Statistical Analysis Plan

Clinical Investigation Plan Title	SPYRAL DYSTAL
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Document Version	3.0 04Feb2022
NCT Number	NCT04311086

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• First version	Cheryl Shen, Statistician
2.0	• Add section 9: COVID-19 related analyses • Add section 10: References	Cheryl Shen, Statistician
3.0	• Changed statistical method to require that each stratum contains approximately equal number of subjects from SPYRAL DYSTAL study cohort	Elena Viktorova, Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ABP	Ambulatory Blood Pressure
AE	Adverse Event
CIP	Clinical Investigation Plan
DBP	Diastolic Blood Pressure
eGFR	Estimated Glomerular Filtration Rate
OBP	Office Blood Pressure
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure

3. Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of the Medtronic SPYRAL DYSTAL Study: Renal denervation in the distal portion of the main renal arteries and first order branches. The objective of this single arm interventional study is to determine if renal denervation performed in the distal main and first order branch renal arteries is as effective in reducing blood pressure as the procedural approach used in the SPYRAL HTN-OFF MED clinical study. Specifically,

the SAP has the following purpose: to prospectively outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the trial 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 biostatistical analysis in the medical device industry. Results obtained from the analyses outlined in this document will be the basis of the Clinical Study Report (CSR) for this trial.

4. Study Objectives

The objective of this single arm interventional study is to determine if renal denervation performed in the distal main renal arteries and branch vessels coming off the main renal artery (first order branches) is as effective as the procedural approach in the SPYRAL HTN-OFF MED clinical study.

5. Investigation Plan

The SPYRAL DYSTAL study is a multi-center, international, prospective, interventional, single arm study. Denervation will be performed using the Symplicity Spyral™ multi-electrode renal denervation catheter (Symplicity Spyral™ catheter) and the Symplicity G3™ renal denervation radio frequency (RF) generator in a hypertensive population. Subjects will be studied to assess the impact of this renal denervation approach on systolic and diastolic blood pressure. Based on the previous experience with the SPYRAL HTN-OFF MED study, it is anticipated that several subjects will no longer meet study eligibility during the screening period; therefore, approximately 350 subjects with uncontrolled hypertension will be enrolled to ensure approximately 50 hypertensive subjects will undergo the renal denervation procedure at up to 15 sites. Enrollment is expected to take approximately 12 months.

The efficacy endpoints in this study will be compared to the SPYRAL HTN-OFF MED efficacy endpoints using a propensity score stratified analysis. The SPYRAL HTN-OFF MED study was chosen because this study has the same eligibility criteria as the SPYRAL DYSTAL study, except for the anatomical exclusion criteria. The studies both evaluate blood pressure response in the absence of antihyperensive medications (Office Blood Pressure (OBP) and Ambulatory Blood Pressure Machines (ABPM)). The SPYRAL HTN-OFF MED and the SPYRAL DYSTAL studies have different procedural requirements which allows for comparison of blood pressure reductions between the two studies.

6. Determination of Sample Size

This study does not have a statistically powered hypothesis to determine if renal denervation performed in the distal main renal arteries and first order branches is as effective as the procedural approach in the SPYRAL HTN-OFF MED clinical study. The sample size of 50 subjects was chosen to provide a reasonable estimate of the efficacy of this procedural approach. In the original first phase of the SPYRAL HTN-OFF MED, only 38 subjects were sufficient in demonstrating efficacy (ASBP drop of -5.5 mmHg, with 95% CI of -9.1 to -2.0 and significant p-value of 0.003). By enrolling 50 subjects in the current study, we allow for potential missing outcomes data.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

A subject disposition table will be provided for each follow-up visit containing the following information:

- The number of subjects who died or withdrew prior to each follow-up
- The number of subjects eligible for each follow-up visit
- The number of subjects completing each follow-up visit within the protocol specified window
- The number of subjects completing each follow-up outside the protocol specified window
- The number of subjects who did not complete their follow-up

7.1.2. Clinical Investigation Plan (CIP) Deviations

A study deviation is defined as an event where the investigator or site personnel did not conduct the study according to the Clinical Investigational Plan, IRB/EC, applicable laws or regulations, or the investigator Agreement. Investigators are not allowed to deviate from the protocol, except under emergency circumstances to protect the rights, safety and well-being of human subjects. Deviations shall be reported to Medtronic regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency. Deviations to protect the life or physical wellbeing of the subject in an emergency must be reported to Medtronic and the EC/IRB within five working days. Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). More details can be found in section 9.4 of the study protocol.

