 40-subject analysis cohort. Following the completion of the 40 pivotal cohort of the TPV 22 and TPV 25, the TPV 25 was modified and is referred to as modified TPV 25 (mTPV 25). There will be an added cohort of up to 15 subjects implanted with the mTPV 25. This additional cohort will include 10 US implants and up to 5 OUS implants from Canada and/or Japan. The mTPV 25 cohort is described in Section 8.5. Addition of mTPV 25 Cohort in CIP version 6.The following measures will be implemented to minimize risks to the study subjects:

- All subjects will be acceptable surgical candidates

- Implanting physicians will have considerable experience in interventional congenital cardiology procedures
- Investigative sites will have comprehensive congenital cardiology and surgery programs, with established capacity for emergency catheterization and cardiovascular surgery should it become necessary
- Patients being considered for the study will be rigorously screened
- Subjects will undergo thorough assessments during their pre-implant workup
- Subjects will be rigorously followed over the course of the study. The follow-up protocol includes frequent contact with the investigative clinicians, echocardiography, magnetic resonance imaging and radiography. Collectively, the follow-up protocol will enable detection of deterioration in TPV function should it occur, and allow appropriate intervention, as adjudicated by the implanting physician
- Radiation dosages will be monitored and documented for the implant procedure and for each radiography and CT angiography procedure. If the Substantial Radiation Dose Level (SRDL) of 500 Gy*cm$^2$ is met for any given procedure, the subject will be educated about examining the tissue site for a possible skin reaction within 30 days and clinical follow-up will be required.
- Any unanticipated or unforeseen complications will be reported to the Institutional Review Board (IRB)/Ethics Committee (EC), to the appropriate regulatory agencies, and to Medtronic
- An independent Data Monitoring Committee (DMC) will review adverse events and interim results in order to advise Medtronic regarding study conduct, should safety concerns be identified

Inclusion Criteria

- Subject has pulmonary regurgitation as per one or more of the following criteria:
  - Severe pulmonary regurgitation as measured by Doppler echocardiography, or
  - Pulmonary regurgitant fraction ≥ 30% as measured by cardiac magnetic resonance imaging
- Clinical indication for surgical placement of a RV-PA conduit or prosthetic pulmonary valve per one or more of the following criteria:
  - Subject is symptomatic secondary to pulmonary insufficiency (e.g. exercise intolerance, fluid overload) as classified by the investigator, or
  - Right ventricular end diastolic volume index (RVEDVi) ≥ 150 ml/m$^2$, or
  - Subject has RVEDV: LVEDV Ratio ≥ 2.0

Exclusion Criteria

- Anatomy unable to accommodate a 25 Fr delivery system
- Obstruction of the central veins
- Clinical or biological signs of infection including active endocarditis
- Planned concomitant procedure at time of Harmony™ TPV implant
- Positive pregnancy test at baseline (prior to CT angiography and again prior to implant procedure) in female subjects of child bearing potential

- Patients with right ventricular outflow tract obstruction (RVOTO) lesions surgically treated with a RV- PA conduit implant
- A major or progressive non-cardiac disease (e.g. liver failure, renal failure, cancer) that results in a life expectancy of less than one year
- Planned implantation of the Harmony™ TPV in the left heart
- RVOT anatomy or morphology that is unfavorable for device anchoring
- Known allergy to aspirin, heparin, or nickel
- Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
- Pre-existing prosthetic heart valve or prosthetic ring in any position

While the primary safety endpoint is measured at 30 days, primary objective analysis will be completed upon completion of the primary efficacy endpoint, which is measured at 6 months. Therefore, the analysis for primary objectives will be performed when all subjects have reached their 6 month endpoints.

Final analysis on the additional outcome measures will be performed when the implanted subjects have reached their 5year endpoints, with the exception of the following endpoints, which will be analyzed in conjunction with the primary objective analysis (when all implanted subjects have reached their 6-month visit):

- Technical success at exit from catheterization lab/operating room (OR)
- Procedural success at 30 days

# 6. Determination of Sample Size

There is no sample size calculation for the primary objectives. The primary analysis will include 40 pivotal cohort of the TPV 22 and TPV 25. For the modified TPV 25 (mTPV 25), an additional cohort of up to 15 subjects implanted with the mTPV 25 (10 US implants and up to 5 OUS implants from Canada and/or Japan).

