Apogee Statistical Analysis Plan (SAP)

Destination Therapy (DT) Post Approval Study (PAS) Addendum

Product Surveillance Registry (PSR) Platform Addendum

Version 28APR2022

NCT03697980

Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	The Mechanical Circulatory Support (MCS) Product Surveillance Registry (PSR) Platform Base Protocol, Destination Therapy (DT) Post Approval Study (PAS) Addendum, and Apogee Addendum
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Kristie Wallace, Pr. Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AD	Addendum
ADE	Adverse Device Effect
AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
CIP	Clinical Investigation Plan
CNS	Central Nervous System
CPB	Cardiopulmonary Bypass
CSR	Clinical Study Report
CT	Computed Tomography
DRF	Data Request Form
DT	Destination Therapy
EC	Ethics Committee
eCRF	Electronic Case Report Form
EPPY	Events Per Patient-Year
FAS	Full Analysis Set
FU	Follow Up
GI	Gastrointestinal
ICF	Informed Consent Form
ICH	Intracranial Hemorrhage
ICU	Intensive Care Unit
INR	International Normalized Ratio
IRB	Institutional Review Board
LVAD	Left Ventricular Assist Device
MAP	Mean Arterial Pressure
MCS	Mechanical Circulatory Support
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
NYHA	New York Heart Association
PAS	Post Approval Study
PSR	Product Surveillance Registry
QoL	Quality of Life

Abbreviation	Definition
RHF	Right Heart Failure
RVAD	Right Ventricular Assist Device
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SC	Steering Committee
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIA	Transient Ischemic Attack
TTR	Time in Therapeutic Range
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VAD	Ventricular Assist Device

3. Introduction

Most patients receiving mechanical circulatory support (MCS) experience severe adverse event (AE) burden. The 2013 Intermacs report showed that approximately 70% of patients experience a major adverse event within the first 12 months following left ventricular assist device (LVAD) implant, with major event defined as the first occurrence of infection, bleeding, device malfunction, stroke, or death. (Kirklin)

Medtronic is sponsoring the Apogee study as a subset of the Destination Therapy (DT) post approval (PAS) study. Co-enrollment in Apogee is allowed for patients participating in the DT PAS. Medtronic is sponsoring the DT PAS to further understand the implant technique and patient management when used as intended, in "real-world" clinical practice.

Given the heavy adverse event burden, there is an opportunity to understand best practice guidelines. The purpose of Apogee is to further understand the effects of implant technique and patient management (i.e. implant procedure, optimized blood pressure (BP) management, and anticoagulation / antiplatelet therapies. The goals of Apogee are:

- To evaluate the collective impact of Apogee standardized guidelines and characterize impact on 12-month aggregate adverse event rate
- To better understand the effects of implant technique and patient management on clinical outcomes

Apogee is conducted within Medtronic's Product Surveillance Registry (PSR) platform. The Apogee addendum (AD) outlines data collection, any applicable procedures, objectives, statistical methodology, analysis cohort, and reporting timelines specific to the Apogee study which are not defined in the PSR

core and MCS appendix (MCS PSR platform base protocol) or the DT PAS addendum. The combination of these elements together defines the requirements for Apogee study.

The PSR platform is sponsored by Medtronic and is comprised of a global network of hospitals, clinics and clinicians from which reliable "real-world" product safety and patient clinical outcome information is generated. It leverages a common infrastructure/designed for the rapid collection, analysis and dissemination of surveillance information for multiple Medtronic device technologies.

This statistical analysis plan (SAP) has been developed based on the Apogee addendum, DT PAS addendum and PSR MCS platform base protocol. The SAP will be used for the final analysis of the post-market Apogee US data.

On 03-Jun-2021, Medtronic stopped the distribution and sale of the HVAD System. As a result, new implants of the HVAD System were immediately ceased. Given that all patients had been enrolled and that the DT PAS was ongoing (per regulatory guidance), it was decided to continue the Apogee study and analyze the available data.

4. Study Objectives

4.1 Primary Objective

To characterize the 12-month overall major adverse event rate after the collective impact of Apogee standardized protocols and best practices. Major adverse events are defined to be the occurrence of major infection, major bleeding, device malfunction, stroke (includes ischemic stroke, acute symptomatic ICH, and clinically covert ischemic stroke or ICH) or death.

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5. Investigation Plan

5.1 Study Design

The Apogee study is a prospective, observational, multi-site study in destination therapy patients. The Apogee study includes three areas of data collection:

- Implant Procedure
- Blood Pressure Management
- Anti-coagulation/Anti-platelet Therapy

Sites choosing to participate in Apogee are expected to collect data in each of these three areas.

5.2 Study Population

Approximately 50 sites from the United States (US) will participate in the DT PAS. The DT PAS cohort will be comprised of 300 newly enrolled and implanted DT PAS patients.

Patients intended to be newly implanted with a HVAD System per the current guidelines and fulfill all the inclusion and none of the exclusion criteria outlined in the MCS PSR platform base protocol are eligible for enrollment into DT PAS/Apogee and must be consented for DT PAS and Apogee prior to the HVAD System implant. The patient must be consented with the DT PS consent prior to consenting with the Apogee consent.

It is expected a subset of the DT PAS sites will participate in Apogee. DT PAS sites can choose to participate in Apogee, or they can decline Apogee and limit their participation to the DT PAS. As an estimate, if one-third of the approximately 50 DT PAS sites participate in Apogee, it is expected the Apogee cohort will be comprised of approximately (but not limited to) 100 patients from approximately (but not limited to) 17 Apogee sites. In general, it is expected that any site participating in Apogee would enroll all of their eligible patients in Apogee; however, there may be exceptions due to timing of Apogee activiation, lack of patient interest, or concerns regarding non-compliance. There are 34 sites who are co-activated for Apogee, with 124 patients co-enrolled.

