# STATISTICAL ANALYSIS PLAN

## B. Braun Peripheral Advantage Program

Assessment of the Effect of B. Braun Peripheral Advantage Program on Complications, Indwell Time and First Stick Success of PIVC Therapy

| | |
|---|---|
| **Protocol Number:** | US-N-H-1801 Amendment 1 |
| **Protocol Version** | 2.0 |
| **Name of Test Devices:** | Introcan Safety® IV Catheters<br>Christie VeinViewer® Vision 2<br>STEADYCare™ Smallbore Extension Set with Wedge™ Catheter Stabilizer |
| **Phase:** | Post Market |
| **Methodology:** | Frequent |
| **Sponsor:** | B. Braun Medical Inc. |
| **Sponsor Representative:** | Chris Curtin<br>Manager, Clinical Development, Medical Affairs<br>B. Braun Medical Inc.<br>901 Marcon Blvd.<br>Allentown, Pennsylvania 18109<br>Phone: 610-596-2726<br>Email: chris.curtin@bbraunusa.com |
| **Document Date:** | 3-DEC-2021 |
| **Document Version:** | 3.0 |

# 1. SIGNATURES PAGE

**Protocol title**: Assessment of the Effect of B. Braun Peripheral Advantage Program on Complications, Indwell Time and First Stick Success of PIVC Therapy

**Sponsor**: B. Braun Medical Inc.

**Protocol Number**: US-N-H-1801

| **Plan Author** | |
|---|---|
| Peter Yao<br>Peter Yao (Dec 3, 2021 14:23 EST) | 03-Dec-2021 |
| Peter Yao<br>Manager, Biodata Sciences Statistics<br>Clinlogix | Date |
| **Plan Approval** | |
| Christopher R. Curtin<br>Christopher R. Curtin (Dec 3, 2021 14:40 EST) | 03-Dec-2021 |
| Christopher R. Curtin<br>Manager Clinical Development, Medical Affairs<br>B. Braun Medical Inc. | Date |
| Diana Valencia Martinez<br>Diana Valencia Martinez (Dec 7, 2021 22:46 EST) | 07-Dec-2021 |
| Diana Valencia, MD<br>Director, Medical Affairs<br>B. Braun Medical Inc. | Date |
| Patricia Guaglianone<br>Patricia Guaglianone (Dec 3, 2021 16:33 EST) | 03-Dec-2021 |
| Patricia Guaglianone<br>Clinical Project Manager<br>Clinlogix | Date |

# Table of Contents

## 2. STUDY SYNOPSIS

| | |
|---|---|
| Protocol Number | US-N-H-1801 |
| Title | Assessment of the Effect of B. Braun Peripheral Advantage Program on Complications, Indwell Time and First Stick Success of PIVC Therapy |
| Study Devices | Peripheral Advantage Program |
| Objective(s) | **Primary Objective**<br>The primary objective of this study is to evaluate the impact of B. Braun Peripheral Advantage (PA) Program on the incidence of complications associated with PIVC use.<br><br>**Secondary Objective**<br>The secondary objectives of this study are to evaluate the effects of B. Braun PA on catheter indwell time, first attempt success rates (first stick success), and aggregate costs associated with catheter insertion. |
| Design | Single sequence multi-center clinical study designed to evaluate the effectiveness of B. Braun PA on improved clinical outcomes, indwell time and first stick success of PIVC using B. Braun PA by Registered Nurses (RNs).<br><br>The study will be divided into 4 Stages: 3 Clinical Stages and 1 Interventional (Educational) Stage. These 4 Stages are: Baseline (Stage 1), Intervention (Stage 2, education), Run-In (Stage 3), and Post-Interventional (Stage 4). The 3 clinical Stages require patient care which includes daily follow-up care for the catheter (Baseline, Run-In, and Post-Interventional). The Intervention (education) Stage is for the RNs to be trained in B. Braun PA and thus will not involve any patients.<br><br>The study will be conducted in the Emergency Department (ED) and/or Medical Surgical (MS) floor(s)/unit(s) in multiple hospitals. A core group of RNs on all shifts who have completed all required institution clinical study training and the protocol required training (Study RNs) will participate in the study. In the event all RNs from the participating Unit are not able to participate in the study, the Investigator will take reasonable measures to ensure all specifically study related procedures are performed by the Study RNs. |
| Study Population | **Registered Nurses:** RNs from the ED or MS unit(s)/department(s) of the hospital can be on any shift and will not be required to have a minimum level of clinical experience. Any RNs from the participating floors or the hospital ED are eligible to participate in Stage 1 of the study. Those RNs who have not completed all of the |