7.1.3. Analysis Sets

7.1.3.1. Intention-To-Treat (ITT) Population

All enrolled subjects are included in the intention-to-treat population. Subjects who meet the antihypertensive medication escape criteria (confirmed OSBP ≥ 180 mmHg or safety reasons) will be analyzed using Last Observation Carried Forward (LOCF) for their blood pressure measurements, safety outcomes, and office and ambulatory blood pressure outcomes from procedure up to 3 months will be presented for this population.

The LOCF will be determined for the subjects who meets all following criteria:

1. Include any office or ambulatory BP values performed ≤ escape date.
2. Include any office or ambulatory BP values performed ≥ 30 days post procedure date.
3. Use most recent remaining greater than 30 days post-procedure measurement up to 3 months, including unscheduled BP measurements.

7.1.3.2. Modified Intention-To-Treat (ITT) Population

All enrolled subjects except subjects who meet the anti-hypertensive medication escape criteria (OSBP ≥ 180 mmHg or safety reasons) will be excluded from the modified intention-to-treat population. Office and ambulatory blood pressure outcomes from procedure up to 3 months will be presented for this population.

7.1.3.3. Per Protocol Population

All treated subjects, meeting the following criteria:

1. Subjects showing medication compliance in blood and/or urine (via drug testing data) at screening visit 2 (SV2) and 3-months.
2. Exclude subjects with protocol deviation code 101 (consent not obtained).
3. Exclude subjects who do not meet the following Inclusion/Exclusion criteria.
   - Inclusion: Individual has an office systolic blood pressure (SBP) ≥150 mmHg and <180 mmHg and an office DBP ≥90 mmHg measured at SV2, according to the guidelines in Appendix 16.5 of the study protocol.
   - Inclusion: Individual has a 24-hour ABPM average SBP ≥140 and <170 mmHg measured at SV2, according to guidelines in Appendix 16.5 of the study protocol.
   - Exclusion: Individual has undergone prior renal denervation.
   - Exclusion: Individual has renal artery anatomy that is ineligible for treatment.
   - Exclusion: Individual has one or more of the following conditions: stable or unstable angina within 3 months of enrollment, myocardial infarction within 3 months of enrollment; heart failure; cerebrovascular accident or transient ischemic attack or atrial fibrillation at any time.
4. Exclude Subjects meeting the anti hypertensive medication escape criteria (OSBP ≥180 mmHg or safety reasons).
5. Exclude subjects who did not receive the treatment.

Office and ambulatory blood pressure outcomes up to 3 months will be presented for this population.

7.2. General Methodology

Descriptive statistics of continuous measures will be presented and include sample size, mean, standard deviation, median, first and third quartiles, minimum and maximum. For categorical outcomes, the number and percentage of subjects in each category will be presented. Paired t-tests will be used to compare changes in continuous measures from baseline to follow-up. All statistical analyses will be performed using SAS for Windows (version 9.4 or higher) or other widely accepted statistical or graphical software. Subject data listings and tabular or graphical presentations of results will be provided.

7.3. Handling of Missing Data and Dropouts

No imputation of missing data will be performed.

7.4. Adjustments for Multiple Comparisons

This study contains no powered endpoints or formal hypotheses, therefore adjustments for multiple comparison will not be made.

7.5. Demographic and Other Baseline Characteristics

Baseline variables will be tabulated. Categorical variables, including binary variables, will be reported by giving the number and percentage of patients in each category. Continuous variables will be reported by presenting the number of values, mean, standard deviation, median, first and third quartiles, minimum and maximum value for each. No imputation will be performed for missing data.

7.6. Treatment and Anti-hypertensive Medications Characteristics

Renal denervation treatment measures will be summarized separately for each kidney, and combined. Anti-hypertensive medication use will also be summarized at baseline and at each follow-up.

