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Measurement of NonInvasive Blood Pressure with DINAMAP SuperSTAT and Datex-Ohmeda with Intra-arterial Blood Pressure in Neonates through Adults and Special Populations (MISSION Trial)

03Mar2017

GE Healthcare

Study Title:	Measurement of NonInvasive Blood Pressure with DINAMAP SuperSTAT and Datex-Ohmeda with Intra-arterial Blood Pressure in Neonates through Adults and Special Populations (MISSION Trial)
Study Number:	123.04-2013-GES-0008
Revision/Amendment:	Revision 7.0
Version Date:	03/Mar/2017

Confidentiality Statement

GE Healthcare

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Investigator's Signature Page

I hereby agree to:

(i) Conduct the investigation in accordance with the agreement, the investigational plan, FDA or applicable government regulations, and conditions of approval imposed by the reviewing Ethics Committee, IRB or governing regulatory body;

(ii) Supervise all testing of the device involving human subjects; and

(iii) Ensure that the requirements for obtaining informed consent are met.

_____ _____

Investigator Signature Date

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Print Name

_____

Site Name

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Site Address


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This document contains the following sections:

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Document and Version Control

This section records all changes made to the protocol for a specific study. In the table below, record each and every relevant change by indicating what changes were made.

Revision	Date *(DD/Mmm/YYYY)*	Revision Author	Comments/Changes
1.0	31/Oct/2013	Angela Johnson	Initial draft.
2.0	03/Dec/2014	Stephanie Karwedsky	Table 3: Updated Neonate III Weight to "≥ 2000g" Section 6.4: Updated Inclusion Criteria 1 and 2 Section 7.11: Removed Date of Birth, added Age Section 7.1.3: Removed reference to evaluation to be performed by two observers and a supervisor as this is a requirement of ISO 81060-2:2013 (E) Chapter 5 and therefore is not applicable to this study Section 7.1.3: Removed numbering of 7.1.4 as formatting was incorrect Section 7.1.3: Blood Pressure Assessments- Corrected verbiage to match ISO 81060-2:2013 (E) for #2
3.0	26/May/2015	Stephanie Karwedsky, Angela Johnson	Revised as per Appendices A (Amendment 1) and Appendix B (Amendment 2) to include detail of changes in version 2.0 and 3.0.
4.0	18/Jan/2016	Angela Johnson	Revised as per Appendix C (Amendment 3) to include detail of changes in version 3.0 to 4.0.
5.0	30/Jun/2016	Angela Johnson	Revised as per Appendix D (Amendment 4) to include detail of changes in version 4.0 to 5.0.
6.0	16/Feb/2017	Angela Johnson	Revised as per Appendix E (Amendment 5) to include detail of changes in version 5.0 to 6.0.
7.0	03/Mar/2017	Angela Johnson	Revised as per Appendix F (Amendment 6) to include detail of changes in version 6.0 to 7.0.

ABBREVIATIONS

AAMI	Association for Advancement of Medical Instrumentation
BP	BP
DCS	Data collection system
ECG	Electrocardiogram
GEHC	GE Healthcare
GxP	Good Processing Tools (validated research tools, not for commercial use)
LCS	Life Care Solutions
IABP	Intra-arterial blood pressure
IBP	Invasive blood pressure
ISO	International Standards Organization
MAA	Maximum amplitude algorithm
MAP	Mean blood pressure
NIBP	Noninvasive blood pressure
PAD	Peripheral Artery Disease
PDM	Patient Data Module (for CARESCAPE B650)
PSM	Patient Side Module (for CARESCAPE B650)
P_{sys}	Systolic pressure
P_t	Target pressure

1. STUDY SYNOPSIS

Study Title: Measurement of NonInvasive Blood Pressure with DINAMAP SuperSTAT and Datex-Ohmeda with Intra-arterial Blood Pressure in Neonates through Adults and Special Populations (MISSION Trial) **Study Number:** 123.04-2013-GES-0008	**Research Type:** Clinical (human) ☒ Pre-Clinical (animal) ☐ External Bench ☐

Brief Description of Study Purpose: This study is required to demonstrate that the non-invasive blood pressure (NIBP) measurement algorithms on two commercially available multifunction hemodynamic acquisition modules, the Patient Data Module (PDM) equipped with the DINAMAP® SUPERSTAT algorithm ("PDM-SUPERSTAT") and the Patient Side Module (PSM) equipped with Datex-Ohmeda GE algorithm ("PSM-Datex-Ohmeda"), provide accurate NIBP measurements in accordance with the guidelines provided by the most recent International Organization for Standardization (ISO) 81060-2:2013.

Notably, the new ISO 81060-2:2013 supersedes the previous 2009 version of this standard, and this study is being conducted in accordance with the most recent applicable standards.

This study will assess neonate, infant, children, pediatric, adolescent, and adult patients as well as adults with chronic atrial fibrillation in a population that requires non-emergent heart catheterization.

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Device/Product GEHC Modality: Life Care Solutions (LCS)
Device/Product Class: Monitoring Solutions

Device/Product Description:
Non-invasive blood pressure (NIBP) measurement algorithms of two multifunction hemodynamic acquisition modules compatible with the CARESCAPE Monitor B650 patient monitor are under study in this trial, as follows:

- **PSM-Datex-Ohmeda**: Patient Side Module (PSM) with Datex-Ohmeda GE NIBP algorithm.
- **PDM-SuperSTAT**: Patient Data Module (PDM) with DINAMAP® SuperSTAT NIBP algorithm.

The control used in this study is gold standard aortic invasive blood pressure (IBP). Data may be collected on the DASH® 4000 patient monitor equipped with the non-commercial GEHC DC-EDIT and GEHC DC-COLLECTOR GxP software that can be compared with data either manually collected from the NIBP CARESCAPE Monitor B650 monitor, or data may be collected using the GxP-validated GEHC PDM Data Collection Module, which is capable of collecting electronic data typically displayed using patient monitors. The GxP-validated systems used in this study serve the sole function of enabling the device to directly output data such as blood pressure waveforms and parameters to the computerized data collection system (DCS) for storage and analysis purposes.

Regulatory Status:

Pre-Market ☒ *The commercial DASH® 4000 patient monitor (control system) equipped with GxP validated non-commercial DC-COLLECTOR and DC-Edit software programs for data collection is considered investigational. The acquisition modules PDM-SuperSTAT and PSM-Datex-Ohmeda with the PSM-Datex-Ohmeda and PDM-SuperSTAT algorithms and used on the CARESCAPE Monitor B650 and accessories are commercially available, The PDM is considered investigational when GxP-validated PDM Data Collection Module is used, which functions in the same manner as the PDM but with additional ability to collect research data typically displayed on a patient monitor. Though pre- and post- market devices are utilized, all aspects of the study will be considered investigational.*

Post-Market ☐

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2. PRELIMINARY INVESTIGATIONS AND JUSTIFICATION

2.1. Literature Review

Introduction

Accurate blood pressure measurement is essential to providing optimal care in hospitals and other clinical settings, and non-invasive blood pressure (NIBP) has overwhelmingly become the contemporary clinical standard for blood pressure measurement.[1] Accurate blood pressure (BP) measurement is dependent on a trained observer using validated, calibrated, and properly maintained equipment, which has led to increasing emphasis on adherence of commercial NIBP devices to validated standards for accuracy and reliability.[2] While previous studies have shown that arterial waveforms can be accurately and reproducibly reconstructed using oscillometric algorithms, such as the DINAMAP® SUPERSTAT and Datex-Ohmeda GE algorithms studied in this trial, the accuracy of these NIBP measurement algorithms has also been shown to have high variability in patients with variant age and cardiac disease status.[3] Thus, there is a need to evaluate these algorithms against a validated clinical standard applicable to commercial sphygmomanometers.