The pooled analysis cohort will include data from this study in addition to the data from the Native Outflow Tract Transcatheter Pulmonary Valve Research Clinical Study (IDE #G120175, n=20).

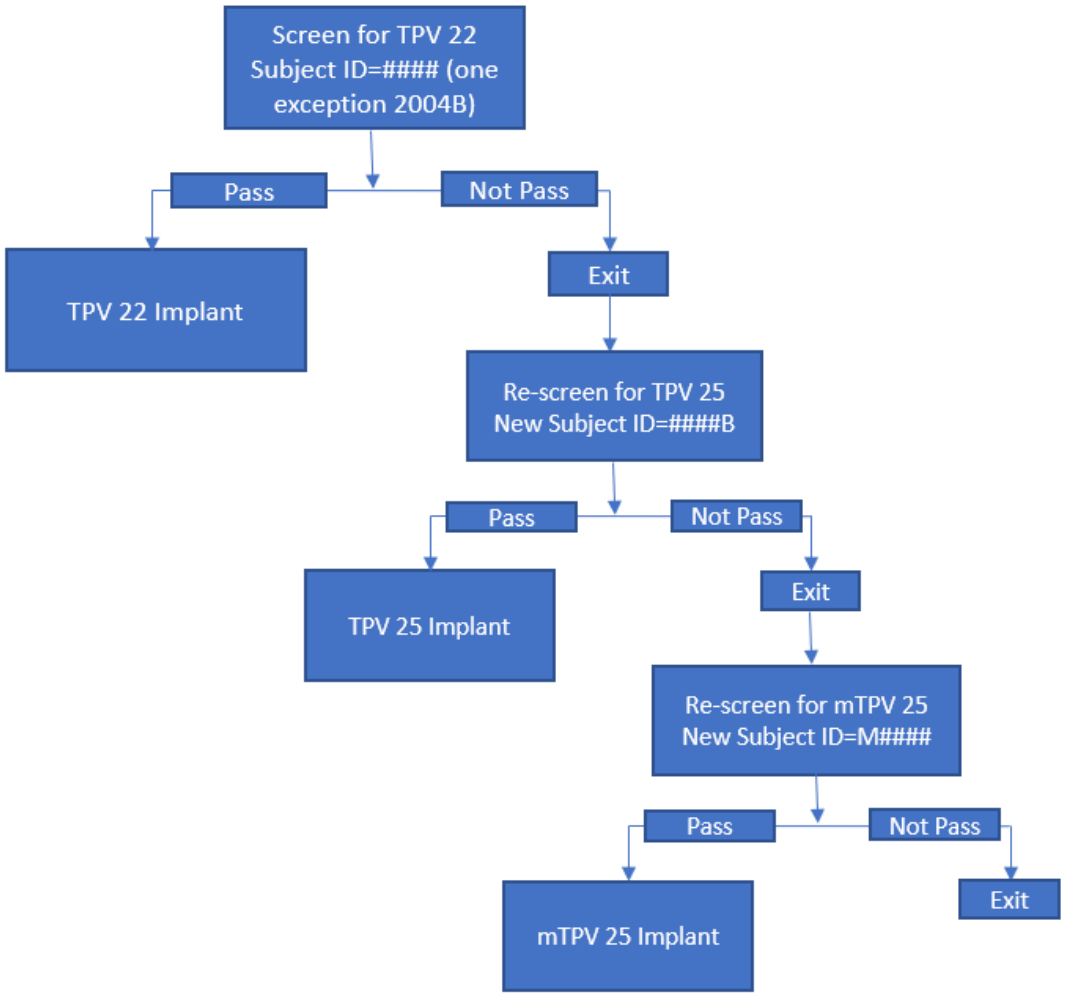
# 7. Statistical Methods

## 7.1 Study Subjects

### 7.1.1 Disposition of Subjects

The CONSORT flow diagram will be used to summarize the disposition of enrolled subjects. In the enrollment process, subjects who failed screening for TPV 22 were rescreened when the TPV 25 became available. The subjects re-screened for TPV25 were assigned the same subject ID plus the letter B

If the subject was re-screened for mTPV 25 when the mTPV25 became available, the subject was given M plus the subject ID. The flowchart below displays the process of rescreening for subjects initially screened for TPV 22. The baseline data collected during the most recent screening process will be used for all analysis.