5.3 Inclusion/Exclusion Criteria

MCS PSR base platform Inclusion Criteria:

- Patient or legally authorized representative provides written authorization and/or consent per institution and geographical requirements
- Patient has or is intended to receive or be treated with an eligible product
- Patient is consented prior to the treatment/therapy received.

MCS PSR base platform Exclusion Criteria:

- Patient who is, or is expected to be inaccessible for follow-up
- Patient with exclusion criteria required by local law
- Patient is currently enrolled in or plans to enroll in any concurrent drug and/or device study that may confound results (i.e. no required intervention that could affect interpretation of all-around product safety and or effectiveness)

DT PAS/Apogee Addendum Exclusion Criteria:

- Persons less than 18 years of age
- Patients previously supported by long-term mechanical support (not including temporary MCS support)

5.4 Minimization of Bias

The following methods may be incorporated to minimize potential bias (from the MCS PSR base protocol):

- Sites will consider enrollment of all eligible patients
- Enrollment may be limited at a site level by product and or by therapy
- Diverse geographical site representation
- Sites represent various types of practice settings including university, community, public and private
- Sites must meet pre-defined criteria to be selected to participate
- Procedures and data collection requirements are standardized

Every effort will be made to collect all data points in the registry. Medtronic plans to minimize the amount of missing data by appropriate management of the prospective clinical registry, proper screening of study patients, and training of participating investigators, monitors, and study coordinators.

The original sample size allows for attrition due to explants and withdrawals. No hypothesis testing was planned for this final report, and the sample size will include all consented and implanted patients in Apogee.

No additional potential bias beyond that outlined in the MCS PSR base protocol is expected to be introduced with the Apogee AD elements.

5.5 Study Procedures

Data collection will begin at baseline and will continue at implant, discharge/1 month, 3 months, 6 months and 12 monthsuntil transplant (where applicable), explant, exchange or the end of the study (death, exit or 12 months post implant). Follow-up is consistent with routine clinical practice and training will be provided to sites to facilitate a robust data set and ensure reporting consistency. Sites will report procedure-related, device-related, and therapy-related AEs, and all Serious Adverse Events (SAE) upon site's first awareness. Table 1 shows the summary of data collection requirements for the MCS PSR base platform and Figure 1 shows the follow up schedule.

DT PAS patients are required to fill out an mRS score at baseline, in addition to the neurological dysfunction requirement (at time of diagnosis, 12- and 24-weeks post event). The data collection requirements can be found in Table 2.

The Apogee patients will have follow-up assessments at 1 month, 3 months, 6 months and 12 months post-implant or as prompted by reportable AEs, as defined in the MCS PSR platform base protocol. In addition, Apogee will focus on detailed implant data, blood pressure management and anticoagulation/antiplatelet data to support ancillary objectives. The additional Apogee data collection requirements can be found in Table 3.

While all assessments were still required for the study, some specific assessments may not have been completed. In addition, COVID-19 could have impacted the amount of in-person follow up visits.

Table 1: Summary of Data Collection Requirements

	Enrollment	Baseline	Implant	Discharge	Follow-up	System Modification	Neurological Dysfunction Adverse Event	Exit
Informed Consent Form (ICF) or Data Request Form (DRF) Signed and Dated, and Eligibility Verification	X							
Demographics		X						
Medical History and Co-Morbidities		X						
Intermacs Patient Profile		X						
Procedure Details/Device Information			X			X[1]		
In-Hospital/Discharge Details				X				
NYHA Functional Classification		X			X			
Medications[2]		X	X		X			
Vital Signs Data[2]		X			X			
Hemodynamics Parameters Data		X						
Echocardiographic Data		X						
LVAD Device Data Uploads					X			
Laboratory Results[2]		X			X			
Quality of Life (QoL)		X			X			
Exercise Function (6-Minute Walk)		X			X			
modified Rankin score (mRS)[3]		X					X (at diagnosis and at 90 ±14 days post-event)	
National Institutes of Health Stroke Scale (NIHSS)[4]							X (at diagnosis)	
LVAD Parameters					X			
Patient Status/Treatments								X
Adverse Events and Device Deficiencies Assessments			Reported upon site's first awareness					
Death			Reported upon site's first awareness					
System Modifications			Reported upon site's first awareness					
Re-hospitalizations					Reported upon site awareness			
Deviations	Reported upon site's first awareness							

[1] At the time of exchange, the same device information will be collected as during the initial implant procedure

[2] Medications, vital signs, and INR (at least monthly) will be performed per routine care and collected through the entire registry

[3] At baseline, mRS will be collected for any patients with a history of neurological dysfunction. From time of implant until exit, mRS is to be collected at time of diagnosis for any neurological dysfunction event, and at 90 ± 14 days post-event regardless of subsequent pump explant for transplant, recovery, or exchange, or if the pump is turned off but not explanted. mRS is to be collected as close to recommended timepoints as possible, however there may be variation in 'real world' clinical practice for a number of reasons. Therefore, mRS not within this recommended time can and should be collected. Post-event mRS is to be

collected regardless of subsequent pump explant for transplant, recovery, or exchange, or if pump is turned off but not explanted.

[4] NIHSS will be collected, as close as possible, to the time of diagnosis of neurological dysfunction event. However, if NIHSS is not available at time of diagnosis, report NIHSS when available.