ISO 81060-2:2013

Because the widely-accepted International Organization for Standardization (ISO) 81060-2:2009 standard has recently been updated to the ISO 81060-2:2013 version, it is necessary to reassess algorithms that have been previously tested under the predicate standard under the newest available standard in order to be compliant with United States regulatory standards. Notably, the new ISO 81060-2:2013 supersedes the previous 2009 version of this standard, and this study is being conducted in accordance with the most recent applicable ISO standard. ISO 81060-2:2013 standard provides a well-accepted set of requirements for the clinical assessment of sphygmomanometers used for intermittent, non-invasive, automatic estimation of arterial blood pressure using blood pressure cuffs against gold standard IBP measurement. This standard provides an objective basis for the assessment of all sphygmomanometers that sense or display pulsations, flow, or sounds in order to generate estimations, displays, or recordings of blood pressure in human patients. Notably, these standards are applied broadly across devices that use very different blood pressure assessment algorithms. The basis of this standard is comparison of the studied NIBP assessment devices to widely-accepted gold standard invasive blood pressure (IBP) measurement, less commonly referred to as intra-arterial blood pressure (IABP).

Noninvasive Blood Pressure (NIBP) vs. Gold Standard Intra-Arterial Invasive Blood Pressure (IBP) measurements

Direct blood pressure readings taken from major arteries, such as the aorta, are considered the gold standard in blood pressure assessment. In adults, IBP is a very common procedure used in Intensive Care Units that involves advancing a catheter into a major artery for continuous blood pressure monitoring.[4] Umbilical artery catheters are also among the most commonly used blood pressure monitoring methodologies in neonatal intensive care units, in part because of their high accuracy.[5] Because of the notable risks associated with arterial catheterization,

alternative NIBP measurements have also become routinely used in modern clinical practice. [1] Numerous studies, have, however reported discrepancies between the blood pressure measurement provided by NIBP devices measurements and IBP measurements, particularly in special patient populations such as those with cardiac disease. [3, 1] Thus, contemporary NIBP algorithms should be validated against highly accurate gold standard IBP measurements to ensure accuracy and reliability of these devices.

Oscillometric NIBP Measurement

The basic physiological principles that underlie NIBP technologies were first documented in the mid-1970s, and significant improvements have since been made in the algorithms that drive NIBP assessment. [6] In the past decade, there has been increasing theoretical discourse regarding the optimal methods for evaluation of arterial mechanical properties and blood pressure pulse using noninvasive oscillometric maximum amplitude algorithm (MAA) estimates of the mean blood pressure obtained with air-filled occlusive cuffs. [7] These data, once collected, can be mathematically extrapolated from experimental IBP measurements and waveform simulations and then recorded as exponential models. Most recently, automatic NIBP measurement systems have come to market that use highly specialized software algorithms to account for cuff pressure oscillations caused by the peripheral flow of blood either as discrete intervals or areas under a curve, allowing greater accuracy to be achieved using NIBP monitoring methods. [8] As a result, modern NIBP algorithms are generally more accurate than their predecessors. [7]

Noninvasive indirect oscillometric determination of blood pressure has significant advantages over invasive blood pressure assessments, as cuff inflation and deflation results in minimal discomfort and complications. [9] Oscillometric NIBP assessment algorithms are able to noninvasively estimate systolic, mean, and diastolic pressure. [10] In fact, this technique has become so popular that one survey reported more than 400 commercial device employing monitors that use NIBP algorithms available from numerous suppliers worldwide, though the accuracy of these models vary widely and may be poor in certain patient subpopulations. [11]

Both the Datex-Ohmeda GE algorithm and the DINAMAP® SuperSTAT algorithms investigated in this study are oscillometric algorithms for assessment of NIBP from data collected using an occlusive air-filled cuff.

2.2. Pre-Clinical (animal) Trials and Previous Clinical (human) Experience

Previous study has indicated that the GE DINAMAP® SuperSTAT algorithm on the GE CARESCAPE Patient Monitor Series or DASH® Monitor Series is accurate in adult, children, and neonate patients, including hypotensive and hypertensive patients. [12] Furthermore, the GE DINAMAP® SuperSTAT algorithm and the Datex Ohmeda GE algorithm have also been reported to satisfy the ANSI/AAMI SP10-2002 and SP10A-1996 American National Standard for Electronic or Automated Sphygmomanometers in adults and, for GE DINAMAP® SuperSTAT only, neonatal populations, meaning that all values were ±5 mmHg with a standard deviation of ≤ 8 mmHg of reference standards.

The Datex-Ohmeda GE algorithm has been successfully used to monitor blood pressure in adult patients and to predict vascular change and fluid loading, demonstrating results similar to

reference standard intra-arterial monitors in 26 patients according to the Association for Advancement of Medical Instrumentation (AAMI) standards. [13] Compared to other oscillometric blood pressure measurement algorithms, Datex Ohmeda GE was shown to be somewhat slower but equally accurate in a study involving 160 blood pressure recordings. [14]

2.3. Device Risk Analysis

Participation in this study has no direct benefit to participants; however, participants may benefit from more reliable assessment of blood pressure readings during their procedure due to the use of multiple devices and multiple recordings for blood pressure measurement. The NIBP device does not pose additional risks to patients, but there are risks associated with the additional IBP comparator procedures above the required clinical care for participating subjects. Use of existing indwelling lines in very young patients is designed to minimize additional disruption of care in pediatric patients.

The NIBP measurement (PDM-SuperSTAT and PSM-Datex-Ohmeda) devices and all patient monitors used in this study under study are commercially available, and all devices will be used according to their labeling. The GxP-validated GEHC PDM Data Collection Module may, when possible, be used to enable digital export of research data typically displayed on patient monitors.. The GxP-validated GEHC PDM Data Collection module works in the same way as the commercially available PDM module, but also has software to enable digital export of the data for research use. The validated non-commercial DC-EDIT and DC-COLLECTOR equipment for the DASH® 4000 and GEHC PDM Data Collection Module serve as a data output connections only and are not expected to impact the clinical function of the device. Participation in this study is not expected to impact patient management, clinical diagnosis, or treatment strategy compared to that which would be determined by the standard of care outside of this study.

2.3.1. Risk Analysis for Subjects with Indwelling Lines (≤29 days of age)

Eligible subjects aged 29 days or less will be recruited only if they currently have, or are scheduled to have, an indwelling femoral, radial, or umbilical arterial monitoring line placed. The type of line places will be determined according to the site standard of care, and not altered based on participation in the study. While radial lines are the most commonly placed indwelling lines in neonates, femoral and umbilical lines share a similar safety profile and, in some cases, are preferred in order to preserve integrity of vessels when future interventions may be required. [15] Like radial and femoral line placements, umbilical lines have been shown to have a minimal complication rate even during longer procedures when performed by experienced physicians. [5, 15] For these subjects, NIBP measurements will be taken in a minimally disruptive manner in order to minimize possible interruption in their care. No additional lines will be placed for study purposes. These patients may participate for up to three days, taking as few determinations as necessary to accomplish research objectives each day under the supervision of a medically qualified investigator. There is not expected to be a significant risk to subjects based on placement of measurement devices in this study.

2.3.2. Risk Analysis for Subjects undergoing Non-Emergent Aortic Catheterization (aged >29 days to adult)

Patients aged 29 days or older having prescribed non-emergent aortic catheterization procedures will be enrolled. Typical catheterization procedures in pediatric patients involve the use of general anesthesia for the duration of the clinically indicated procedure. The risks associated with general anesthesia are well documented and are widely considered safe when prudently administered. [16, 17, 18] Due to study participation, the duration of general anesthesia may be slightly increased by a period of about 25 minutes (1-2 minutes for each study NIBP measurement), after which no further research procedures will be performed. General anesthesia is widely recognized as a neuromodulator with potential neurotoxic effects; [19, 20, 21, 22, 23, 24] however, it is widely believed that prudent use of general anesthesia in pediatric patients does not pose significant acute or chronic risks to patients at routine clinical dosages and non-repeating administrations. [19, 25, 26] As used in this study, the devices and study procedures are not expected to pose significant risks to participating subjects beyond those of their clinically indicated catheterization procedure.