### 7.1.2 Clinical Investigation Plan (CIP) Deviations

A protocol deviation is defined as an event where the clinical investigator or site personnel did not conduct the study according to the protocol or the Investigator Agreement. Examples of protocol deviations include but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain IRB/EC approval before the start of the study

- Enrolled subject did not meet inclusion/exclusion criteria[1]
- Required testing and/or measurements not done or incorrectly done
- Subject does not attend follow-up visit or follow-up visit outside window
- Unauthorized use of investigational devices
- Adverse events not reported in the required time frame as required by regulation or as specified in the CIP
- Control of study devices not maintained
- Source data permanently lost
- Enrollment of patients during lapse of IRB/EC approval

The number of subjects with protocol deviations and the number of protocol deviations will be summarized by type of deviation.

### 7.1.3 Analysis Sets

The analysis subsets are defined as follows

**Enrolled Cohort**

The enrolled cohort consists of all enrolled subjects. Subjects are considered enrolled at the point of signing the Informed Consent Form.

**Catheterized Cohort**

The catheterized cohort consists of all subjects who undergo catheterization for possible implantation of the Harmony™ TPV.

**Attempted Implant Cohort**

The attempted implant cohort consists of all subjects who undergo catheterization and a Harmony™ TPV implantation was attempted (Harmony™ TPV is introduced into the subject's body).

**Implanted Cohort**

The implanted cohort consists of all subjects who undergo catheterization and a Harmony™ TPV was implanted.

**Implanted > 24 hours Cohort**

[1] Subjects must meet all inclusion/exclusion criteria to be eligible for implantation. However, it will not be considered a protocol deviation if study related testing (e.g., echo, CT cardiac angiography, or Screening Committee assessment) of a consented subject identifies implantation eligibility criteria that are not met.

The implanted >24 hours cohort consists of all subjects who have a Harmony™ TPV implanted which remains implanted for greater than 24 hours.

## 7.2 General Methodology

Descriptive statistics will be used to report patient population characteristics, operative, and postoperative data. Continuous variables will be summarized with means, standard deviations (SD), medians, first and third quartiles, minimums, and maximums. Categorical variables will be summarized with frequencies and percentages.

## 7.3 Center Pooling

No poolability analyses are planned. Comparison among centers or any particular groups will only be conducted per request by Food and Drug Administration (FDA).

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

Every effort will be undertaken to minimize missing data. In time-to-event outcomes drop-outs will be censored at the time of discontinuation, consistent with the Kaplan-Meier approach.

Unless otherwise specified in each objective, no statistical techniques will be used to impute missing data for continuous or categorical outcomes. If a subject's data are missing for any reason, that subject will not be included in that portion of the analysis. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

In the case of partial dates, if only the month and year are known, the event or assessment will be analyzed as if it occurred on the 15$^{th}$ of that month. If only the year is known, the event or assessment will be analyzed as if it occurred on June 30$^{th}$ of that year. These resolutions of partial dates are subject to the restrictions that pre-procedure assessments must occur between the enrollment date and the procedure date or within the window defined in the CIP. The post-procedure events and assessments must occur no earlier than the procedure date. According to the section 6.1 of the CIP, the windows for pre-procedure assessments are:

- CMR exam (functional): within 52 weeks prior to the implant date
- Clinical evaluation: within 24 weeks prior to the implant date

## 7.5 Adjustments for Multiple Comparisons

No adjustments will be made for multiple comparisons.

## 7.6 Demographic and Other Baseline Characteristics

The analysis of baseline characteristics will be descriptive in nature. Summary statistics will be provided for baseline demographic and clinical variables for the enrolled cohort and catheterized cohort as defined in section 7.1.3, respectively.

## 7.7 Treatment Characteristics

The analysis of procedure characteristics and concomitant procedures will be descriptive in nature. Summary statistics will be provided as appropriate.

## 7.8 Interim and Supplemental Analyses

### 7.8.1 Interim Analysis for TPV 25 Roll-in Cohort

The procedural feasibility, and hemodynamic performance and safety profile at hospital discharge following Harmony TPV 25 implantation of the Roll-In cohort will be analyzed. The outcome measures are defined as:

**Procedural Feasibility:**

- No device- or procedural-related mortality, with
- successful access, delivery and removal of the delivery system, and
- deployment and correct positioning (including minor repositioning if needed) of the device.