Figure 1: Expected Follow-up Schedule and Windows for MCS Therapy

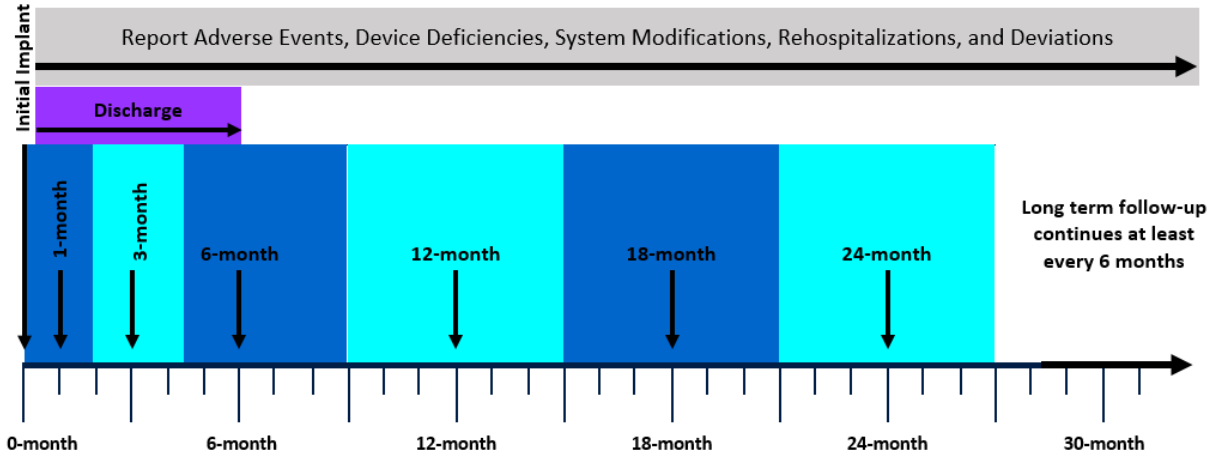

Table 2: Summary of DT PAS Additional Data Collection Requirements

		Neurological Dysfunction		
	Baseline (in all patients)	At time of diagnosis	12 weeks post-event	24 weeks post-event
mRS Score*	X	X	X	X

*Note: Obtain mRS assessment as close to the recommended timepoint as possible, however, there may be variation in 'real world' clinical practice for a number of reasons. Therefore, if mRS is not available within recommended timepoints, data should be collected when available.

Table 3: Summary of Apogee Additional Data Collection Requirements

		Enrollment	Baseline	Implant	Discharge	1M F/U	3M F/U	6M F/U	12M F/U	Unsch <12M
	Consent	X								
Implant Procedure	Detailed Implant Collection			X						
	Echo for 2D Velocimetry evaluation (digital image)		X	X (2 TEEs*)	X *With Lavare On x 5 min & Off x 5 min*		X			
	CT Scan Post-implant (digital			X *if performed*						
	Right Heart Cath (RHC) Hemodynamics		X *If subsequent RHC performed*	X *If performed*						
	Chest x-ray (digital image)			X Post-op						
	Videotape proced			X *if obtained*						

BP	Patient BP Diary**				*Every morning ≥ 40 minutes after taking BP meds and while sitting. Collect whether HCP contacted for values out of range*					
	Medication BP Control				*Consider Medication Guidelines; Report Medication Changes*					
Anticoagulation/Antiplatelet	Home INR monitoring				*. Collect weekly INR and prescribed Warfarin dosing.*					
	VerifyNow Aspirin Assay Laboratory	X *≤7 days pre-implant preferred*			**X**	**X**	**X**	**X**	**X**	X *If seen for bleeding or thrombotic complication*
	Enoxaparin bridging and GI									**X** *angiopoietin-2 levels if collected*

*Two abbreviated echos are performed in the operating room (OR): 1) TEE in OR after chest is open before going on cardio- pulmonary bypass, and 2) TEE in OR post-implant, after coming off cardio-pulmonary bypass, while chest is still open

** Diary includes Doppler pressure, presence of palpable pulse, LVAD parameters, and dizziness symptom

6. Determination of Sample Size

The total sample size will be dependent on the number of sites and patients interested in participation in Apogee. The DT PAS is to enroll 300 newly implanted DT patients. It is expected a subset of the DT PAS sites will participate in Apogee. DT PAS sites can choose to participate in Apogee, or they can decline Apogee and limit their participation to the DT PAS. As an estimate, if one-third of the approximately 50 DT PAS sites participate in Apogee, it is expected the Apogee cohort will be comprised of approximately (but not limited to) 100 patients from approximately (but not limited to) 17 Apogee sites. In general, it is expected that any site participating in Apogee would enroll all of their eligible patients in Apogee; however, there may be exceptions due to timing of Apogee activiation, lack of patient interest, or concerns regarding non-compliance.

All implanted patients will be followed under both the DT PAS and Apogee AD until one year post implant, or until Apogee withdrawal/exit, transplant, explant for a non-HVAD device or death, whichever comes first. If patient is still on an HVAD device, their participation in Apogee ends at the 12 months post-implant visit but patients will remain enrolled in DT PAS and will have follow-ups as outlined in the MCS PSR platform base protocol and DT PAS addendum.

Full enrollment is anticipated to require approximately 30 months from the date of first DT PAS enrollment (actual was 27.4 months from first implant to last) and therefore with 12 months of follow-up, total study duration is expected to require 42 months. There is no minimum or maximum number of enrollments per site since data is being used for characterization purposes only.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Patient disposition will be summarized by a STROBE flow diagram, including details on patient follow-up and attrition. A STROBE flow diagram will include the number of individuals at each visit of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed) and reasons for non-participation at each visit. The number of consented patients and patients who received the HVAD System will be counted. The number of patients in DT PAS will be provided, but all follow up details will be for those patients consented and implanted under Apogee.

7.1.2 Clinical Investigation Plan (CIP) Deviations

A deviation is defined as an event that did not occur according to requirements specific to regulations, CIP and/or associated Addendum. Examples include but are not limited to: improper or incomplete informed consent form (ICF), did not meet eligibility criteria, etc.