| | |
|---|---|
| | B. Braun protocol required trainings in Stage 2 cannot continue on to Stages 3 and 4 and thus will be removed from participation in the study. Study RNs should not be currently using the B. Braun Introcan Safety® IV Catheters, the STEADYCare™ Smallbore Extension Set or the Christie VeinViewer utilized in this study.<br><br>**Subjects:** At least 632 PIVC successful placements are to be performed in the ED or medical surgical unit(s) running the study (Stage 1, at least 316 successful PIVC placements and Stage 4, at least 316 successful PIVC placements). Subjects or his/her Legally Authorized Representative (LAR) ,if appropriate, will be consented by Study RNs before participating in Stage 1 and/or Stage 4 and may participate in either, or both, of those stages. Subjects consented for Stage 1 may participate as patients in Stage 3 (Run-In). No study related data will be collected for any patients in Stage 3. |
| Sample Size | At least 632 successful PIVC placements (316 successful PIVC placements in Stage 1 and 316 successful PIVC placements in Stage 4) are required to complete the study. |
| Inclusion Criteria | RNs must complete all of the required B. Braun trainings in Stage 2 in order to participate in Stages 3 and 4.<br><br>Subjects must meet all of the following Inclusion Criteria:<br>1. Male or female aged ≥18 years;<br>2. The subject or the subject's LAR voluntarily agrees that the subject will participate in this study and is able to understand and sign the Informed Consent Form (ICF);<br>3. Have a medical condition that requires a PIVC lasting for at least 48 hours;<br>4. Have intact skin at the site of insertion;<br>5. If the patient has an existing IV in one arm he/she must have a viable contralateral arm for additional PIVC insertion. |
| Exclusion Criteria | Subjects must not meet any of the following Exclusion Criteria:<br>1. Are currently participating in another medical device or pharmaceutical study;<br>2. In the opinion of the Investigator, would not be suitable candidates for this study;<br>3. The subject or his/her LAR is an employee of the Investigator or study center, or the sponsor, or have direct involvement in the study or other studies under the direction of that Investigator or study center, or are a family member of the employees or the Investigator;<br>4. Have a laboratory confirmed bloodstream infection within 48 hours prior to participation in the study. The assessment |

| | |
|---|---|
| | is based on clinical observations and not routine for all subjects;<br>5. Patient has an existing non-study IV;<br>6. Was removed from any stage of the study due to an AE associated with the PIVC. |
| Analysis Population | *Intent-to-Treat (ITT) Population*<br>The ITT population consists of all subjects who are consented, meet all of the inclusion criteria and none of the exclusion criteria, and are enrolled into the study.<br>*Modified Intent-to-Treat (MITT) Population*<br>The MITT population is a subset of the ITT subjects. This population will have had an attempted PIVC placement (successful or not successful) in Stage 1 and/or in Stage 4.<br>*Per Protocol (PP) Population*<br>The PP population is a subset of the MITT analysis. This population will have met the following criteria:<br>• No major deviations from the protocol eligibility criteria<br>• Subject received a successful PIVC placement from a Study RN<br>• Subject has a primary efficacy endpoint assessment at Stage 1 and/or Stage 4<br>The primary efficacy endpoint and all secondary endpoint analyses will be carried out on available data in the MITT population; supportive analyses of primary efficacy endpoints will be carried out on the PP population, as well. Demographic summaries will be provided for the ITT population. Safety data will be summarized for the MITT population. |
| Statistical Methods and Planned Analyses | Standard statistical methods will be utilized in this study to analyze all data. Endpoints that measure rates (e.g., primary endpoint of rate of complications) will be tested for significance using a binomial test (such as Fisher's exact test). Continuous endpoints will be tested for significance using standard parametric tests (such as Student's t-test), or non-parametric equivalent (such as Wilcoxon signed rank test) if parametric methods are found to be inappropriate.<br><br>Two interim analyses are planned for the purpose of sample size re-estimation: one in Stage 1 and another one in Stage 4. Using the method of Pocock & Mehta, the sample size can be either held constant or increased – it cannot be reduced based on the results of the re-estimation. |