2.3.3. General Controls and Risk Mitigations (all subjects)

No medicinal agents, including anesthesia and sedatives, are specifically required by the study; however, being in the study will not prevent subjects from receiving medications that are otherwise prescribed for their procedure. Extension of administration of general anesthesia consisting of approximately 25 minutes is foreseeable. Because repeat anesthesia administration has been identified as a central risk factor, particularly amongst pediatric subjects, [25] the study will not enroll any subject aged greater than 29 days but less than 12 years of age that has recently received anesthesia outside of the study within the last 3 months. Additionally, no subject will be allowed to participate more than once to mitigate any possible risks associated with repeat anesthesia administrations.

3. RESEARCH DEVICE AND/OR PRODUCT

3.1. Identification and Description of Research Device/Product

3.1.1. PSM and PDM Multiparameter Hemodynamic Acquisition Modules (NIBP Measurement Devices)

The blood pressure measurement functions of two commercially available multiparameter hemodynamic acquisition add-on modules, the Patient Data Module equipped with the DINAMAP® SuperSTAT algorithm (PDM-SuperSTAT) and the Patient Side Module equipped with Datex-Ohmeda GE algorithm (PSM-Datex-Ohmeda) (Fig. 1), are being investigated in this study. The PDM and PSM devices are hardware add-ons that are compatible with the CARESCAPE B650 patient monitor as well as several other GEHC patient monitor products (not under study). Both the PDM and PSM acquisition modules are designed to enable the use of special software algorithms on existing patient monitors, thus allowing additional function on existing patient monitoring equipment without the need to purchase entirely new patient monitors. One of the capabilities of these devices is to allow NIBP measurement, which are determined using

oscillometric NIBP algorithms in the acquisition module. Using raw data collected by air-filled occlusive cuff on the patient's body that is attached to the patient monitor, this software on the patient acquisition module allows existing patient monitors to report NIBP. Both the DINAMAP® SuperSTAT and Datex Ohmeda GE have been shown to satisfy ANSI/AAMI SP10-2002 and SP10A-1996 American National Standard for Electronic or Automated Sphygmomanometers standards.

Figure 1 – PSM (Datex-Ohmeda GE) and PDM (DINAMAP® SuperSTAT) hemodynamic acquisition modules for the CARESCAPE Monitor B650.

3.1.1.1. Patient Data Module (PDM) with DINAMAP® SuperSTAT Algorithm (PDM-SUPSERSTAT)

The Patient Data Module (PDM) is a high-acuity mobile hemodynamic acquisition module designed to help eliminate gaps and ECG resets when moving patients. The device can interface with the Solar® and CARESCAPE module patient monitors at the bedside and can quickly snap into and provide power for a Transport Pro® monitoring device. The detachable PDM docking station interfaces to the module frame flex board, and the 10-pin connector provides the VSYS ePort supply voltage and the Ethernet communication lines to the PDM module. The PDM includes GE's clinical algorithms, including 12SL™ 12-lead ECG, 12RL™ derived 12-lead ECG, GE EK-Pro four-lead arrhythmia analysis, GE DINAMAP® SuperSTAT non-invasive blood pressure, and Masimo® SET® or Nellcor® OxiMax® SpO_2. PDM uses the DINAMAP® SuperSTAT NIBP measurement algorithm.

The GxP-validated GEHC PDM Data Collection Module, which enables the digital collection of research data typically manually transcribed from the patient monitor may also be used in the procedure. The modified GEHC PDM Data Collection Module used the same technology as the commercial PDM module, but has additional GxP-validated data collection features that are intended for research use only (serving to minimize potential errors or biases due to manual transcription from the patient monitor) to allow data output. This software program is not otherwise expected to produce any change in function of the commercially marketed patient module.

GE DINAMAP® SuperSTAT NIBP Algorithm

The GE DINAMAP® SuperSTAT algorithm is an oscillometric NIBP software algorithm that can work with lower signal levels while still maintaining accuracy.[12] It is an enhancement of the

predicate DINAMAP® algorithm. It uses the step-deflate technique to help guarantee that the highest quality signals are being used to estimate blood pressure. The main advantage of SuperSTAT over its predecessor is enhanced curve fitting of the oscillometric envelope data to smooth noisy data and reduce the number of steps needed to make blood pressure estimates. It also has the superior ability to use electrocardiogram (ECG) timing to help qualify cuff pulses when irregular rhythm is present. The innovative GE DINAMAP® SuperSTAT algorithm supports speed, comfort and artifact rejection for virtually all types of patients, including neonates, geriatrics and hyper/hypotensive patients. [27]

Use of various signal quality measures is used to reduce the impact of noise. [28, 29, 30] The GE DINAMAP® SuperSTAT algorithm has the ability to obtain an NIBP determination when the target pressure (P_t) is equal to, or even slightly below, the patient's systolic pressure (P_{SYS}). As shown in Figure 2a, this is accomplished through the use of the curve fit algorithm in the GE DINAMAP® SuperSTAT that enables the extrapolation of systolic pressure of up to approximately 10 mmHg beyond the target pressure. Figure 2b shows a recording of an NIBP determination made with a computerized data collection system (DCS). The target pressure was set to 135 mmHg and the GE DINAMAP® SuperSTAT algorithm correctly obtained the patient's blood pressure (145/89). [12]

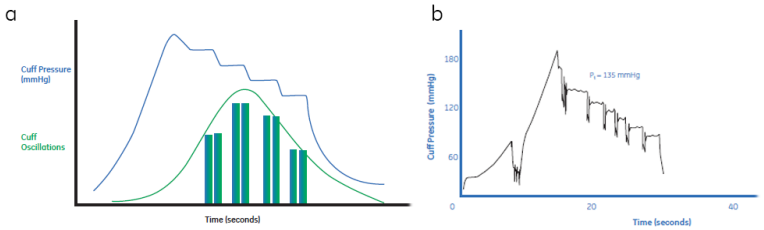

Figure 2 – (a) Extrapolation of Systolic Pressure with GE DINAMAP® SuperSTAT Algorithm and (b) Extrapolation of Systolic Pressure (BP = 145/89)

3.1.1.2. Patient Side Module (PSM) with Datex-Ohmeda GE Algorithm (PSM-Datex-Ohmeda)

The Patient Side Module (PSM) is compatible with many CARESCAPE® platforms as well as many other legacy platforms. The PSM module is capable of measuring the same parameters as the PDM module, with the exception of CO measurement. The PSM connector is part of the modular frame flex board, and the PSM connector provides the +15 VMOd PSM supply voltage and the RS-485 communication lines to the PSM module. PSM uses the Datex-Ohmeda GE NIBP measurement algorithm. The PSM has a venous stasis mode that can be manually initiated. The venous stasis mode initiates inflation and holds a constant pressure in the cuff to assist venous cannulation.

Datex-Ohmeda GE Algorithm

The Datex-Ohmeda GE algorithm is an established oscillometric algorithm that uses contributions from a range of frequencies to determine explicit values for parameters, such as blood pressure. [31] Rather than using a step-wise process (as in DINAMP® SuperSTAT), the Datex-Ohmeda GE algorithm is used to acquire and process continuous raw data signals, such as those

obtained from an occlusive cuff during NIBP procedures. [32] The Datex-Ohmeda GE algorithm has been successfully used to monitor blood pressure in adult and pediatric patients and to predict vascular change and fluid loading. [13]

3.1.2. Patient Monitoring Devices

3.1.2.1. CARESCAPE Monitor B650

The CARESCAPE Monitor B650 (Fig. 3) includes standard docking for both the PSM and PDM hemodynamic modules. The CARESCAPE Monitor B650 is a flexible patient monitoring solution that is highly configurable and provides many monitoring possibilities with a flexible software licensing model. The CARESCAPE Monitor B650 will employ the most recent FDA cleared software version. The CARESCAPE Monitor B650 improves data integration and connectivity by directly linking to the GE Healthcare CARESCAPE portfolio of monitoring products—including bedside, central station and transport monitors—as well as existing GE Healthcare monitors and peripheral third-party devices.