All deviations will be reported and submitted to Medtronic each time a deviation occurs. The description of the deviation and justification must be documented and submitted to Medtronic.

Once a deviation has been identified it should be reported to Medtronic via electronic case report form (eCRF) as soon as possible. Deviations may be identified through numerous sources, including but not limited to: telephone conversations, site monitoring, patient record, or data review.

It is the site's responsibility to report deviations in compliance with their Ethics Board policies and/or local laws.

Medtronic is responsible for reviewing deviations, assessing their significance, and identifying any necessary corrective and/or preventive actions. Medtronic will determine whether any subsequent action is needed (e.g. amending the CIP or training). Repetitive or serious compliance issues may represent a need to initiate a corrective action plan and, in some cases, may necessitate suspending a site's ability to enroll until the problem is resolved.

Every attempt must be made to avoid study deviations. If the clinician anticipates, contemplates, or makes a conscious decision to deviate from PSR requirements, agreements or regulations, prior approval by Medtronic's Registry team is required. Prior approval is not necessary in situations where unforeseen circumstances are beyond the clinician's control.

Deviations from the CIP will be summarized in the clinical study report (CSR) by coded category, while a patient is participating in Apogee (DT PAS exit, Apogee withdrawal, the 12 month follow up, or 365 days post implant, whichever comes first). The number of deviations per category, and the number and percentage of patients with a deviation in each category will be reported.

7.1.3 Analysis Sets

Consented Set: This analysis set includes all patients who signed consent to participate in MCS PSR, DT PAS addendum, and the Apogee addendum.

Full Analysis Set (FAS): This analysis set includes all patients who received an HVAD System according to product labeling.

Safety Analysis Set: This analysis set is the same as the FAS.

The primary endpoint will be performed on the FAS. The safety endpoints will be performed on the Safety Analysis Set. All other analyses will be done on the FAS.

7.2 General Methodology

Medtronic employees or designees will perform all statistical analyses using either SAS or R software. Additional exploratory analyses of the data may be conducted as deemed appropriate.

7.3 Center Pooling

Centers will be pooled for all analyses of study objectives. No poolability assessment will be conducted.

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

Data entry error or non-reasonable values will be cleaned before data analysis. In the event of patient exit or withdrawal of consent, the patient's data collected prior to study exit will still be included in the final statistical analysis. The specific reasons for patient exit or withdrawal will be provided in detail in the study report.

All available data (i.e., not missing) will be included in the tabulations and applicable data listings to be analyzed as described in this plan. Missing data will not be imputed.

[redacted]

This study will use the survival analysis method for the primary objective. If a patient withdraws or prematurely exits the study and no failure criteria were met, the last known date the patient was alive on device (same type as originally received – would include follow-up post exchange to another HVAD) and actively participating in the study will be used for the censoring date in the Kaplan-Meier analysis.

7.5 Adjustments for Multiple Comparisons

No adjustments are planned for multiple comparisons.

7.6 Demographic and Other Baseline Characteristics

Baseline characteristics and relevant medical history will be collected on eCRFs for all enrolled patients. Baseline characteristics will be summarized for all implanted patients. Baseline variables to be summarized include, but are not limited to: age, sex, Intermacs patient profile, height, weight, body mass index (BMI), body surface area (BSA), general and cardiovascular medical history, echocardiography test results, and hemodynamics.

Summary statistics will be obtained: frequency and percentage will be reported for categorical data; mean, standard deviation, minimum, maximum, median, the 1st and 3rd quartiles will be reported for continuous data.

7.7 Treatment Characteristics

The investigator must assess for any AEs and evaluate the study device to verify study device function after enrollment in Apogee, and at each protocol required follow-up, including implant.

7.7.1 Implant/Hospitalization and Discharge

Implant information will be collected on eCRFs for all enrolled and implanted patients. For patients with successful implants, variables to be summarized include, but are not limited to: device strategy at the time of implant (with reason not eligible for destination therapy patients), duration of implant, surgical approach, cardiopulmonary bypass time, aortic cross clamp time, concurrent cardiac procedures, right ventricular assist device (RVAD) use, transfusions, and driveline and outflow graft locations. The duration in the intensive care unit (ICU) and in the hospital post implant will be summarized.

Variables related to the implant procedure will be summarized, including additional implant variables collected, as applicable and desired by the study team.

Summary statistics will be obtained: frequency and percentage will be reported for categorical data; mean, standard deviation, minimum, maximum, median, the 1st and 3rd quartiles will be reported for continuous data.

7.7.2 System Modification

In the event a system modification occurs, the data will be collected on the eCRFs. A system modification occurs when the pump is removed from the body and not replaced (e.g., heart transplant, explant for recovery), the pump is removed from the body and is replaced by another HVAD or other mechanical support device (i.e., exchange), if the pump is turned off but not removed from the body (e.g., for recovery, hospice/end of life), or if the pump needs to be repositioned. A summary of the number of patients with a system modification and total number of system modifications will be provided, breaking out the reason for system modification. A separate table will further subclassify the new device received for exchanges and the reason for a heart transplant. Only events while a patient participated in Apogee will be included (12 month follow up visit, 365 days post implant, withdrawal from Apogee, or exit from DT PAS).

Note that any system modifications after 03-Jun-2021 which result in an exchange should be to a non-HVAD device, given the stop of implants of the HVAD.

7.8 Interim Analyses

No interim analyses were planned for this cohort.

Descriptive summaries of the study data may be conducted as deemed appropriate throughout the study. All efforts will be made to ensure such descriptive analyses will not jeopardize the study final report.