7.7. Evaluation of Objectives

7.7.1. Safety Objectives

The following safety endpoints will be evaluated:

- Major Adverse Events (MAE), defined as a composite of the following event at 1 month post-procedure (6 months for renal artery stenosis):
  - All-cause mortality
  - End-stage renal disease (ESRD)
  - Significant embolic event resulting in end-organ damage
  - Renal artery perforation requiring intervention
  - Renal artery dissection requiring intervention
  - Vascular complications
  - Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications or the protocol
  - New renal artery stenosis >70%, confirmed by angiography and as determined by the angiographic core lab at 6 months follow-up
- Composite safety endpoint, defined as a composite of the following event at 3, 6 and 12-month post-procedure:
  - All-cause mortality
  - End-stage renal disease (ESRD)
  - Significant embolic event resulting in end-organ damage
  - Renal artery perforation requiring intervention
  - Renal artery dissection requiring intervention
  - Vascular complications
  - Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications or the protocol

  - New renal artery stenosis >70%, (For the composite safety endpoint at 3 and 6 months, use RAS at 6 months, which confirmed by angiography and as determined by the angiographic core lab at 6 months follow-up. For the composite safety endpoint at 12 months use RAS available at 12 months)
- Myocardial infarction
- Stroke
- Renal artery re-intervention
- Major bleeding according to TIMI definition (i.e. intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure)
- Increase in serum creatinine >50% from SV2 (not CEC adjudicated)

All the safety endpoints except "Increase in serum creatinine >50% from SV2" will be adjudicated by the Clinical Events Committee (CEC). The following algorithm will be used to evaluate the safety event rates: The denominator will include all subjects who either had a CEC adjudicated event prior to the time of interest (180 days for 6 months events, for example), or had last contact date that is beyond the lower window of the follow up (166 days for 6 month events, for example). The numerator will include all subjects who had CEC adjudicated events up to the time of interest (180 days for 6 months events, for example).

The safety endpoints will be summarized using counts and percentages, and no comparison group will be used for the safety analysis. These analyses will be performed for the ITT population defined in 7.1.3.1.

7.7.2. Efficacy Objectives

The following efficacy endpoints will be compared to the SPYRAL HTN-OFF MED efficacy endpoints using a propensity score stratified analysis at 3 months. The multiple sources of study patients in HTN-OFF MED study are shown in Table 1. At 6 months and 12 months, the endpoints will be analyzed within the SPYRAL DYSTAL study only.

- Change in systolic blood pressure (SBP) from baseline (SV2) to 3, 6, and 12 months postprocedure as measured by 24-hour ABPM.
- Change in office SBP from baseline (SV2) to 3, 6 and 12 months post-procedure.
- Change in diastolic blood pressure (DBP) from baseline (SV2) to 3, 6, and 12 months postprocedure as measured by 24-hour ABPM.
- Change in office DBP from baseline (SV2) to 3, 6, and 12 months post-procedure.
- Incidence of achieving target office SBP <140 mmHg at 3, 6 and 12 months.

Table 1: Study Sources of Patients in HTN-OFF MED for Efficacy Endpoint Data (RDN arm only)

Study
SPYRAL HTN-OFF MED data (First 80 Subjects) Randomized 1:1 to RDN:CONTROL
SPYRAL PIVOTAL – SPYRAL HTN-OFF MED Randomized 1:1 to RDN:CONTROL

SPYRAL PIVOTAL – SPYRAL HTN-OFF MED
(Secondary Cohort)
Randomized 1:1 to RDN:CONTROL

7.7.2.1. Efficacy Objectives Evaluation at 3 Months

Since subjects in the two comparative groups were not directly randomized, a direct comparison may not be appropriate. The efficacy endpoints at 3-months will be compared to the RDN treated subjects from the SPYRAL HTN-OFF MED clinical study using propensity score stratification (subclassification) adjustment. A propensity score will be estimated for each patient from a multivariable logistic regression model, which is the probability that the patient is in DYSTAL cohort. In this model, the DYSTAL cohort (binary variable) is the outcome variable, and the following covariates will be considered as independent variables for propensity score analysis model: baseline Office SBP and DBP as well as the SBP and DBP measured by 24-hour ABPM (continuous), age (continuous), gender (dichotomous), BMI (continuous), diabetes (dichotomous).