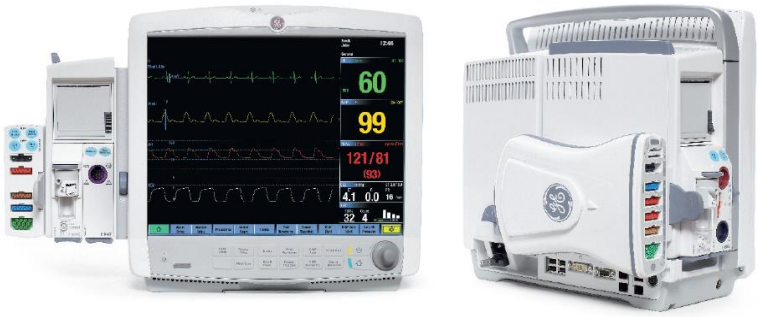

Figure 3 – Image showing the anterior (screen) and posterior (ports) view of the CARESCAPE monitor 650. PSM module is installed (left) and PDM acquisition module is installed (right)

Parameters and modules

Parameters	Patient Side Module	CARESCAPE Patient Data Module /Tram®
ECG	3, 5, 6, 12-lead ECG	3, 5, 6**, 12-lead ECG
SpO_2	GE SpO_2	Masimo SET®, Nellcor OxiMax®
NIBP	GE	GE DINAMAP® SuperSTAT™ algorithm**
InvBP	0 or 2	0 or 4
Temp	2	2, Optional with C.O.
Cardiac output	-	Optional with temperature

Figure 4 - Parameters and Modules for the Patient Side Module (PSM) and Patient Data Module (PDM) multiparameter hemodynamic acquisition modules from the *GEHC CARESCAPE Monitor B650 Cut Sheet* [33]

The CARESCAPE Monitor B650 has the following features:

- 15 in (diagonal) display
- Active matrix color TFT LCD
- 1024 x 768 pixels (XGA) resolution
- 0.625, 6.25, 12.5, 25, 50 mm/sec sweep speed
- Automatic and manual configurations
- 8 individual traces, with up to 14 with overlays and insets

Developed with tens of thousands of hours of testing, the CARESCAPE Monitor B650 is intuitive to use. It enables efficient clinical decision-making via the following benefits [34]:

- **Ease of clinical customization**: To tailor the monitor for a specific patient condition or caregiver specialty, clinicians can simply use customized patient profiles within the monitor or plug in a new clinical measurement module. Traditionally, caregivers needed to move a different, specialized patient monitor to the point of care.
- **Enhanced usability**: The CARESCAPE Monitor B650 includes an intuitive touch screen interface, as well as a barcode reader, enabling fast and secure patient data input. From the CARESCAPE Monitor B650, caregivers can view data and alarms from remote monitors without leaving the patient's bedside.
- **Ease of installation and training:** With the CARESCAPE Monitor B650, a hospital can easily duplicate hospital-specific clinical settings across all patient monitors on the network. Because the CARESCAPE Monitor B650 leverages similar software interfaces as other devices on the GE Healthcare enterprise monitoring platform, training can be streamlined.
- **Monitor mobility**: The monitor can run via a wireless local area network and can be battery operated, reducing the need for wall cables. The CARESCAPE Monitor B650 continuously transmits data to the central station, even when the monitor is moved while connected to a patient.

The CARESCAPE Monitor B650 combines the strong clinical heritage of Datex-Ohmeda anesthesia and Marquette Electronics cardiac expertise, providing a significant level of backwards compatibility that allows hospitals to leverage prior technology and training.

While the CARESCAPE Monitor B650 equipped with the DASH® 4000 may be used in the study, use of these patient monitoring devices will not be required for procedures conducted using the GxP-validated GEHC PDM Data Collection Module, which enables the digital collection of research data typically manually transcribed from the patient monitor.

GE Critikon SOFT-CUF® and CLASSIC-CUF® blood pressure cuffs (Fig. 5) are commercial cuffs cleared for use with the CARESCAPE Monitor B650. Similarly, all hoses are standard commercial hoses cleared for use with the patient monitor system.

Figure 5 – Five sizes of GE CRITIKON SOFT-CUF® arm occlusive blood pressure cuffs for infants, children, pediatric patients, adolescents, and adults (left) as well as one size of thigh cuff (left, brown); five sizes of GE CRITIKON CLASSIC-CUF® occlusive blood pressure cuffs for neonates are shown on the right.

3.1.3. Patient Monitoring Devices: DASH® 4000

The DASH® 4000 is a commercially available multifunction patient monitor that can be used to record IBP. The full featured Dash® 4000 monitor offers a 10.4-inch screen and is a comprehensive portable bedside monitoring solution.

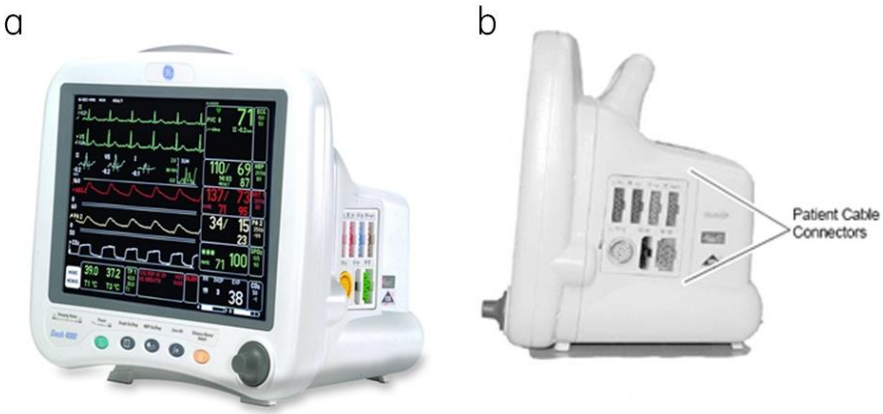

Figure 2– (a) Front view and (b) side view of the DASH® 4000 reference standard device for measuring intra-arterial blood pressure.

The DASH® 4000 Patient Bedside Monitor used for this study is a monitor that obtains many vital signs for patients. It is mainly used in patient care areas of higher acuity. The monitor is used for obtaining both invasive and noninvasive blood pressures, ECG tracings, and other vital signs. The DASH® 4000 used in this study is considered investigational because the unit is equipped with DC-COLLECTOR and DC-EDIT, special additional software programs that can send ECG, invasive blood pressure, and noninvasive blood pressure waveforms in addition to other relevant blood pressure data to data collection system (DCS) on a laptop computer. The only

function of DC-COLLECTOR and DC-EDIT is to allow data output, and these software programs are not otherwise expected to produce any change in function of the commercially marketed patient monitor. Although the device is not in direct contact with the patient, it is connected to the patient via a fluid filled catheter to a pressure transducer to collect the arterial (invasive) blood pressure data.

The Dash® 4000 patient monitor features innovative parameter technology, [27] as follows:

- GE EK-Pro four lead arrhythmia analysis: The GE EK-Pro™ clinical algorithm provides advanced atrial fibrillation detection and alarming. Early and accurate identification of AFib may help prevent this arrhythmia from becoming chronic.
- GE 12SL simultaneous 12 lead ECG detection: The 12SL™ algorithm provides improved P-wave detection, age and gender-specific interpretation and 12 lead buffer (if MUSE® is offline, up to 12 ECGs are stored).