**Hemodynamic Performance:**

- Mean RVOT gradient ≤ 40mmHg as measured by echocardiography

**Safety Profile:**

None of the following device- or procedure-related serious adverse events:

- Life-threatening major bleed
- Major vascular or cardiac structural complications required unplanned reintervention or surgery
- Pulmonary embolism

### 7.8.2 Supplemental Analysis for mTPV 25 Cohort

The procedural feasibility, hemodynamic performance, and safety profile of mTPV 25 at 1 month following mTPV 25 implantation will be analyzed. The outcome measures are defined as:

**Procedural Feasibility:**

- No device- or procedural-related mortality, with
- successful access, delivery and removal of the delivery system, and
- deployment and correct positioning (including minor repositioning if needed) of the device.

**Hemodynamic Performance:**

- Mean RVOT gradient ≤ 40mmHg as measured by echocardiography

**Safety Profile:**

None of the following device- or procedure-related serious adverse events:

- Life-threatening major bleed

- Major vascular or cardiac structural complications required unplanned reintervention or surgery
- Pulmonary embolism

## 7.9 Evaluation of Objectives

### 7.9.1 Primary Safety Endpoint

The primary safety endpoint is freedom from procedure or device-related mortality at 30 days post implant.

#### 7.9.1.1 Hypothesis and/or Parameters to Be Estimated

The objective is descriptive, and no statistical hypothesis test will be performed.

#### 7.9.1.2 Data Collection and Analysis Methods

CEC adjudicated data will be used to assess the safety endpoint. The analysis cohort will be the catheterized cohort. The endpoint will be described by using Kaplan-Meier method. The loglog transformed two-sided 95% confidence interval using the Peto standard error at 30 days will be presented. The primary safety objective will be met if the point estimate of the freedom from procedure or device-related mortality rate at 30 days post-procedure is equal to or greater than the performance target of 95%.

### 7.9.2 Primary Efficacy Endpoint

The primary efficacy endpoint is percentage of subjects with acceptable hemodynamic function composite at 6 months as defined by:

- Mean RVOT gradient as measured by continuous-wave Doppler ≤40 mmHg
    - If a catheterization is performed for clinical purposes, the catheterization peak gradient measurement will supersede the continuous-wave Doppler measurement and be used to support the primary endpoint. Acceptable hemodynamic function as measured by catheterization will be considered to be peak gradient ≤40 mmHg.

-AND-

- Pulmonary regurgitant fraction as measured by magnetic resonance imaging <20%
    - If magnetic resonance imaging is contraindicated, a continuous-wave Doppler measurement will be used to support the primary endpoint. Acceptable hemodynamic function as measured by continuous-wave Doppler will be considered to be < moderate pulmonary regurgitation.

-AND-

- No prior Harmony valve reinterventions

The primary efficacy endpoint will be calculated using Core lab data, and analysis cohort will be the implanted >24 hours cohort. Analysis method details are provided in section 7.9.2.2.

#### 7.9.2.1 Hypothesis and/or Parameters to Be Estimated

The objective is descriptive and no statistical hypothesis test will be performed.

#### 7.9.2.2 Data Collection and Analysis Methods

Core lab data will be used to assess the efficacy endpoint, with an exception in the case that a catheterization is performed to measure mean RVOT gradient, in which site reported data will be utilized. The analysis cohort for the primary efficacy endpoint will be the implanted > 24 hours cohort. The percentage of subjects with acceptable hemodynamic function at 6 month and a two-sided 95% Clopper-Pearson confidence interval will be provided. The primary efficacy objective will be met if the point estimate is equal to or greater than the performance target of 75%.

The efficacy endpoint will be assessed using the 6-month echo, diagnostic catheterization performed during the 6-month protocol window, and reintervention status through 6 months. If 6-month echo occurred prior to 6-month time window opening or missed, next available echo that is after the 6-month window opening will be used, unscheduled or 1-year echo, which ever came first. Tables below define success or failure for all possible scenarios. Only subjects whose procedure were 6 months prior will be included in the analysis. Modified TPV 25 subjects will be excluded from the primary analysis for PMA. The primary endpoint will be evaluated again when all subjects reach 6-month visit.