The missing values in the covariates will be imputed first before the propensity score stratification. For continuous variables, the missing values will be imputed by CALL STREAMINIT(seed) and RAND('NORMAL', MU, S^2), where MU denotes the sample mean of the specific continuous variable, S denotes the sample standard deviation. If the imputed value is above the maximum value of that variable, the maximum value will be used as the imputed value; if the imputed value is below the minimum value of the variable, the minimum value will be used as the imputed value. For binary categorical variables, the missing values will be imputed as RANBIN(seed, 1, p), where p denotes the observed proportion of the specific binary baseline variable in each arm. The seed will be set as 121919, applied for both continuous and binary variable imputations.

After propensity scores are estimated, the entire population will be divided into 5 stratums using the quintiles of the ordered propensity scores, with approximate equal number of subjects from Dystal study cohort in each stratum. This will be done using PROC PSMATCH in SAS 9.4, specifying the option KEY=TREATED in STRATA statement to require that each stratum contain approximately equal number of subjects from Dystal cohort. The option STRATUMWGT=TOTAL in STRATA statement, which uses the proportional size (number of total units in the stratum divided by the total number of units) of the stratum, will provide the average treatment effect weight for each observation.

After stratification, analysis of covariance (ANCOVA) models adjusting for the baseline BP measurements will also be presented for each propensity score stratum to obtain the strata-specific treatment effect, which can be combined to yield an overall treatment effect (DYSTAL minus SPYRAL HTN-OFF MED RDN arm). The overall treatment effect together with two-sided 95% confidence interval will be calculated as follows:

$$(\mu_D - \mu_R) \pm 1.96 \times \mathrm{SE}(\mu_D - \mu_R),$$

where $\mu_D - \mu_R$ is the weighted mean of overall treatment effect given by

$$\mu_D - \mu_R = \sum_{k=1}^{5} w_k \, (\mu_{kD} - \mu_{kR}),$$

with k the number of stratum ($k = 1, 2, 3, 4, 5$), and w_k as the weight for k^{th} stratum defined by

$$w_k = \frac{N_{kD} + N_{kR}}{\sum_{k=1}^{5}(N_{kD} + N_{kR})}$$

Additionally, $\mu_{kD} - \mu_{kR}$ is the mean of treatment effect in k^{th} stratum from an ANCOVA adjusted model, and $\mathrm{SE}(\mu_D - \mu_R)$ is the weighted standard error of overall treatment effect

$$SE(\mu_D - \mu_R) = \sqrt{\sum_{k=1}^{5} w_k^2 * SE^2(\mu_{kD} - \mu_{kR})},$$

where $\mathrm{SE}(\mu_{kD} - \mu_{kR})$ is the standard error of treatment effect in k^{th} stratum.

The ITT population will be the primary analysis population, and secondary analyses will be performed on the modified ITT and per protocol populations in 7.1.3.2 and 7.1.3.3.

7.7.3. Additional Objectives

The following additional analyses will be conducted. Additional procedural characteristics, including treatment duration, frequency of distal renal artery treatment, ablations per vessel, location of ablations, number of ablations per patient, number of applications per patient (1 application is defined as "<4 ablations delivered simultaneously") and other characteristics will be presented with descriptive statistics to assess their impact on blood pressure. These additional analyses will be presented for the ITT study population defined in section 7.1.3.1.

7.8. Safety Evaluation

Adverse Event (AE) information will be collected by the site from subject enrollment (consent) through study termination or study exit (AEs up to 6 months follow-up, SAEs up to 12 months follow-up). AEs will be followed until the event has resolved (in the case of permanent impairment, the event will be followed until it stabilizes and the overall clinical outcome has been ascertained), subject exit or study termination.

The Investigator will report any adverse events that may occur to the Sponsor, and will assess seriousness, relationship (to the device, procedure and renal denervation therapy where applicable), subsequent intervention required, resolution status and whether the adverse event resulted in the subject's discontinuation from the study. The Investigator will provide further information regarding adverse events as requested by the Sponsor.

7.9. Subgroup Analyses

No subgroup analysis will be performed.

7.10. Changes to Planned Analysis

There are no changes to the planned analysis at this time.

8. Validation Requirements

Two statistical programmers will work independently to produce and validate all the tables, listings and graphs for the study reports.

9. COVID-19 Related Analyses

In accordance with FDA guidance document "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic" [1], we will provide AE and SAE tables summarizing the site-reported adverse events attributed to COVID-19 in separate tables.