The DASH®400 used in this study is equipped with validated non-commercial tools DC-EDIT and DC-COLLECTOR that allow output of waveform data and parameters to a computerized Data Collection System (DCS).

3.2. Regulatory Status

The PSM and PDM acquisition modules and CARESCAPE B650 used in this study are commercialized in the United States and have been cleared by the US FDA. Because the PSM module is not currently cleared for using in neonates or infants under 5 kg (approximately 11 lbs.), no patients in this age range will be examined with PSM in this study. The PDM device is cleared for use in patients of all ages. When possible, sites may also use the modified GxP-validated GEHC PDM Data Collection module, which uses the same technology as the commercially available PDM module with additional features to enable digital collection of research data. The GxP-validated PDM Data Collection Module is considered a pre-market device used for research purposes only, and is not intended to be commercialized.

The DASH® 4000 patient monitors are commercialized; however, when the Good Processing Tools (GxP) validated DC-EDIT and DC-COLLECTOR are equipped on the DASH®4000 the device is considered non-commercial (investigational) and is to be used for research purposes only. Notably, DC-EDIT and DC-COLLECTOR have been validated for use in clinical data collection for the purpose of regulatory submissions. The results of the current study may be used as part of regulatory submissions to the US FDA or other global regulatory bodies to support the use of the investigational NIBP software algorithms with other patient monitoring systems.

3.3. Risk Category/Rationale (US Only)

The CARESCAPE Monitor B650, acquisition modules (PDM and PSM), and peripheral cuffs and hoses used in this study are cleared for commercial use and will be used as intended in their labeling. All commercial devices are considered to be IDE Exempt per 21 CFR 812.2(c)(2). The DASH® 4000 is a commercial device; however, when equipped with the GxP validated non-commercial DC-EDIT and DC-COLLECTOR tools for data output it is to be used for research purposes only. Similarly, the GxP-validated PDM Data Collection Module used in place of manual

transcription from patient monitors is intended for research use only. DC-EDIT and DC-COLLECTOR (for DASH®4000) as well as the PDM Data Collection Module tools are not expected to impact the function of other devices or the integrity of the study, but instead are intended solely to enable digital collection of study data while minimizing biases associated with manual transcription of data. When using a DASH® 4000 equipped with DC-EDIT and DC-COLLECTOR or the PDM Data Collection Module in place of manual data transcription from patient monitors, the devices investigated in this research study are considered non-significant risk devices per the 21 CFR 812.3 definition:

1. it is not intended as an implant;
2. is not purported or represented to be for a use in supporting or sustaining human life;
3. is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; and
4. it does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

3.4. Device/Product Classification and Rationale

The PSM acquisition module (using Datex-Ohmeda GE for NIBP assessment) is cleared for commercial use under US FDA 510(k) K062576 (2006), and the PDM acquisition module (using DINAMAP® SuperSTAT for NIBP assessment) is cleared for commercial use under US FDA 510(k) K071073 (2007) as a non-invasive blood pressure measurement system (DXN) under CFR 870.1130.

When available, the pre-market PDM Data Collection GxP Module may be used in place of manual transcription from patient monitors using the commercial PDM module, enabling research data to be collected digitally. The PDM Data Collection GxP Module has been qualified per Good Processing Tools (GxP) by GE Healthcare for collection of ECG, blood pressure data in clinical settings, is considered investigational and intended for research use only.

The CARESCAPE Monitor B650 is a Class II medical device classified as a Patient Physiological Monitor (with arrhythmia detection or alarms) by the US FDA and cleared under 510(k) K131223 (2013). The most recent FDA cleared software version for the CARESCAPE Monitor B650 at the time of the study will be used on the CARESCAPE Monitor B650.

The DASH® 4000 patient monitor is a Class II medical device classified as a Patient Physiological Monitor by the US FDA and cleared under 510(k) K073462 (2008). Non-commercial DC-EDIT and DC-COLLECTOR tools used on the DASH®4000 have been qualified per Good Processing Tools (GxP) by GE Healthcare for collection of ECG and arterial data in clinical settings). When equipped with these tools, the DASH® 4000 patient monitor will be considered investigational.

All occlusive blood pressure cuffs and hoses used in this study have been cleared for use with their respective patient monitors in this study.

3.5. Device/Product Issuance and Replacement

The Sponsor will issue the following devices to the investigational site(s) for the purpose of this study:

- Patient monitors (DASH® 4000 and CARESCAPE Monitor B650 with the most recent software versions installed) with the appropriate software versions installed. DASH® 4000 patient monitors will be equipped with DC-EDIT and DC-COLLECTOR and labeled as investigational (for research purposes only).
- PSM and PDM acquisition modules for the CARESCAPE Monitor B650 with appropriate software versions already installed, or, based on availability, the PDM Data Collection Module labeled as investigational (for research purposes only).
-
- Required cuffs, hoses, ECG equipment, and wired connector s
- Laptops for use as IBP data collection systems (DCS) with appropriate software installed to capture physiologic and waveform data outputted from DASH® 4000 patient monitors equipped with DC-EDIT and DC-COLLECTOR
- Standard digital calibrated reference manometer(s) with error limit(s) of 1 mmHg (0,1 kPa)

The investigational site will select and provide all required catheterization equipment and transducers per their standard of care and applicable hospital policy. The study will not influence the hospital's selection of catheterization and/or transducer devices.

The Sponsor will record the manufacture, serial number, and last calibration for all manometers and the size (cm x cm) for all cuffs used.

3.6. Disposition of the device/product

All devices issued to the site by the Sponsor will be returned to the Sponsor after the study is completed. All identifiable patient data is intended to be removed from the devices prior to removal from the site. The Sponsor may provide the site with instructions for disposal of non-reusable devices or device components. All study devices provided by the Sponsor will be used only for study-related activities.

4. OBJECTIVES OF RESEARCH STUDY

4.1. Hypothesis

This is a study conducted to satisfy the ISO 81060-2:2013 standard for two NIBP devices (PSM-Datex-Ohmeda and PDM-SuperSTAT) and, as such, does not require a statistical hypothesis. The Pass/Fail criteria are described in **Section 9.5 - Pass/Fail Criteria**.

4.2. Study Objectives

4.2.1. Primary Objective:

The primary objective of the study is to determine if the PSM-Datex-Ohmeda and PDM-SuperSTAT NIBP measurement devices provide accurate blood pressure measurements in all indicated patient populations (neonates, children, pediatrics, adolescents and adults, and special populations) according to the definitions set forth by ISO 81060-2:2013.

4.3. Study Endpoints

4.3.1. Primary endpoints:

Per patient, NIBP and IBP endpoints will be collected for:

- Systolic BP (mmHg)
- Diastolic BP (mmHg)
- NIBP and IBP Mean Arterial Blood Pressure (MAP)

Per patient, for NIBP only:

- Accuracy, determined according to ISO 81060-2:2013

4.3.2. Secondary endpoints:

Per patient, endpoints will be collected for:

- Baseline data, including demographics
- Per-procedure data
- Static calibration of device

5. DESIGN OF RESEARCH STUDY

5.1. Type of Research Study

This is an open-label, multi-site, dual arm, prospective study with demographics-based stratification quota.