| | |
|---|---|
| | **Interim Data Analysis Stage 1:** Upon successful completion of approximately 70% of the originally planned PIVC placements in Stage 1, an interim analysis of the primary endpoint on uncleaned data will be performed. If the observed complication rate is statistically significantly greater than 50%, the sample size will not be modified. If the observed complication rate is not statistically significantly greater than 50%, the sample size may be re-estimated (increased).<br>**Interim Data Analysis Stage 4:** Upon successful completion of approximately 50% of the initial sample size in Stage 4, another interim analysis on uncleaned data for the complications will be performed. This sample size re-estimation will follow the method of Pocock and Mehta to calculate the conditional power of the study to conclude that the complication rate in Stage 4 is lower than the complication rate in Stage 1, given the observed complication rates at the interim analysis.<br><br>In the event the conditional power is found to be in the Favorable or Unfavorable zone, the study will continue to the originally planned sample size in Stage 4. In the event the conditional power is in the Promising zone, the total study sample size may be increased to the required sample size to achieve conditional power of 90% at the completion of the study. |
| Safety Analyses | All adverse events reported over the course of the study will be categorized based on the MedDRA coding system and tabulated by system organ class and preferred term within the system organ class.<br><br>Events may include but are not limited to: minor and major complications, infection, thrombus phlebitis, accidental needle sticks, and device failures (i.e., disconnection, twisted port hub, leakage, and failure of the safety feature). |
| Subject Screening and Enrollment Process | Any subject who signed or whose LAR signed the Informed Consent but subsequently was found to not meet Inclusion/Exclusion Criteria is considered a Screen Failure. Any subject who signed or whose LAR signed the Informed Consent and meets all inclusion criteria and none of the exclusion criteria is considered Enrolled. |
| Study Duration | The enrollment period is expected to last approximately 31 months. The study duration from Stage 1 through Stage 4 is expected to be approximately 48 months from study initiation. |
| Primary Effectiveness Endpoint | The primary endpoint is the rate or percentage of complications (e.g., phlebitis/thrombophlebitis, occlusion, infection (localized or |

| | |
|---|---|
| | Catheter Related Bloodstream Infection [CRBSI]), dislodgement or infiltration, extravasation, accidental removal, etc.). |
| Secondary Endpoints | The Secondary Endpoints are as follows:<br>• Indwell time for catheters with and without complications (measured in hours)<br>• First attempt insertion success rate (first stick success) for PIVC<br>• Rate of insertion of a Peripherally Inserted Central Catheter (PICC) or Midline Catheter due to inability to insert the PIVC or removal of the initial PIVC due to complications (rescue PICC or rescue Midline)<br>• Healthcare costs associated with PIVC use in a clinical setting |

# 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| B. Braun | B. Braun Medical Inc. |
| CP | Conditional Power |
| CRBSI | Catheter Related Bloodstream Infection |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| ED | Emergency Department |
| EDC | Electronic Data Capture |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| ITT | Intent to Treat |
| IRB | Institutional Review Board |
| ISO | International Organization for Standardization |
| LAR | Legally Authorized Representative |
| MITT | Modified Intent to Treat |
| PA | Peripheral Advantage |
| PICC | Peripherally Inserted Central Catheter |
| PIVC | Peripheral Intravenous Catheter |
| PP | Per Protocol |
| RN | Registered Nurse |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SD | Standard Deviation |
| SOP | Standard Operating Procedure |
| US | United States |
| WHO | World Health Organization |

# 4. INTRODUCTION

Peripheral intravenous catheters (PIVCs) are used to deliver medication and fluids directly into the bloodstream. The placement of PIVCs is the most common invasive hospital procedure. In the US alone, 60% to 90% of hospitalized patients require an IV catheter (Helm, 2015). Despite this large medical demand for PIVCs, there is a high failure rate and large cost associated with replacing the catheter due to complications. Therefore, there is a clinical unmet need to improve PIVC first stick success by developing a clinical education program.

B. Braun Medical Inc. is developing the Peripheral Advantage (PA) Program which includes the PA Education Curriculum; Christie VeinViewer® Vision2; Introcan Safety® IV Catheters; and STEADYCare™ Smallbore Extension Set to improve patient care at the bedside and decrease PIVC-associated complications, resulting in increased catheter indwell time and improved financial outcomes.

This study is designed to assess the effect of the B. Braun Peripheral Advantage (PA) Program that includes clinician education and specific B. Braun peripheral intravenous catheter (PIVC) therapy products designed to improve the clinical outcomes associated with a PIVC.