In June 2021, Medtronic decided to halt the production and sale of the HVAD. In agreement with the steering committee (SC), it was decided to continue the Apogee study through its one year follow up for all enrolled and implanted patients. A final clinical study report will be created and shared with institutional review boards (IRBs) and sites, as applicable.

7.9 Evaluation of Objectives

Many ancillary objectives are not statistical in nature and since this is an observational study no hypothesis tests are planned.

The Apogee study might observe variations in data collection due to 1) variations in routine care practices across participating sites and 2) the COVID-19 pandemic. Apogee does not have statistical hypotheses; thus, available data will be analyzed.

If any of the analysis does not have enough data to provide a summary, metrics for completion and expected values will be provided in its place.

7.9.1 Primary Objective

To characterize the 12-month overall major AE rate after the collective impact of Apogee standardized protocols and best practices. Major AEs are defined to be occurrence of infection, bleeding, device malfunction, stroke death.

Events counted as “major adverse events” are:

- Major infection as defined by Intermacs adverse events V5
- Major bleeding as device by Adverse Events
- Device Malfunction as defined by Adverse Events
- Any stroke (includes both ischemic stroke, acute symptomatic ICH, and clinically covert ischemic stroke or ICH) as defined by Adverse Events as a sub-category of neurological dysfunction
- All-cause death

Time to first major adverse event will be analyzed using Kaplan-Meier methods, with Time 0 being exit from the operating room following implant. Patients will be censored upon the earliest of explant of the original device (e.g., transplant, recovery, exchange), study exit, Apogee withdrawal, last known follow-up, and the date of their 12-month follow-up (365 days will be used if 12-month follow-up was not completed and greater than 365 days was completed). Patients who have the device turned off, but not removed will continue to be followed the same as those patients who still have the device implanted and turned on. Patients who have devices repositioned will continue to be followed as per the regular follow up schedule. Failure time is the time to a primary objective

event. There is no planned formal comparison of the major AE rate, though it could be informally compared to results from other studies, or non-Apogee patients in DT PAS.

The number of patients left, survival rate and exact 95% confidence intervals (CI) will be summarized for all patients. In addition, the number of patients who met a failure endpoint (first failure) from implant to the time interval as well as the reasons for censoring will be summarized.

Failure:

- Major Infection
- Major Bleeding
- Device Malfunction
- Stroke
- Death

Censored:

- Survival on original device – 12 month follow up, 365 days post implant, or last known follow up
- Exchange
- Explant for Transplant
- Explant for Recovery

A stroke is a neurological dysfunction event specified as an ischemic stroke, acute symptomatic ICH, or clinically covert ischemic stroke or ICH. These must be confirmed with computed tomography (CT).

Events where the "What is the relative time from the procedure" is recorded as "DURING PROCEDURE" will be excluded from the analysis.

Patients who withdraw (either from the PSR or from just the Apogee study), are lost to follow up, or otherwise do not have a 12 month follow up (or 365 days post implant), but do not have a qualifying failure event, will be censored as of their last known date in the study.

Code similar to below will be used:

```
ods listing close;
proc lifetest data=alldata plots=survival (nocensor) outsurv=output1
maxtime=12 method=km;
   time endptmonth*censor(0);
   label endptmonth = "Months";
   ods output productlimitestimates=rate;
run;
ods listing;
```

Additionally, the individual types of major adverse events will be summarized. A cause of death table summarizing which Intermacs AE V5 resulted in a fatal outcome will also be summarized. See section 7.9.5.2 for further details.

Only DT PAS patients successfully implanted with the HeartWare HVAD and enrolled in the Apogee study will be included in this analysis.

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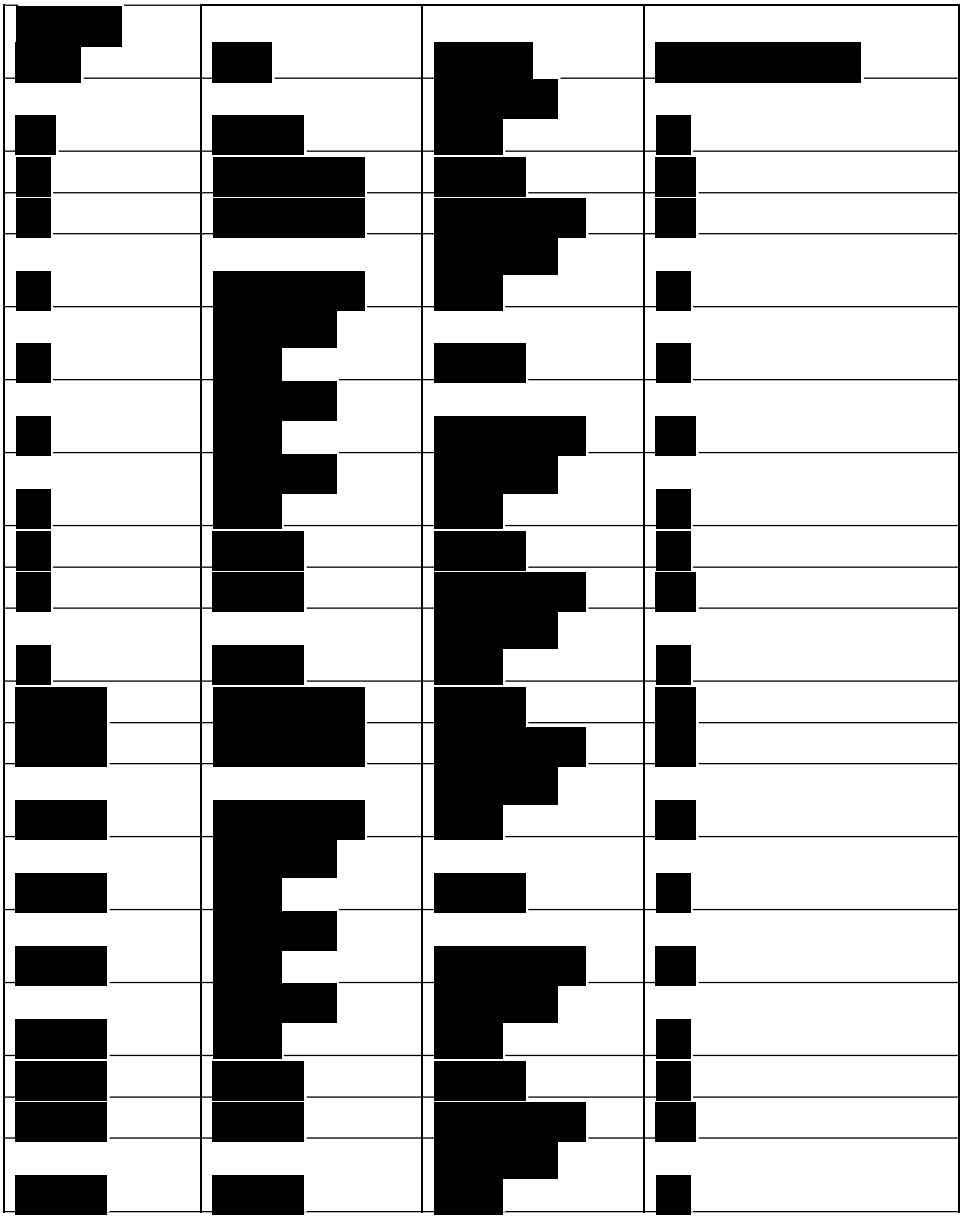
[redacted]