Open-Label	☒	*Patients or patients' legal representatives and investigators will have knowledge of all treatments*
Blinded	☐	
Double-Blinded	☐	
Single-site	☐	
Multi-site	☒	*The study will be conducted at three (3) sites*
Randomization Procedure:	☐	
Not randomized:	☒	*Patients will be consecutively assigned to PDM-SuperSTAT or PSM-Datex-Ohmeda groups based on demographics-based stratification*
Single arm	☐	
Comparator	☐	
Parallel	☐	
Crossover	☒	*Patients will receive NIBP and IBP assessments, with NIBP type (PDM-SuperSTAT or PSM-Datex-Ohmeda) determined by study arm. Each patient will act as their own control for NIBP vs. IBP comparisons*
Prospective	☒	*Patients are enrolled and then undergo study procedures.*


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5.2. Controls and Minimization of Bias

Patients will be enrolled consecutively into the PDM-SuperSTAT study arm and, if stratification quotas are met, then into the PSM-Datex-Ohmeda study arm until each arm's stratification quota reaches its minimum allotment. Thereafter, patients may be enrolled consecutively without regard to stratification quota until the minimum total patient population is reached. Consecutive enrollment is designed to limit selection bias. The devices with algorithms and required peripherals, including cuffs and hoses, will be provided by the Sponsor to ensure consistency between procedures and limit possible bias due to variations in storage, handling, or lot numbers.

6. STUDY SUBJECTS

6.1. Subject Population

The study will include neonates with indwelling femoral, radial, or umbilical arterial monitoring lines and infant, pediatric, adolescent, and adult subjects requiring non-emergent surgery involving aortic catheterization (including chronic atrial fibrillation patients among adults and adolescents).

6.2. Protection of Vulnerable Subjects

The information collected in this study could not have been obtained in a less vulnerable, consenting population, necessitating the use of minor patients. Adolescent, pediatric, and neonatal patients will be recruited and enrolled according to all US FDA, ISO 14155:2011 GCP, and other applicable local requirements for protection of vulnerable subjects. Special measures will be taken to protect the rights of these vulnerable study participants and to shield them from undue risk. Study procedures for pediatric and neonate subjects will be modified to minimize interruption in normal medical care, which includes additional limitations on sampling frequency beyond the minimums suggested by ISO 81060-2:2013 (as shown in Table 2) for the general population. This is done to ensure minimal risk for participating subjects.

6.3. Number of Subjects

The total minimum enrollment for the two study arms is 83 total evaluable patients (maximum of 200 patients), as follows:

1. **PDM-SuperSTAT Arm** (N_{PDM}): 45 evaluable patients with GE DINAMAP® SuperSTAT algorithm (PDM Module) on CARESCAPE Monitor B650, to achieve a total target of ≥150 BP data pairs in patients ≥3 years old (up to 10 paired measurements per subject) and ≥150 BP data pairs in patients <3 years old (as described in Table 2).
2. **PSM-Datex-Ohmeda Arm** (N_{PSM}): 29 evaluable patients with Datex-Ohmeda algorithm (PSM module) on CARESCAPE Monitor B650, to achieve a total of ≥150 BP data pairs in patients ≥3 years old (up to 10 paired measurements per subject) and ≥150 BP data pairs in patients <3 years old (as described in Table 2).

6.3.1. Stratification of Subjects

Subject enrollment will be stratified based on prospective criteria to ensure diversity in the population, as described in ISO 81060-2:2013 and set forth in Table 1. Patients will be enrolled concurrently in both arms until all minimum quotas are reached, and thereafter up to the maximum enrollment for the study. Incomplete/non-evaluable datasets, as determined by the Sponsor, will not be considered to satisfy minimum requirements in Table 1. Additionally, multiple cuff sizes will be used, including a minimum of 1/(2 x *n*) per stratification group (except for the children/infants/neonates group), where *n* is the total within a stratification group able to be tested using the cuff in accordance with its labeling (Table 1).

Table 1 – Summary of Patient Enrollment Stratification by Characteristics

Enrollment Stratification	Minimum Total in PDM-SuperSTAT arm	Minimum Total in PSM-Datex-Ohmeda arm	Age (years) requirement	Weight (g) requirement	Gender (M/F)	Minimum number of patients (*n*)
Adults and Adolescents (General population) [b]	15 total patients	15 total patients	>12 yr	(*no weight requirement*)	F[#]	*n* ≥ 5
			>12 yr		M[#]	*n* ≥ 5
Adults and Adolescents Chronic Atrial Fibrillation [b]	7 total patients	-	>12 yr		M or F[#]	*n* ≥ 7
Pediatrics	5 total patients	5 total patients	≥3 AND ‹12 yr		F[#]	*n* ≥ 2
			≥3 AND ‹12 yr		M[#]	*n* ≥ 2
Children/Infants/ Neonates	18 total patients	-	≥1 yr AND <3 yr		M or F	*n* ≥ 3
			>29 days AND <1 yr		M or F	*n* ≥ 3
			(*no age requirement*)*	< 1000 g	M or F	*n* ≥ 3
				1000-2000 g	M or F	*n* ≥ 3
				>2000 g	M or F	*n* ≥ 3
	-	9 total patients	≥1 yr AND <3 yr	>5 kg (~11 lbs) [a]	M or F	*n* ≥ 3
			>29 days AND <1 yr	>5 kg (~11 lbs) [a]	M or F	*n* ≥ 3
			(*no age requirement*)*	>5 kg (~11 lbs) [a]	M or F	*n* ≥ 3
TOTAL	**45 TOTAL**	**29 TOTAL**				

Abbreviations: M = male; F = female; *n*, number of patients

* No age requirement within the children/infant/neonates category may include subjects aged birth to <3 yrs

Investigators should equitably represent male and female patients, which must each make up a minimum of 30% of the final population upon completion (i.e. at least 30% male and 30% female, the remaining may be either male or female based on enrollment).

***Important*: Additional Stratification requirements**

[a] Only patients weighing >5 kg (approximately 11 lbs) can be examined with PSM-Datex-Ohemda under the current labeling

[b] Among adult/adolescents, at least 10% should have baseline systolic BP of ≤100 and ≥160 as well as diastolic BP of ≤ 70 and ≥ 85 mmHg

6.4. Inclusion Criteria

Subjects will be included that:

1. Are aged >29 days requiring clinically indicated non-emergent heart catheterization OR aged ≤29 days with placed or scheduled placement of an indwelling femoral, radial, or umbilical arterial monitoring line;
2. Have an upper limb (right OR left side) that fits a cuff size of the device (circumference ranging 3 cm to 40 cm) OR have a thigh (right OR left side) that fits a cuff size of the device (circumference ranging 38 to 50 cm);
3. Are expected to be able to provide blood pressure measurements using both IBP and NIBP;
4. Are able and willing to provide written informed consent or have a legally authorized representative willing to provide written informed consent with assent from minor patients, as required by IRB policy.

6.5. Exclusion Criteria

Subjects will be excluded that:

1. Have previously participated in this study (no subject may participate more than once).
2. Exhibit signs or symptoms or have a current diagnosis of peripheral vascular disease in upper AND/OR lower limbs;
3. Have current, uncontrolled circulatory shock;
4. Exhibit injuries, deformities, intravenous lines, or other abnormalities that, in the opinion of the investigator, may prevent proper cuff application or functioning;
5. For women of child-bearing potential, are currently pregnant, suspected to be pregnant, or are currently lactating;
6. Have any condition that could interfere with the subjects ability to tolerate the procedure, including having a maximum of 4 fast flushes (adult, adolescent, or pediatric patients aged >29 days) or 1 fast flush (neonates aged <29 days);
7. If aged greater than 29 days but less than 12 years of age, have previously had any clinical or research procedure requiring general anesthesia in the last 3 month period;
8. If aged greater than 29 days but less than 12 years of age, are expected to require more than three (3) total hours of continuous general anesthesia for the scheduled procedure (including clinically necessary anesthesia and anticipated 25 minute extension for study purposes).

6.6. Screening Subjects for Enrollment

There are three (3) investigational clinical sites involved in this clinical trial. Patients will be screened for enrollment by the investigational site according to their standard procedure, in accordance with IRB policy. All patients will be consecutively screened and enrolled first into the PDM-SuperSTAT group if eligible. Remaining patients will then be screened for the PSM-Datex-Ohmeda group. All patient enrollment will be conducted according to the stratification criteria and inclusion/exclusion criteria.