10. References

[1] FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic. Guidance for Industry, Investigators, and Institutional Review Boards. March 2020.

11. Statistical Appendices

11.1. Appendix I: Imputation of AE Onset or Anti-Hypertensive Medication Start Dates

The table below specifies how to input missing dates for AE onset or anti-hypertensive medication start dates:

Valid Portion	Missing Portion	Imputed Value for Missing Portion
Month, Year	Day	Set Day = first day of that month and year, then set the day = later of (new onset date, informed consent date).
Year	Day, Month	Set date = later of (January 1st of that year, informed consent date).
None	Day, Month, Year	Informed consent date

11.2. Appendix II: Selection of OBP Values at Follow-Up

The analysis windows are defined as follows:

Study Visit	Target Date (post procedure)	Protocol Defined Window (post procedure)	Expanded Analysis Window (post procedure)
1 Month	30	23-37	14-60
3 Months	90	76-104	61-135
6 Months	180	166-194	136-270
12 Months	360	330-390	271-540

Scenario 1: There are multiple ABPM raw data records with the same ABPM CPEVENT including SV2:

1. Starting with the most recent ABPM raw record, is there any OBP visit (SCHEDULED or UNSCHEDULED) where 'OFFICE follow up BP date' = 'ABPM start date'?
2. If yes, then use that OBP visit if it is in the expanded analysis window.
3. If no, then go to the previous ABPM raw record, and again look for any OBP visit (SCHEDULED or UNSCHEDULED) where 'OFFICE follow up BP date' = 'ABPM start date'. If yes, then use that OBP visit if it is in the expanded analysis window. In no, then go to the previous ABPM raw record…
4. Repeat for all ABPM raw records.

Scenario 2: There is only 1 ABPM raw data record for a given CPEVENT:

This scenario only applies to the follow up measurements in the table above. SV2 and discharge measurements will still use site reported values. In case of multiple measurements for discharge, then take the latest one.

1. Time to follow up will be calculated as (follow up BP date – procedure date). Only SCHEDULED follow up data will be included.
2. All follow up measurements <14 days post procedure will not be included in the follow up analysis unless otherwise specified.
3. The remaining measurements will be categorized per windows defined above. In case of multiple qualifying measurements, first take the one closest to the target follow up date, then take the latest one.

11.3. Appendix III: Selection of ABPM Values at Follow-Up

The analysis windows are defined as follows:

Study Visit	Target Date (post procedure)	Protocol Defined Window (post procedure)	Expanded Analysis Window (post procedure)
3 Months	90	76-104	46-135
6 Months	180	166-194	136-270
12 Months	360	330-390	271-540

1. This algorithm only applies to the follow up measurements in this table. SV2 measurements will still use site reported values. If there are multiple SV2 measurements per subject, the most recent one will be taken.
2. ABPM start date will be used as follow up date.
3. Time to follow up will be calculated as (ABPM start date – procedure date); Only SCHEDULED follow up data will be included in this analysis; If there are multiple measurements per subject per site reported visit (CPEVENT), the most recent one will be taken before applying the expanded analysis window algorithm below.
4. All follow up measurements <46 days post procedure will not be included in the follow-up analysis unless otherwise specified.
5. The remaining measurements will be categorized per windows defined above. In case of multiple qualifying measurements, first take the one closest to the target follow up date, then take the latest one.

11.4. Appendix IV: Derivation of ABPM Values

1. The ABPM raw data will be entered into the database by data management team. The following steps will be done by SAS programming team:
2. Missing values for the NUM field will be deleted as they do not contain BP data.
3. Manual readings are identified by the text "Start of a manual measurement" in the BPNOTE field in the raw data file.
4. Readings after 7:00am and before 10:00pm (7:00am ≤ time <10:00pm) are daytime readings; readings after 10:00pm and before 7am next day (time ≥10:00pm or time <7:00am) are nighttime readings.
5. Keep all the non-manual readings and all the manual readings that are after the non-manual readings.
6. The initial manual readings (all the manual readings before the first non-manual reading) will be handled as following:
   - Starting from the last initial manual reading and compare it with the reading immediately after that, if it is more than (>) 30 minutes before the next reading, then all the manual readings will be removed; if it is within (≤) 30 minutes before the next reading, then move to the second last manual reading and compare it with the reading immediately after that.
   - Repeat this until all the manual readings are included or some manual readings are excluded.