This Statistical Analysis Plan (SAP) is intended to prospectively (*a priori*) outline the analyses and presentations of data that will form the basis for conclusions to be reached to 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 biostatistical analysis in clinical trials. Results obtained from the analyses outlined in this document will be the basis for the clinical study report (CSR) and or publications for this study. This plan is based on Version 1.0 of the study protocol, dated 11 July 2019 and the Protocol Amendment 1 dated 03 February 2021.

# 5. STUDY OBJECTIVES

## 5.1. Primary Objectives

The primary objective of this study is to evaluate the impact of the B. Braun PA Program on the incidence of complications associated with PIVC use.

## 5.2. Secondary Objectives

The secondary objectives of this study are to evaluate the effect of the B. Braun PA Program on catheter indwell time, first stick success rates (first stick success), and aggregate costs associated with catheter insertion.

# 6. INVESTIGATIONAL PLAN

## 6.1. Overall Study Design and Plan

This is a single sequence multi-center study to evaluate the effectiveness of the B. Braun PA Program on improved clinical outcomes by decreasing PIVC complications, increasing PIVC indwell time, improving first PIVC stick success and improving estimated aggregated costs utilizing B. Braun PA.

The study will be divided into 4 Stages: three (3) clinical stages and one (1) interventional (educational) Stage. The four (4) Stages are: Baseline (Stage 1), Intervention/Education (Stage 2), Run-In (Stage 3), and Post-Interventional (Stage 4). The three (3) clinical stages (Baseline, Run-In, and Post-Interventional) require patient care which includes daily follow-up care for the catheter. The Intervention (education) stage (Stage 2) may include all RNs from the ED and or the medical surgical floor(s)/unit(s) of the hospital. The Stage 2 intervention and the Stage 3 run-in will not involve any study patients.

The study will be conducted in the Emergency Department (ED) and/or Medical Surgical (MS) floor(s)/unit(s) in multiple hospitals. All RNs from these floors may participate in Stage 1 and Stage 2 of the study. A core group of RNs (Study RNs) on all shifts who have completed the institution's required clinical study training and required study protocol training will participate in Stage 1. These Study RNs will be responsible for PIVC insertions and monitoring in Stage 1.

The Study RNs from Stage 1 and all RNs from the medical/surgical unit(s) or ED who have met all study requirements and also completed the Peripheral Advantage Program specific training/intervention (Stage 2) will participate in Stage 3 and Stage 4 of the study. These Study RNs will be responsible for PIVC insertions and monitoring in Stage 4. Non-Study RNs should not perform any study related procedures (i.e., catheter insertion, site evaluations including documentation of both positive and negative findings, and catheter removal). In the event all RNs from the participating floor(s)/unit(s) are not able to participate in the study, the Investigator will take reasonable measures to ensure all study-related procedures are performed by the Study RNs.

A minimum of 632 successful PIVC placements are required to complete the study (316 successful PIVC placements in Stage 1 and 316 successful PIVC placements in Stage 4). Each study Stage must be completed before proceeding to the next study Stage. The final sample sizes of Stage 1 and Stage 4 will be determined by an interim analysis of raw data in each Stage.

The study will be conducted in compliance with this protocol, Good Clinical Practices (GCP), and any other applicable regulatory requirements.

### 6.1.1. *Choice of Control Groups*

There is no control group in this study because it is a single-arm study. This is a single sequence study with Stage 1 (Baseline) followed by Stage 2 (Intervention), Stage 3 (Run-In), and Stage 4 (Post-Interventional).

### 6.1.2. *Method of Assigning Subjects to Treatment Groups*

RNs from the medical surgical unit(s) or ED of the hospital can be on any shift and will not be required to have a minimum level of clinical experience. All participating RNs within the unit must complete the B. Braun Peripheral Advantage Program required trainings (Stage 2). Those RNs who have not completed all of the B. Braun Peripheral Advantage Program required trainings in Stage 2 cannot continue on to Stages 3 and 4 and thus will be removed from participation in the study. Study RNs should not be currently using the B. Braun Introcan Safety® IV Catheters, the STEADYCare™ Smallbore Extension Set or Christie VeinViewer® Vision2 utilized in this study.

#### 6.1.3. *Blinding*

The study is an open-label study. Therefore, there is no blinding procedure applied in this study.