7. PROCEDURES FOR RESEARCH STUDY

7.1. Setup Procedures

7.1.1. IBP Data Collection on the Data Collection System (DCS)

The PDM Data Collection Module may be used to collect research data (based on availability) for PDM procedures, else IBP and ECG data will be collected using a DASH® 4000 patient monitor with the hardware and software tools to connect to a computerized data collection system (DCS) housed on a Sponsor-provided laptop computer. A laptop will be connected for electronic data capture, when GxP-validated data capture tools are used. The investigator is responsible for setting up the data collection according to the "Setup of Data Collection" section of the *Device Set-Up Manual* provided by the Sponsor. For applicable procedures, the control panel for the DASH® 4000 patient monitor is shown in the "DASH® 4000 Control Panel" section of the section of the *Device Set-Up Manual* provided by the Sponsor, which provides details on user setup and operation of the DASH® 4000 patient monitor.

The patient procedure for IBP setup is shown in the "IBP Setup" section of the *Device Set-Up Manual* provided by the Sponsor. Similarly, the *Device Set-Up Manual* provides instructions for setup and use of the PDM Data Collection Module for electronic data capture during PDM procedures.

7.1.2. NIBP Data Collection

NIBP will be recorded on a commercial CARESCAPE Monitor B650 with most recent commercial software version installed. NIBP data will be transcribed by hand from the display of the CARESCAPE B650 monitor onto the Sponsor-provided Case Report Form (CRF) when the PDM Data Collection Module is not available. When the PDM Data Collection Module is available, data collection may be performed electronically using this tool.

For patients in the PDM-SuperSTAT arm of the study, NIBP will be measured with a CARESCAPE Monitor B650 equipped with a PDM acquisition module or the GxP PDM Data Collection Module. For patients in the PSM-Datex-Ohmeda arm of the study, NIBP will be measured with a CARESCAPE Monitor B650 equipped with a PSM acquisition module.

7.2. Study Procedures

7.2.1. Baseline Examination

For enrolled patients that have provided informed consent the following baseline information will be collected on CRFs after informed consent requirements have been satisfied and before the procedures are performed:

1. Demographics (Age and Gender)
2. Gestational Age at Birth (*for Neonates only*)
3. Height and Body Weight
4. Relevant Medical History
5. Physiological Condition (Stable/Unstable)
6. Urine pregnancy test, if applicable (females of childbearing potential)
7. Arm or Thigh Circumference (cm)
8. Appropriate Cuff Brand (Critikon® Soft-Cuf or Classic-Cuf) and Size
9. Baseline Non-Invasive Blood Pressure (NIBP), consisting of systolic blood pressure (SBP) and diastolic blood pressure (DBP)
10. Location of NIBP Measurement (Arm/Thigh) and measuring circumstance
11. Mean Arterial Pressure (MAP)
12. Current medications
13. Pulse rate

7.2.2. Before the Procedure

For each patient, the following procedure-specific information will be recorded on CRFs:

1. Model and serial number for the DASH® 4000 (if applicable)
2. Model and serial number for CARESCAPE B650 (if applicable)
3. Model and serial number for the PSM or PDM acquisition module used
4. Catheter cross-section, length, and trade name
5. Trade name of pressure transducer
6. Site/artery used for IBP measurements
7. Monitor filter settings and recording settings, if applicable
8. Identification of the observer making the recordings (name and position)
9. Details of any special circumstances during measurement
10. Pulse rate at the start of device evaluations
11. Time and date of last manometer calibration

Three ECG sensors will be placed with leads on the left and right arm and left leg connected to the DASH® 4000 or the PDM Data Collection Module

Before each patient procedure, static calibration will be conducted for the IPB system to ensure measurement accuracy according to the “Static Calibration” section of the *Device Set-Up*

Manual provided by the Sponsor. Each system will be calibrated at 5 static pressures spread across the working range of the device to be tested, recorded as:

1. Pressure for each of the 5 calibration static pressures tested
2. Calibration completion status (success/fail)
3. Descriptions of any errors during any static calibration procedure

7.2.3. Patient Procedures

Each patient will undergo intra-arterial aortic catheterization according to the standard of care at the investigational site. All tubing, transducers, and stopcocks will be filled with fluid and purged of all bubbles prior to data recording for IBP or NIBP in this study. If general anesthesia and/or other medicinal products are prescribed outside of the study, they will be administered according to the local standard of care prior to study measurements.

Dynamic calibration will be performed in the beginning of each procedure according to the "Dynamic Calibration" section of the *Device Set-Up Manual* provided by the Sponsor. For patients that the procedure will extended beyond one day, dynamic calibration will be conducted once each day prior to determinations. A maximum of 1 flush is to be conducted for patients aged <29 days. A maximum of 4 flushes may be conducted for patients aged ≥29 days. During calibration, values will be recorded for:

1. Number of fast flushes
2. Damping coefficient
3. Natural frequency

For subjects less than 29 days of age, care will be taken to minimize disruption of care, and, when possible, procedures will be performed during times when feeding or other care is provided.

7.2.4. Blood Pressure Assessments

NIBP will be measured using the CARESCAPE Monitor B650 patient monitor equipped with an acquisition module (either PDM-SuperSTAT or PSM-Datex-Ohmeda, determined by study arm). IBP will be measured using the DASH® 4000 plus DC-COLLECTOR and DC-EDIT software. For PDM procedures where the PDM Data Collection Module is used for electronic data capture, this may be used in place of manual transcription from the patient monitor to paper CRFs. During the blood pressure assessments, values will be recorded for:

1. Study Arm
2. Time of first and last blood pressure measurement
3. Systolic, Diastolic, Mean, Test Duration
4. If the prescribed wait time was taken between tests
5. Any measurements with no determination

Both NIBP and IBP assessments will be conducted simultaneously, using either digital data recording tools (when available) or recorded by hand onto a paper Case Report Form (CRF). If

necessary, assistance will be provided by other study staff to ensure that accurate and simultaneous blood pressure data is recorded.

IBP data will be continuously collected throughout the study.

For cases where manual data collection of NIBP data is necessary, it will be recorded according to the following procedure:

1. Use the patient monitor equipped with either PDM-SuperSTAT or PSM-Datex-Ohmeda according to the patient's study arm to determine the patient's blood pressure.
2. Clear the patient monitor memory of the previous determination and wait at least 3 min
3. Have the observers using the reference IBP monitoring equipment (DASH® 4000) and the NIBP monitoring equipment (CARESCAPE Monitor B650 with either PSM or PDM) simultaneously record and determine the patient's blood pressure, as follows.
    a. Start continuous collection on the IBP DCS system at the same time as recording of NIBP begins
    b. Collect each NIBP measurement from the CARESCAPE Monitor B650
4. Wait the appropriate amount of time between determinations (as defined in Table 2).
5. Repeat steps 3 and 4 adhering to the requirements in Table 2 until the target number of recordings and determinations have been performed or the subject leaves the study. In the event that any blood pressure determination is not successful, the procedure may be repeated to achieve the target number of successful blood pressure determinations. No more than the maximal number of total blood pressure determinations as specified in Table 2 will be performed on any patient.
6. When all NIBP measurements are complete, stop the IBP data collection.

For PDM procedures where the PDM Data Collection Module is used, data may be captured electronically instead of using the manual procedure according to the following procedure:

1. Use the PDM Data Collection Module to determine the patient's blood pressure.
2. Wait at least 3 min.
3. Simultaneously record and determine the patient's blood pressure, as follows.
    a. Start NIBP measurement from the PDM Data Collection Module
4. Wait the appropriate amount of time between determinations (as defined in Table 2).
5. Repeat steps 3 and 4 adhering to the requirements in Table 2 until the target number of recordings and determinations have been performed or the subject leaves the study. In the event that any blood pressure determination is not successful, the procedure may be repeated to achieve the target number of successful blood pressure determinations. No more than the maximal number of total blood pressure determinations as specified in Table 2 will be performed on any patient.
6. When all NIBP measurements are complete, stop the data collection.