| **Previous Reinterventions or Diagnostic Catheterization Procedures** | | | |
|---|---|---|---|
| | 6-Month Echo Not Performed or Evaluable | 6-Month Echo Acceptable Hemodynamics | 6-Month Echo Unacceptable Hemodynamics |
| Any Harmony Reintervention Prior to 6-Month Window Closing | Fail | Fail | Fail |
| Diagnostic Cath Acceptable Hemodynamics **Prior** to 6-Month Window | Not Evaluable | Success | Fail |
| Diagnostic Cath Acceptable Hemodynamics **During** 6-Month Window | Success | Success | Success |
| Diagnostic Cath Unacceptable Hemodynamics **Prior** to 6-Month Window | Not Evaluable | Success | Fail |
| Diagnostic Cath Unacceptable Hemodynamics **During** 6-Month Window | Fail | Fail | Fail |

| No Previous Reinterventions or Diagnostic Catheterization Procedures | | | |
|---|---|---|---|
| | 6-Month Echo Not Performed or Evaluable | 6-Month Echo Acceptable Hemodynamics | 6-Month Echo Unacceptable Hemodynamics |
| Previous Echo Acceptable Hemodynamics | Not Evaluable | Success | Fail |
| Previous Echo Unacceptable Hemodynamics | Not Evaluable | Success | Fail |

#### 7.9.2.3 Sensitivity Analysis

For the primary efficacy endpoint, percentage of subjects with acceptable hemodynamic function composite at 6 months, the primary outcome will be calculated by excluding subjects whose 6-months echo data were not evaluable. Additionally, a sensitivity analyses will be calculated using the following criteria:

- worst-case outcome assumed all unable-to-be-assessed cases were failures
- best-case outcome assumed unable-to-be-assessed cases were successes
- last value carried forward outcome assumed all unable-to-be assessed cases were successes or failures using the last available information prior to 6-month window

### 7.9.3 Subgroup Analysis

The primary endpoints will be assessed by pediatric (<22 years old) and adult (⩾22 years old) cohorts as defined per the FDA Guidance: Premarket Assessment of Pediatric Medical Devices (24 March 2014) [1] and by gender.

## 7.10 Safety Evaluation

Assessment of safety is defined as assessment of:

- All procedure-related serious adverse events
- All device-related serious adverse events
- Death (all-cause, procedural, and device-related)

For assessment of safety, the CEC data will be used for analysis. The analysis cohorts are:

- All procedure-related adverse events: Catheterized cohort
- All device-related adverse events: attempted implanted cohort
- Death (all-cause, procedural, and device-related): Catheterized cohort

Adverse events will be analyzed either via survival analysis using the Kaplan-Meier method or summarized by count and percent as appropriate.

## 7.11 Additional Outcomes Measures

Final analysis on the additional outcome measures will be performed when the implanted subjects have reached their 5 year endpoints, with the exception of the following endpoints, which will be analyzed in conjunction with the primary objective analysis (when all implanted subjects have reached their 6-month visit):

- Technical success at exit from catheterization lab/operating room (OR)
- Procedural success at 30 days

**Outcome Measure #1: Technical success at exit from catheterization lab/operating room (OR)**

Technical success is defined as:

- No device- or procedural-related mortality, with
- Successful access, delivery and retrieval of the delivery system, and
- Deployment and correct positioning (including minor repositioning if needed) of the single intended device, and
- No need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure

The analysis cohort for technical success will be the attempted implant cohort. The percentage of subjects with technical success will be presented. If an element of the composite is missing and available elements meet the success criteria, the subject will be excluded from the analysis.

**Outcome Measure #2: Device success out to 5 years**

Device success is defined as:

- No device- or procedural-related mortality, with
- Original intended device in place, and
- No additional surgical or interventional procedures related to access or the device since completion of the original procedure (i.e., exit from the catheterization lab), and
- Intended performance of the device, as defined as:
    - Structural performance: No migration, embolization, detachment, major stent fracture, hemolysis, thrombosis, endocarditis, and
    - Hemodynamic performance: Relief of insufficiency (PR < moderate) without producing the opposite (mean RVOT gradient > 40 mmHg) as measured by continuous wave Doppler[2], and
- Absence of para-device complications, as defined by:

[2] If a catheterization is performed for clinical purposes, the catheterization peak gradient measurement will supersede the continuous-wave Doppler measurement and be used to support the outcome measure.

- PVL ≥ moderate, or
- Erosion, or
- RVOT or PA rupture

The analysis cohort for device success will be the attempted implant cohort. The endpoint will be reported as Kaplan-Meier estimate for device failure which will be the opposite of device success. The loglog transformed two-sided 95% confidence interval using the Peto standard error at 6 months (183 days), 1 year (365 days), 2 years (730 days), 3 years (1095 days), 4 years (1460 days) and 5 years (1825 days) will be presented.