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[redacted]

[redacted]

7.9.5 Other Objectives

7.9.5.1 Overall Survival

Overall patient survival will be summarized descriptively with Kaplan-Meier curves. Time is measured from the day of implant of the study device. A patient is censored if the patient is explanted (e.g. transplant or recovery), if the patient is exchanged to a non-HVAD, the study is terminated (either overall or at the patient's investigative site), the patient withdraws consent (either from Apogee or PSR), or the patient is otherwise lost to follow-up. Patients who have the device turned off, but not removed or the device repositioned will continue to be followed the same as those patients who still have the device implanted and turned on. Only follow up and events (deaths) while a patient participated in Apogee will be included (12 month follow up visit, 365 days post implant, exit from DT PAS or withdrawal from Apogee). Failure time is the time to death on device.

The number of patients left, survival rate and exact 95% confidence intervals (CI) will be summarized for all patients. In addition, the number of patients who met a failure endpoint from implant to the time interval as well as the reasons for censoring will be summarized.

Patients who withdraw (either from the PSR or from just the Apogee study), are lost to follow up, or otherwise do not have a 12 month follow up (or 365 days post implant), but do not have a qualifying failure event, will be censored as of their last known date in the study.

Code similar to below will be used:

```
ods listing close;
proc lifetest data=alldata plots=survival (nocensor) outsurv=output1
maxtime=12 method=km;
   time endptmonth*censor(0);
   label endptmonth = "Months";
   ods output productlimitestimates=rate;
run;
ods listing;
```

Only DT PAS patients successfully implanted with the HeartWare HVAD and enrolled in the Apogee study will be included in this analysis.

7.9.5.2 Intermacs-Defined Adverse Events

All Intermacs V5-defined events will be summarized.

Patients will be assessed for AEs at all scheduled and unscheduled visits. Intermacs-defined AEs after HVAD implant will be summarized by severity, causal relationship to device, and outcome. The SAE, Serious Adverse Device Effect (SADE) and Unanticipated Serious Adverse Device Effect (USADE) will also be summarized. All AE incidence and rates (events per patient-year (EPPY)) will be summarized. Only events while a patient participated in Apogee will be included (12 month follow up visit, 365 days post implant, DT PAS exit, or withdrawal from Apogee).

The number and percentage of patients experiencing each specified AE using the Intermacs version 5 definitions, as well as number of events and event rate per patient-year will be summarized. All adverse events from induction of anesthesia until pump removal (with no replacement to another HVAD) will be summarized. If the device is turned off, but not removed, or if the device is repositioned, adverse events should be continued to be collected throughout follow-up.

The PSR MCS database underwent multiple changes to the AE forms throughout the lifecycle of the Apogee study. Cardiac arrhythmias, device malfunctions/failures, neurological dysfunctions, right heart failure, and other Intermacs AE categories will be reviewed by Medtronic Safety to reclassify the event to meet Intermacs Version 5.0 AE definitions as needed. Other events as needed will also be reviewed and reclassified. Detailed subcategory information (e.g., neurological dysfunction type) will be provided, as applicable and available. Reclassified events will be used in the summary tables if available; otherwise, the site entered data will be used. The AEs will be summarized using Intermacs V5.0 definitions.

Analyses will be done on the Safety Analysis Set.

The following subsets of the AEs will be summarized:

1. Intermacs V5 Adverse Events
2. Serious Adverse Events (SAE)
3. Adverse Device Effects (ADE)
4. Serious Adverse Device Effects (SADE)
5. Unanticipated Serious Adverse Device Effects (USADE)
6. Adverse Events Resulting in Death
7. Non-serious Adverse Events where frequency is greater than 5%

7.10 Safety Evaluation

7.10.1 Adverse Events

All study device and procedure related events, as well as reportable events, listed below, are required to be reported to Medtronic upon awareness. All AEs defined according to INTERMACS Manual of Operations Version 5.0 (See the PSR MCS base protocol with DT PAS and Apogee specific amendments) will be summarized.