### 6.2. Description of Study Hypotheses

The primary hypothesis is that the rate or percentage of complications in the patients in Stage 4 utilizing the B. Braun Peripheral Advantage Program will be lower than the rate in the baseline at Stage 1 utilizing the site's current standard of care with regards to PIVC insertion technique used and Institution's PIVC type.

The study's null and alternative hypotheses are as follows:

$$H_0: P_{Stage\ 4} \geq P_{Stage\ 1}$$
$$H_a: P_{Stage\ 4} < P_{Stage\ 1}$$

where $P_{Stage\ 1}$ and $P_{Stage\ 4}$ represent the rate or percentage of complications in Stage 1 and Stage 4, respectively.

**Decision Criterion:** The null hypothesis will be rejected and the alternative hypothesis will be concluded if the upper confidence limit for the rate difference, i.e. $P_{Stage\ 4} - P_{Stage\ 1}$, of a 1-sided 95% confidence limit (normal approximation) is less than zero.

### 6.3. Study Endpoints

#### 6.3.1. *Primary Efficacy Endpoint*

The primary endpoint for this study is the rate/percentage of complications (e.g., phlebitis/thrombophlebitis, occlusion, infection (localized or Catheter Related Bloodstream Infection (CRBSI), dislodgement or infiltration, extravasation, accidental removal, etc.).

#### 6.3.2. *Secondary Endpoints*

The following acute secondary endpoints will be assessed:

- Indwell time for catheters with and without complications (measured in hours)
- First attempt insertion success rate (first stick success) for PIVC
- Rate of insertion of a Peripherally Inserted Central Catheter (PICC) or Midline Catheter due to inability to insert the PIVC or removal of the initial PIVC due to complications (rescue PICC or rescue Midline)
- Healthcare costs associated with PIVC use in a clinical setting.

## 7. DATA QUALITY ASSURANCE AND COMPUTING ENVIRONMENT

Case report forms (CRFs) for data collection were created in an Electronic Data Capture (EDC) system specifically for this study and were used to record data. The forms were completed by the study site personnel with oversight and approval by the Investigator. All procedures for the handling and analysis of data were conducted using GCP and meeting the International

Organization for Standardization (ISO) 14155 and the International Conference on Harmonization (ICH) guidelines and the US Food and Drug Administration regulations for the handling and analysis of data for Clinical Investigations.

All statistical analyses will be performed using the Statistical Analysis System (SAS) Software package, Version 9.4 or higher (SAS Institute, Cary, NC).

# 8. PATIENT POPULATIONS

The trial study population consists of male and female subjects eighteen (18) years of age or older with a medical condition that requires a PIVC anticipated to last for at least 48 hours. The subjects meet all inclusion criteria and do not meet any of the exclusion criteria described in Sections 4.1 and 4.2, respectively, of the study Protocol. Subjects in the patient population will be classified as 1 or more of the following based on their individual participation in the study:

- Screen Failure: Any subject who signed the Informed Consent or who's LAR provided consent and then the subject failed to meet the inclusion and or exclusion criteria,
- Enrolled: Any subject who signed the Informed Consent or who's LAR provided consent and then the subject met all of the inclusion and exclusion criteria, ,
- Early Termination: Any subject who was Enrolled but never had an attempted PIVC insertion or who was Enrolled and did not have a successful PIVC insertion by a study RN,
- Early Withdrawal: Any subject who was Enrolled, but who voluntarily withdrew their consent or was withdrawn by their LAR or was withdrawn by the PI,
- Study Completer: Any Enrolled Subject who had a successful PIVC insertion by a Study RN and had the PIVC removed for any reason

However, there will be three (3) analysis populations to be used in this analysis as described in Section 8.1.

## 8.1. Data Sets to be Analyzed

The following analysis populations have been defined for this study: an Intent-to-Treat (ITT) population, a Modified Intent-to-Treat (MITT) population, and a Per Protocol (PP) population.

**Study Analysis Populations**

| Population | Subjects Included |
|---|---|
| ITT | The ITT population consists of all subjects who are consented, meet all of the inclusion criteria and none of the exclusion criteria, and are enrolled into the study. |
| MITT | The MITT population consists of all ITT subjects for whom treatment with the PIVC is attempted (successful or not successful). |
| PP | The PP population is a subset of the MITT analysis set who meet the following criteria:<br>• there are no major deviations from the protocol eligibility criteria; |

| | |
|---|---|
| | • the subject receives a successful PIVC placement from a Study RN;<br>• the subject has a primary efficacy endpoint assessment at Stage 1 and/or Stage 4. |

The primary endpoint, the primary safety endpoint, and all secondary endpoint analyses will be carried out on available data in the MITT population; supportive analyses of primary endpoints will be carried out on the PP population as well. Demographic and safety summaries will be provided for the ITT and MITT populations, respectively.