**Outcome Measure #3: Procedural success at 30 days**

Procedural success is defined as:

- Device success at 30 days, and
- None of the following device- or procedure-related serious adverse events:
  - Life-threatening major bleed
  - Major vascular or cardiac structural complications required unplanned reintervention or surgery
  - Stage 2 or 3 acute kidney injury (AKI) (includes new dialysis)
  - Pulmonary embolism
  - Severe heart failure (HF) or hypotension requiring IV inotrope, ultrafiltration, or mechanical circulatory support
  - Prolonged intubation >48 hours

The analysis cohort for procedural success will be the attempted implant cohort. The percentage of subjects with procedural success will be presented. If an element of the composite is missing and available elements meet the success criteria, the subject will be excluded from the analysis.

**Outcome Measure #4: Freedom from TPV dysfunction out to 5 years**

TPV dysfunction is defined as any one of the following:

- RVOT reoperation for device-related reasons
- Catheter re-intervention of TPV
- Hemodynamic dysfunction of the TPV (moderate or greater pulmonary regurgitation, and/or a mean RVOT gradient > 40 mmHg)

The analysis cohort will be the implanted > 24 hours cohort. The endpoint will be described by Kaplan-Meier statistics. The loglog transformed two-sided 95% confidence interval using the Peto standard error at 6 months (183 days), 1 year (365 days), 2 years (730 days), 3 years (1095 days), 4 years(1460 days) and 5 years (1825 days) will be presented.

**Outcome Measure #5: Assessment of safety**

Detailed information about how adverse events will be summarized is delineated in section 7.10.

**Outcome Measure #6: Characterization of right ventricle remodeling following TPV implant as assessed via CMR**

Summary statistics by visit interval will be provided for the following measures at pre-implant, 6 months post-implant, and 2 to 5 years post-implant.

- Right Ventricular End Diastolic Volume (RVEDV)
- Left Ventricular End Diastolic Volume (LVEDV)
- Right Ventricular End Diastolic Volume Index (RVEDVi)
- Left Ventricular End Diastolic Volume Index (LVEDVi)
- Right Ventricular End Systolic Volume (RVESV)
- Light Ventricular End Systolic Volume (LVESV)
- Pulmonary Regurgitation Fraction (PRF)
- Right Ventricular Ejection Fraction (RVEF)
- Left Ventricular Ejection Fraction (LVEF)
- Net Right Ventricular Stroke Volume
- Net Left Ventricular Stroke Volume
- Right ventricular to left ventricular end-diastolic volume ratio

The analysis cohort will be implanted longer than 24 hours cohort. Summary statistics such as mean, standard deviation, median, minimum, maximum, first and third quartiles will be provided for continuous variables and count and percentage will be provided for categorical variables.

## 7.12 Health outcomes

**Outcome Measure #7: Characterize quality of life scores over time**

Quality of life will be assessed by the subjects completing the RAND 36-Item Short Form (SF-36) questionnaire. Completion of the SF-36 questionnaire is required at the following intervals: pre-implant, 1-month post-implant, 6 months post-implant, and annually post-implant out to 5 years. The analysis cohort will be the implanted >24 hours cohort.

Summary statistics such as mean, standard deviation, minimum, median, and maximum will be provided for quality of life scores over time as assessed by the SF-36 at pre-implant, 1-month post-implant, 6 months post-implant, and annually post-implant out to 5 years.

The responses will be scored by using the 36-Item Short Form Survey (SF-36) Scoring Instructions published by Rand Corporation [2]. The scoring is a two-step process as described in Table 1 and Table 2:

**Table 1.** Step 1: Recoding Items

| Item numbers | Change original response category * | To recoded value of: |
|---|---|---|
| 1, 2, 20, 22, 34, 36 | 1 → | 100 |
| | 2 → | 75 |
| | 3 → | 50 |
| | 4 → | 25 |
| | 5 → | 0 |
| 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 | 1 → | 0 |
| | 2 → | 50 |
| | 3 → | 100 |
| 13, 14, 15, 16, 17, 18, 19 | 1 → | 0 |
| | 2 → | 100 |
| 21, 23, 26, 27, 30 | 1 → | 100 |
| | 2 → | 80 |
| | 3 → | 60 |
| | 4 → | 40 |
| | 5 → | 20 |
| | 6 → | 0 |
| 24, 25, 28, 29, 31 | 1 → | 0 |
| | 2 → | 20 |
| | 3 → | 40 |
| | 4 → | 60 |
| | 5 → | 80 |
| | 6 → | 100 |
| 32, 33, 35 | 1 → | 0 |
| | 2 → | 25 |
| | 3 → | 50 |
| | 4 → | 75 |
| | 5 → | 100 |

* Pre-coded response choices as printed in the questionnaire.