- Arterial Non-Central Nervous System (CNS) Thromboembolism
- Cardiac Arrhythmias

- Device Malfunction/Failure
- Hemolysis
- Hepatic Dysfunction
- Hypertension
- Major Bleeding
- Major Infection
- Myocardial Infarction
- Neurological Dysfunction
- Pericardial Fluid Collection
- Psychiatric Episode
- Renal Dysfunction
- Respiratory Failure
- Right Heart Failure (RHF)
- Venous Thromboembolism
- Wound Dehiscence
- Other SAE

All AEs collected during the study post initial implant while the device is implanted in the body will be included in the tables. The tables will provide the number of patients who experienced an event, the number of events and the events per patient year. Tables for AEs, SAEs, SADEs, and USADEs will be summarized. Refer to section 7.9.5.2 for further detail.

The PSR MCS database underwent multiple changes to the AE forms throughout the lifecycle of the Apogee study. Cardiac arrhythmias, device malfunctions/failures, neurological dysfunctions, right heart failure, and other Intermacs events will be reviewed by Medtronic Safety to reclassify the event to meet Version 5.0 of the Intermacs definitions as needed. Other events as needed will also be reviewed and reclassified. Detailed subcategory information (e.g., neurological dysfunction type) will be provided, as applicable and available. The AEs will be summarized using Intermacs V5.0 definitions. Only events while a patient participated in Apogee will be included (12 month follow up visit, 365 days post implant, DT PAS exit, or withdrawal from Apogee).

Analyses will be done on the Safety Analysis Set.

7.10.2 Deaths

Death information will be collected throughout the trial when the event occurs. Deaths will be gathered from the AE eCRF where the outcome='FATAL', or from the Exit eCRF, if not available on the AE form. Summary tables will be compiled showing the Intermacs category of the adverse event which led to death (see section 7.9.5.2), as well as the relationship of the AE to the procedure, system, and patient condition. The number and percent of patients will be provided. Only events while a patient participated in Apogee will be included (12 month follow up visit, 365 days post implant, exit from DT PAS, or withdrawal from Apogee).

7.10.3 Device Deficiencies

In the event a device deficiency occurs, the data will be collected on the eCRFs, as well as if the device deficiency could have led to an SAE. A listing will be compiled to summarize the device deficiency details, including a description of the deficiency, date of onset, actions taken as a result of the deficiency, and the outcome of the event. Only events while a patient participated in Apogee will be included (12 month follow up visit, 365 days post implant, exit from DT PAS, or withdrawal from Apogee).

7.10.4 Adverse Event Definitions/Classifications

All products enrolled in the PSR platform are approved with demonstrated evidence of safety and effectiveness for their intended use, at the time the study starts. Event definitions align with International Organization for Standardization standard 14155 (ISO 14155); however products followed in the PSR are approved, not investigational and the purpose of the PSR is not to demonstrate product safety and effectiveness for the purpose of obtaining product approval, new material, or design change for medical device already on the market. Table 5 provides additional details below.

Table 5: Adverse Event and Device Deficiency Definitions

Adverse Event (AE) (ISO 14155):	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other person, whether or not related to the investigational medical device and whether anticipated or unanticipated. Note 1: This definition includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedure involved. Note 3: For users or other persons, this definition is restricted to the investigational medical device.
Adverse Device Effect (ADE) (ISO 14155):	Adverse event related to the use of an investigational medical device.

	Note 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use or the deployment, implantation, installation, or operation, or any malfunction of the medical device. Note 2: This definition includes any event resulting from user error or from intentional misuse of the medical device.
Serious Adverse Event (SAE) (ISO 14155):	Adverse event that: a) led to a death b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: • a life-threatening illness or injury • a permanent impairment of a body structure or a body function including chronic disease • in-patient or prolonged hospitalization • medical or surgical intervention to prevent permanent impairment to body structure or a body function c) led to foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment. Note: Planned hospitalization for a pre-existing condition or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE) (ISO 14155):	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Procedure-Related Adverse Event:	Adverse event that is related to the procedure of a device/system of interest.
Unanticipated Serious Adverse Device Effect (USADE) (ISO 14155):	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.
Device Deficiency (DD) (ISO 14155):	Inadequacy of a medical device with respect to its identity, durability, reliability, usability, safety or performance. Note: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. This definition includes device deficiencies related to the investigational medical device of the comparator.

Pre-existing conditions (e.g. disease signs and/or symptoms) that, in the opinion of the responsible clinician, existed prior to registry participation are not considered reportable, unless the condition recurs after the patient has recovered from the pre-existing condition, or the condition worsens in intensity or frequency. Additionally, planned hospitalizations for a pre-existing condition without serious deteriorationin health are not considered serious adverse events. An example of this includes prophylactic admissions to hospital for INR management.

7.11 Health Outcomes Analyses

No specific health outcomes analyses will be performed.

7.12 Changes to Planned Analysis

This SAP has been developed prior to data being analyzed to further describe the statistical methods and planned analyses of the study data to be included in the clinical study report. Any change to the data analysis methods described in the CIP will require a CIP amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP or SAP, and the justification for making the change, will be described in the clinical study report. For endpoints which were not analyzed per the original expectations (due to limited data), a similar analysis, compliance metrics, or count of results will be provided as described in this SAP.

8. Validation Requirements

All statistical analyses for the clinical study report will be carried out and validated by Medtronic statisticians, statistical programmers, or their designees. Levels of validation required for the different elements of the CSR are specified in Table 6 below.