### 8.2. Protocol Deviations

A study deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the study protocol, applicable laws or regulations, or the Investigator Agreement. No deviation from the protocol will be implemented by an Investigator without the prior review and approval by the sponsor. Such approval will be documented in writing and maintained in the study files. The Investigator must document and notify the sponsor of any deviation from the study protocol no later than five (5) working days after becoming aware of the deviation. Deviations to the protocol will be reported by the site to their Institutional Review Board (IRB), as required.

Major deviations include those that involve the primary endpoint, the informed consent process and the inclusion/exclusion criteria of the study, or any deviation that involves or leads to a serious adverse event in a study participant. The protocol deviations classified as Major include, at a minimum:

- Date and time of insertion/removal not recorded
- Informed consent
- Inclusion/Exclusion
- Failure to record daily observation of catheter
- Failure to record reason for catheter withdrawal

Under certain circumstances, deviations from the study protocol to protect the rights, safety and well-being of human subjects may occur. Such deviations shall be documented in writing and reported to the Sponsor and the IRB, if required, as soon as possible, and no later than five (5) working days.

Subject specific deviations will be reported on the Protocol Deviation CRF. Investigators will adhere to procedures for reporting study deviations to their IRB as required. Deviations from the clinical protocol will be reviewed and evaluated by the sponsor on an ongoing basis and, as necessary, appropriate corrective actions put into place.

## 9. STATISTICAL METHODS

### 9.1. Determination of Sample Size

Based on initial study design assumptions, at least 316 successful PIVC insertions are necessary to complete Stage 1 and at least 316 successful PIVC insertions are necessary to complete

Stage 4 in order to detect a statistically significant difference between the current standard-of-care products and B. Braun PA at 90% power and two-sided confidence level of 5.0%. The estimated complication rate in Stage 1 is 50% and the estimated complication rate in Stage 4 is 35% (Helm, 2015).

Two (2) interim analyses of raw data are planned solely for the purpose of sample size re-estimation. Using the method of Pocock & Mehta, the sample size can be either held constant or increased – it cannot be reduced based on the results of the re-estimation.

#### 9.1.1. *Interim Data Analysis Stage 1*

Upon successful completion of approximately 70% of the originally planned PICV placements in Stage 1, an interim analysis of the primary endpoint on uncleaned data will be performed. The observed complication rate in Stage 1, utilizing actual data collected in the study up to this point, will be compared to the originally estimated complication rate of 50%. If the observed complication rate is statistically significantly greater than 50%, the sample size will not be modified, and Stage 1 enrollment will continue to the original sample size of at least 316 successful PIVC insertions. If the observed complication rate is not statistically significantly greater than 50%, the sample size may be re-estimated with the assumed Stage 1 complication rate equal to the observed interim analysis complication rate, with other assumptions held constant.

#### 9.1.2. *Interim Data Analysis Stage 4*

The final sample size in Stage 1 (based on the results of the sample size re-estimation in Stage 1) will be used as the initial sample size for Stage 4. Upon successful completion of approximately 50% of the initial sample size in Stage 4 (which is determined at the interim analysis in Stage 1), another interim analysis on uncleaned data for the complications will be performed. This sample size re-estimation will follow the method of Mehta and Pocock to calculate the conditional power of the study to conclude that the complication rate in Stage 4 is lower than the complication rate in Stage 1, given the observed complication rates at the interim analysis. The conditional power (CP) will be categorized into one of the following three (3) zones:

- Favorable: $CP \geq 90\%$
- Promising: $41\% \leq CP < 90\%$
- Unfavorable: $CP < 41\%$

In the event the conditional power is found to be in the Favorable or Unfavorable zone, the study will continue to the originally planned sample size in Stage 4 (i.e., final sample size in Stage 1). In the event the conditional power is in the Promising zone, the total study sample size may be increased to the required sample size to achieve conditional power of 90% at the completion of the study. Note that only the sample size in Stage 4 can be increased at this time, as the data collection in Stage 1 has been completed.