**Table 2.** Step 2: Averaging Items to Form Scales

| Scale | Number of items | After recoding per Table 1, average the following items |
|---|---|---|
| Physical functioning | 10 | 3 4 5 6 7 8 9 10 11 12 |
| Role limitations due to physical health | 4 | 13 14 15 16 |
| Role limitations due to emotional problems | 3 | 17 18 19 |
| Energy/fatigue | 4 | 23 27 29 31 |
| Emotional well-being | 5 | 24 25 26 28 30 |
| Social functioning | 2 | 20 32 |
| Pain | 2 | 21 22 |
| General health | 5 | 1 33 34 35 36 |

Table 1 shows that responses 1 through 5 for item 20 should be recoded to values of 100, 75, 50, 25, and 0, respectively. Responses 1 through 5 for item 32 should be recoded to values of 0, 25, 50, 75, and 100, respectively. Table 2 shows that these two recoded items should be averaged together to form the social functioning scale. If the respondent is missing one of the two items, the person's score will be equal to that of the non-missing item. The scale for each of 8 domains will be calculated respectively and will be counted as the quality of life score.

Summary statistics for continuous variable will be provided for the quality of life scores at pre-implant, 1-month post-implant, 6 months post-implant, and annually post-implant out to 5 years.

## 7.13 Pooled Analysis with Early Feasibility Study and Pivotal Study

The analysis population for the Harmony PMA will include subjects from the Harmony Pivotal Study in combination with the data from the Native Outflow Tract Transcatheter Pulmonary Valve Research Clinical Study (IDE #G120175), since the 2 studies have the same inclusion and exclusion criteria except for the inclusion criteria listed below. This difference in the inclusion criteria does not change the patient populations in the studies. Therefore, data can be pooled for analysis. Note the Native study only includes TPV22 implants.

| Harmony Pivotal Study | Early Feasibility Study |
|---|---|
| • Clinical indication for surgical placement of a RV-PA conduit or prosthetic pulmonary valve per one or more of the following criteria:<br>○ Subject is symptomatic secondary to pulmonary insufficiency (e.g. exercise intolerance, | • Clinical indication for surgical placement of a RV-PA conduit or prosthetic pulmonary valve per one or more of the following criteria:<br>○ Subject is symptomatic secondary to pulmonary insufficiency (e.g. exercise intolerance, |

| | |
|---|---|
| fluid overload) as classified by the investigator, or<br>○ Right ventricular end diastolic volume index (RVEDVi) ≥ 150 ml/m$^2$, or<br>○ **Subject has RVEDV: LVEDV Ratio ≥ 2.0** | fluid overload) as classified by the investigator, or<br>○ Right ventricular end diastolic volume index (RVEDVi) ≥ 150 ml/m$^2$ |

The following endpoints will be analyzed with the pooled data sets:

- Primary Safety Endpoint: freedom from procedure or device-related mortality at 30 days post implant
- Primary Efficacy Endpoint: percentage of subjects with acceptable hemodynamic function at 6 months
- Safety Evaluation
- Technical success at exit from catheterization lab/operating room
- Device success
- Freedom from TPV dysfunction
- Characterization of right ventricle remodeling following TPV implant

## 7.14 Changes to Planned Analysis

No procedure- or device- related reintervention was added as one component of being success for the primary efficacy endpoint, acceptable hemodynamic function at 6 months. This criterion is not explicit in the CIP; however, it was intended to be defined in the protocol.

# 8. Validation Requirements

At the minimum the requirements for validation are Primary objective: Level I validation (the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer).

Safety evaluation, health outcome measures, and other analysis results: Level II validation (The peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.)

# 9. References

[1] “FDA Guidance: Premarket Assessment of Pediatric Medical Devices (24 March 2014)” [Online]. Available: https://www.fda.gov/media/73510/download
[2] “36-Item Short Form Survey (SF-36) Scoring Instructions” [Online]. Available:

http://www.rand.org/health/surveys_tools/mos/36-item-short-form/scoring.html. [Accessed: 22-SEP-2016].