Table 6: Validation Requirements

Validation Level	Definition	Required for
Level I	A peer reviewer independently programs output and then compares the output with that generated by the original author of the program to be validated	All analyses in the CSR pertaining to the primary and secondary objectives of the study
Level II*	A peer reviewer reviews the program, and where appropriate, performs calculations or programming checks to verify the output	All other analyses in the CSR (not pertaining to the primary and secondary objectives of the study)

*Level II validation is the minimum requirement; alternatively, level I validation can be performed if desired since it is more rigorous.

9. References

Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, Baldwin JT, Young JB. Fifth INTERMACS annual report: Risk factor analysis from more than 6,000 mechanical circulatory support patients. J Heart Lung Transplant. 2013;32:141–156

Macaluso GP, Pagani FD, Slaughter MS, Milano CA, Feller ED, Tatooles AJ, Rogers JG, Wieselthaler GM. Time in Therapeutic Range Significantly Impacts Survival and Adverse Events in Destination Therapy Patients. ASAIO J. 2022 Jan 1;68(1):14-20. doi: 10.1097/MAT.0000000000001572. PMID: 34524147; PMCID: PMC8700308.

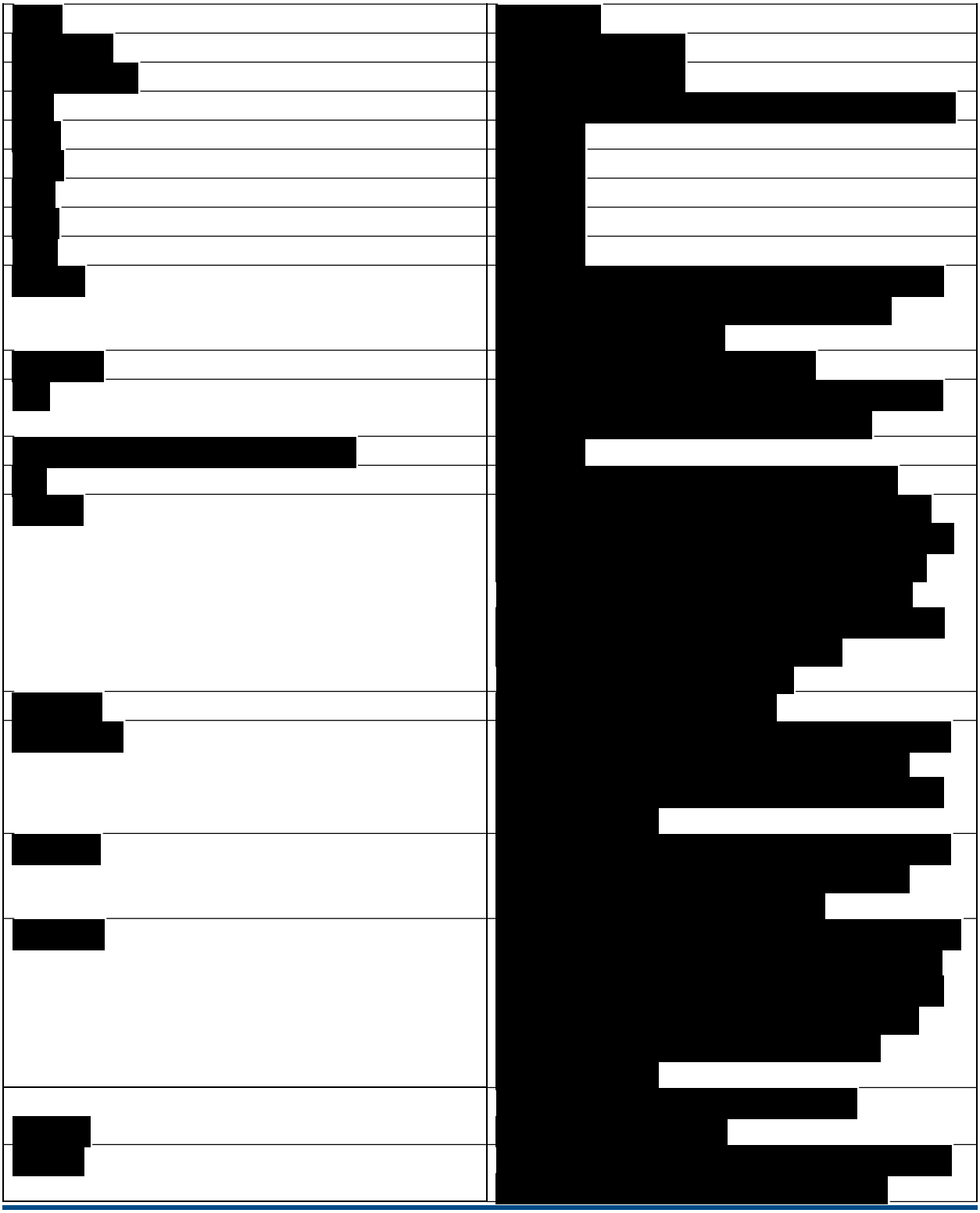
Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993 Mar 1;69(3):236-9. PMID: 8470047.

10. Statistical Appendices

10.1 Follow Up Date Calculation Variables

Take the max non-missing date from the following datasets and variables (date may end up being earlier based on exit, explant, or other reasons).

[redacted]	[redacted]



10.2 General Calculations

1. Last follow up in months: (last follow up days/365.25)*12
2. Patient years: sum of duration on support/365.25, rounded to 2 decimal places
3. Conversion of feet to meters: multiply feet*0.3048
4. Conversion of inches to centimeters: multiply inches*2.54
5. Conversion of pounds to kilograms: multiply pounds*0.4536
6. Conversion of degrees Fahrenheit to degrees Celsius: (F – 32)/1.8
7. BMI: weight (kg)/[height (m)]^2
8. BSA (Mosteller's equation); sqrt((weight (kg)*height (cm))/3600)
9. MAP: (Systolic BP + 2*Diastolic BP)/3