## 9.2. General Considerations

### 9.2.1. *General Methods*

All descriptive statistical analyses will be performed using SAS (Version 9.4 or higher) unless otherwise noted. Derived variables will be programmed by the study programmer/statistician,

and then verified by an independent programmer/statistician. The program review also will include a check as to whether analyses conform to specifications of the SAP. All output will be incorporated into Microsoft Excel or Word files and formatted to the appropriate page size(s).

For categorical variables, the number and percentage within each category of the parameter will be calculated. For continuous variables, the N, median, mean, standard deviation (SD), minimum, and maximum values will be presented. Where appropriate, 95% two-sided confidence intervals may be presented.

If the observed data are found not to follow a normal distribution, appropriate non-parametric methods may be employed.

#### 9.2.2. *Adjustments for Covariates*

Adjustment for covariates such as years of nursing experience will be made.

#### 9.2.3. *Handling of Dropouts or Missing Data*

Every effort will be undertaken to limit premature discontinuations and ascertain completeness of data collection. All other analyses will utilize only actual subject data which is collected; no imputation of missing data will be performed.

#### 9.2.4. *Interim Analysis and Data Monitoring*

See Sections 9.1 and 9.2 for a description of the two (2) planned interim analyses of raw data for sample size confirmations. No other interim analysis is planned for this study at the time of protocol development. This study does not require and thus will not utilize a Data Monitoring Committee for monitoring the trial performance and the safety of enrolled subjects or an independent Clinical Events Committee (CEC) for endpoint adjudication.

#### 9.2.5. *Multicenter Studies*

Protocol Amendment 1 allows for multiple hospitals. Enrollment will be competitive across all study sites. In the event that more than one site is enrolling patients in the study, the stage by site interaction analysis will be performed to evaluate their heterogeneity in the rate of complications. Available data for all sites will be combined at Stage 1 and Stage 4, respectively, to perform analyses for the primary and the secondary endpoints.

#### 9.2.6. *Multiple Comparisons/Multiplicity*

This is a prospective, single-arm sequential study. Comparisons in the rate of complications will be performed between Stage 1 and Stage 4 by sites. There are no multiplicity adjustments.

#### 9.2.7. *Use of an Efficacy Subset of Patients*

Use of an efficacy subset of patients is not applicable to this study.

#### 9.2.8. *Active Control Studies Intended to Show Equivalence*

Active control studies intended to show equivalence are not applicable to this study.

#### 9.2.9. *Examination of Subgroups*

Exploratory analysis in the primary endpoint and secondary endpoints will be performed by site in this study.

#### 9.2.10. *Level of Statistical Significance*

All hypothesis tests will be one-sided and performed at the alpha=0.05 level. No adjustments to the alpha level will be made for the number of significance tests performed.

#### 9.2.11. *Visit Windows and Definitions*

There are no assessment windows at each stage in this study.

#### 9.2.12. *Subject Disposition, Demographics and Other Baseline Characteristics*

A tabulation of subject disposition will be presented including the screen failures, the number enrolled, the number of patients who successfully received a PIVC, the number of subjects who had PIVC durations ≥48hrs and <48hrs, the number of patients who completed Stage 1 and/or Stage 4, and the number of withdrawals, including reasons for withdrawal as documented on the CRF.

Baseline demographic characteristics will be summarized for Nurses and Patients in ITT population and MITT populations, respectively. Other available baseline characteristics will be reported as well.

#### 9.2.13. *Listing of Individual Data*

A by-subject listing of demographics, the primary and secondary endpoints, and adverse events may be provided.

## 9.3. Primary Endpoint Analysis

The primary endpoint analysis will compare the rate/percentage of complications between B. Braun PA in Stage 4 and the hospital's current standard-of-care PIVC in Stage 1. The logistics regression will be used to estimate the differences while controlling the baseline characteristics such as years of nursing experience. Primary efficacy endpoint analysis will be performed at MITT and PP Populations, respectively. If 2 or 3 sites are used, this will be performed individually for each site and across all sites.

## 9.4. Secondary Endpoint Analyses

Secondary endpoints that measure rates (e.g., first stick success and the rate of insertion of a Peripherally Inserted Central Catheter (PICC) or Midline Catheter) will be tested for significance between Stages 1 and 4 using a logistics regression while controlling the baseline characteristics such as years of nursing experience.

Both Indwell Times and Impact of using B. Braun PA on the healthcare costs associated with PIVC use will be compared between Stage 1 and Stage 4 using standard parametric tests (such as Student's t-test) or a non-parametric equivalent (such as Wilcoxon signed rank test) if parametric methods are found to be inappropriate. Appropriate regression models will likely be used to estimate the differences while controlling the baseline characteristics such as years of nursing experience.