   This step can be demonstrated with the examples below:

Reading #	Reading type	Example 1	Example 2	Example 3
1	M	12:00pm	12:00pm	12:00pm
2	M	12:30pm	12:31pm	12:30pm
3		1:00pm	1:00pm	1:01pm

   In Example 1, all the readings will be kept.

   In Example 2, only readings 2 and 3 will be kept.

   In Example 3, only reading 3 will be kept.
7. Truncate all the readings that are more than (>) 25 hours after the remaining first reading.

The overall, daytime and nighttime ABPM will be calculated based on the remaining raw data. Only measurements with at least 21 daytime and 12 nighttime readings will be used for 24 hours ABPM analysis. Only measurements with at least 21 daytime readings will be used for daytime ABPM analysis. Only measurements with at least 12 nighttime readings will be used for nighttime ABPM analysis.

11.5. Appendix V: Selection of Lab Values at Follow-Up

The analysis windows are defined as follows:

Study Visit	Target Date (post procedure)	Protocol Defined Window (post procedure)	Expanded Analysis Window (post procedure)
1 Month	30	23-37	14-60
3 Months	90	76-104	61-135
6 Months	180	166-194	136-270
12 Months	360	330-390	271-540

Scenario 1: There are multiple ABPM raw data records with the same ABPM CPEVENT including SV2:

1. Starting with the most recent ABPM raw record, is there any Lab visit (SCHEDULED or UNSCHEDULED) where 'Lab follow up date' = 'ABPM start date'?
2. If yes, then use that Lab visit if it is in the expanded analysis window.
3. If no, then go to the previous ABPM raw record, and again look for any Lab visit (SCHEDULED or UNSCHEDULED) where 'Lab follow up date' = 'ABPM start date'. If yes, then use that Lab visit if it is in the expanded analysis window. In no, then go to the previous ABPM raw record…
4. Repeat for all ABPM raw records.

Scenario 2: There is only 1 ABPM raw data record for a given CPEVENT:

This algorithm only applies to the follow up measurements in the tables above. SV2 will still use site reported values. In case of multiple SV2 measurements, then take the latest one. Date of specimen collection will be used as lab follow up date.

1. Time to follow up will be calculated as (lab follow up – procedure date). Only SCHEDULED follow up data will be included in this analysis.
2. All follow up measurements <14 days post procedure will not be included in the follow up analysis unless otherwise specified.
3. The remaining measurements will be categorized per windows defined above. In case of multiple qualifying measurements, first take the one closest to the target follow up date, then take the latest one.

11.6. Appendix VI: Selection of Drug Testing Values at Follow-Up

The analysis windows are defined as follows:

Study Visit	Target Date (post procedure)	Protocol Defined Window (post procedure)	Expanded Analysis Window (post procedure)
3 Months	90	76-104	46-135

Scenario 1: There are multiple ABPM raw data records with the same ABPM CPEVENT including SV2:

1. Starting with the most recent ABPM raw record, is there any Drug Testing visit (SCHEDULED or UNSCHEDULED) where 'Drug testing sample performed date' = 'ABPM start date'?
2. If yes, then use that Lab visit if it is in the expanded analysis window.
3. If no, then go to the previous ABPM raw record, and again look for any Lab visit (SCHEDULED or UNSCHEDULED) where 'Drug testing sample performed date' = 'ABPM start date'. If yes, then use that drug testing visit if it is in the expanded analysis window. In no, then go to the previous ABPM raw record…
4. Repeat for all ABPM raw records.

Scenario 2: There is only 1 ABPM raw data record for a given CPEVENT:

This algorithm only applies to the follow up measurements in the tables above. Drug testing sample performed date will be used as drug testing follow up date. In case of multiple SV2 measurements, then take the latest one.

1. Time to follow up will be calculated as (Drug testing sample performed date – procedure date). Only SCHEDULED follow up data will be included in this analysis; If there are multiple measurements per subject per site reported visit (CPEVENT), the most recent one will be taken before applying the expanded analysis window algorithm below.
2. All follow up measurements <46 days post procedure will not be included in the follow up analysis unless otherwise specified.
3. The remaining measurements will be categorized per windows defined above. In case of multiple qualifying measurements, first take the one closest to the target follow up date, then take the latest one.