A survival analysis by Kaplan Meier Curves between Stage 1 and Stage 4 will be performed to further understand the difference in time to any complication or failure of the unit. A catheter will be considered to have been a failure/event if it is removed due to any complication or failure of the device. It will be considered censored/non-event if it is removed as it is no longer

needed by the end of Stage 1 or Stage 4, i.e., the condition improves, or the subject is discharged from the hospital.

All secondary endpoint analyses will be performed in the MITT Population.

## 9.5. Safety Analyses

### 9.5.1. *Adverse Events*

For adverse event (AE) analyses, summary tables and/or listings will be provided for all AEs and severe adverse events (SAEs), respectively, in terms of event category by MedDRA coding for Stage 1 and Stage 4. In addition, both AEs and SAEs, respectively, will be summarized for Stage 1 and Stage 4 in terms of relationship to the procedure, to the device, and severity. Except where indicated, if a subject reports the same AE more than once, or reports the same AE on multiple occasions, the most severe AE will be presented when calculating the number and percentage of subjects with that particular event. AE outcomes will be assessed descriptively.

A descriptive line listing of each AE by subject also will be provided.

All safety analysis will be based on MITT Population, which includes only subjects in whom a procedure is attempted after enrollment.

## 9.6. Medications

Only medications that are used in the treatment of a patient AE/SAE will be collected and coded. Each medication will be coded to a preferred term and an anatomic therapeutic classification (ATC) code using the WHO Drug Dictionary. The number and percentage of patients taking each medication will be summarized by medication class (anatomical classification) and preferred term.

## 9.7. Medical History

Medical history data will not be collected for this study.

# 10. CHANGES TO ANALYSES PLANNED IN THE PROTOCOL

There were no changes to the analyses planned in the protocol version 1.0 Amendment 1. However, due recruitment futility, this study was terminated prior to reaching Stage 2. Therefore, all analyses related to Stage 4 will not be performed.

# 11. REVISION HISTORY

| Date | Version | Revised By | Reason for Revision |
|---|---|---|---|
| March 8, 2021 | 1.0 | N/A | This is the first version of this document. |
| September 15, 2021 | 2.0 | 1.0 | The study was terminated early due to recruitment futility. |
| December 3, 2021 | 3.0 | 2.0 | Additional endpoint analysis |

# 12. REFERENCES

1. ICH Harmonised Tripartite Guideline, E9 Statistical Principles for Clinical Trials, 1998, http://www.ich.org

2. Assessment of the Effect of B. Braun Peripheral Advantage Program on Complications, Indwell Time and First Stick Success of PIVC Therapy. B. Braun Final Clinical Study Protocol. 2019.

# 13. PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications will be provided in separate documents.

# 14. STATISTICAL TABLES TO BE GENERATED

Table 14.1 Patient Disposition -ITT Population

Table 14.2.1 Demographics for Nurses - ITT Population

Table 14.2.2 Demographics and Patient Characteristics - ITT Population

Table 14.3 Summary of Daily Catheter Examination - MITT Population

Table 14.4.1 Summary of Primary Endpoint Analysis - MITT Population

Table 14.4.2 Summary of Primary Endpoint Analysis - PP Population

Table 14.5.1 Summary of Secondary Endpoint Analysis -MITT Population

Table 14.5.2 Summary of Secondary Efficacy Endpoint Analysis – Median Indwell time for Catheters -MITT Population

Table 14.5.3 Summary of Secondary Efficacy Endpoint Analysis – Median Indwell time for Catheters Subgroup Analysis - MITT Population

Table 14.6.1 Summary of Adverse Events -MITT Population

Table 14.6.2 Summary of Device and Procedure Related Adverse Events - MITT Population

# 15. DATA LISTINGS TO BE GENERATED

Listing 15.1 Individual Patient Demographics -ITT Population

Listing 15.2 Individual Patient Incidents -MITT Population

Listing 15.3 Device -MITT Population

Listing 15.4 Adverse Events -MITT Population

Listing 15.5 Protocol Deviation -MITT Population

# 16. FIGURES TO BE GENERATED

Figure 16.1 Summary of Kaplan-Meier of onset of complication – MITT Population

Figure 16.2 Summary of Kaplan-Meier of onset of Adverse Events – MITT Population