The same number and type of determination should be performed whether the manual or digital PDM Data Collection Module is used.

Table 2 – Number of Blood Pressure Assessments and Frequency

Population	Maximum Number of BP Determinations	Target Number of Valid BP Determinations	Frequency of Determinations
Pediatric, Adolescents, and Adults (aged ≥ 3 years)	15 max attempts	10 determinations	At least 60 s between determinations
Children & Infants (<3 years old to >29 days old)	10 max attempts	10 determinations	At least 60 s between determinations
Neonates (‹ 29 days old)	10 max attempts	5-10 determinations	At least 3 minutes between determinations (over max of 72 hours)

7.3. Data Storage

All digitally recorded data will be saved from the DCS folder to a Sponsor-provided external media (e.g., flash drive or CD), and the Investigator will confirm that all data is saved on flash drive or CD and stored in a secured area at the investigational site. When NIBP data is recorded on paper case report forms, it will be stored in a secure area at the investigational sites.

7.4. Withdrawal and Discontinuation Criteria

The patient may withdraw from study participation at any time, for any reason without consequence. The Investigator may withdraw a patient at any time for any reason. The reasons for withdrawal and discontinuation for any patient shall be recorded. These will be reported to the Sponsor. The EC/IRB should be notified per their notification of patient withdrawal policy.

Data collected up until the time of withdrawal may still be disclosed to the Sponsor as part of this study to ensure the integrity of research data.

Continuation and discontinuation of enrollment in any stratification group will be made at the discretion of the Sponsor in the context of applicable regulatory and standards requirements, and the Investigator will be notified by the Sponsor upon such a determination.

8. TRAINING PLAN

8.1. Training Plan for Research Device/Product

All device evaluations will be conducted by trained observers that understand blood pressure measurement and have been recently trained in blood pressure measurement. Training for clinical investigators will be provided by the Sponsor to ensure that procedures are conducted in accordance with procedures outlined in this protocol. The current commercially available *GEHC*

CARESCAPE Monitor B650 User Manual, *DASH® 4000 User Manual*, and a Sponsor-provided *Device Setup Manual* for this study will be provided to the investigational site. The Sponsor may also provide additional training on these materials to ensure proper device usage.

8.2. Training Plan for Protocol

All investigators and study staff will be provided training on the protocol and procedures prior to study initiation. Any investigator or study staff may request additional training to ensure that study procedures are conducted in accordance with the protocol.

9. DATA ANALYSIS AND STATISTICS

9.1. Statistical Analysis Methods

9.1.1. Analysis Populations

Separate analysis will be performed for PSM-Datex-Ohmeda and the PDM-SuperSTAT arms per requirements of the ISO 81060-2:2013 standard. Analyses will be conducted for the following populations:

- adults, adolescents, and pediatric patients, who are ≥ 3 years old and chronic atrial fibrillation patients (PDM-SuperSTAT arm)
- adults, adolescents and pediatric patients, who are ≥3 years old (PSM-Datex-Ohmeda arms)
- neonates and children <3 years of age (PDM-SuperSTAT arm)
- children <3 years of age and weigh over 5 kg (11 lbs) (PSM-Datex-Ohmeda arm)

If deemed necessary by the Sponsor, when the measurement accuracy is compromised in a sub-population, affected sub-populations may be excluded from analysis

9.2. Determining Reference Invasive Blood Pressure Per ISO 81060-2:2013

First, the mean and the standard deviation of the invasive blood pressures derived from the IBP wave recordings during a NIBP determination will be calculated; and the range of reference invasive blood pressure will be determined as mean ±1 standard deviation (SD) of the IBPs. The same method will be used for both systolic and diastolic blood pressures. Calculation of reference IBP from IBP wave recordings is not part of the statistical analysis. Data may be excluded for analysis when the range of invasive systolic BP is wider than 20 mmHg or when the range of invasive diastolic BP is wider than 12 mmHg, as such that analysis is performed in accordance with ISO 81060-2:2013.

9.2.1. Analysis of Blood Pressure Measurement Error

The BP measurement error of the investigational device will be determined as follows:

- If the value obtained from the investigational device lies within the range of reference IBP, an error of 0 mmHg will be assigned to this determination.
- If the value obtained from the investigational device lies outside the range of the IBP, the error for this determination will be calculated by subtracting the

adjacent limit of the IBP range from the value of the NIBP determination (Δ = NIBP - IBP).

Then, mean and SD will be calculated from the errors of each determination of each patient using the following formulae, and will be compared to the acceptance criteria, i.e., mean ≤ 5 mmHg and SD ≤ 8 mmHg. Percentages of measurements with errors within 5 mmHg, 10 mmHg, and 15 mmHg will also be calculated.

Mean: $$\bar{x}_n = \frac{1}{n} \times \sum_{i=1}^{n} x_i$$

SD: $$s_n = \sqrt{\frac{1}{n-1} \times \sum_{i=1}^{n} \left(x_i - \bar{x}_n \right)^2}$$

In addition, Bland-Altman plot will be presented for the measurement agreement between NIBP and reference IBP. The 'average' (x-axis) represents the average of the blood pressure from the investigational device and the mean reference IBP value. The 'difference' (y-axis) is the blood pressure measurement difference calculated as Δ=NIBP- mean IBP.

Population mean bias, between-subject variance, within-subject variance, and limits of agreement will be calculated for the measurement difference using Bland-Altman method as described in the article "Agreement Between Methods Of Measurement With Multiple Observations Per Individual" by Bland and Altman in 2007 Journal of Biopharmaceutical Statistics.

9.2.2. Effect of Arm Circumference on Blood Pressure Measurement Error

A scatter plot of the percent difference in blood pressure measurement over arm size will be presented to evaluate the effect of arm size on measurement error. The percent difference will be calculated as:

$$\text{Percent Different} = \frac{\text{Difference between NIBP and Mean Reference IBP}}{\text{Average of NIBP and Mean Reference IBP}}$$

This analysis will be done for systolic and diastolic blood pressure separately by study arm.

9.2.3. Summary of Blood Pressure Measurement

Number of NIBPs taken from each subject, and total number of NIBPs will be summarized for each analysis population by study arm.

9.3. Analysis of Subject Characteristics

The following subject characteristics data will be summarized using descriptive statistics if applicable per standard requirements for each analysis population by study arm. Continuous

variables will be described using mean, standard deviation, median, minimum and maximum. Categorical variables will be described using count and percentage.

- Number of Adult/adolescents/children/atrial fibrillation patients
- Number of patients <1000g, 1000-2000g,>2000g in weight
- Number of patients <29 days, ≥29 days and < 1 year of age, ≥ 1 year and < 3 years of age, ≥ 3 year and ≤ 12 years of age
- Number of patients over 5 kg (11 lbs) and meet one of the following: ≥29 days and < 1 year of age, ≥ 2 year and < 3 years of age
- Gender
- Height and weight
- Arm Size
- Age
- Adult and adolescent subjects with mean invasive systolic blood pressure ≥ 160 mmHg
- Adult and adolescent subjects with mean invasive systolic blood pressure ≤ 100 mmHg
- Adult and adolescent subjects with mean invasive diastolic blood pressure ≥ 85 mmHg
- Adult and adolescent subjects with mean invasive diastolic blood pressure ≤ 70 mmHg
- Number of subjects tested on each cuff size
- Arterial sites where IBP was taken
- Heart rate

9.3.1. Data Exclusion

The following NIBP data will be excluded from analysis:

- NIBP data from a subject if the range of reference systolic blood pressure is more than 20mmHg or the range of reference diastolic blood pressure is more than 12 mm Hg, or as specified per ISO 81060-2:2013 standard;
- Measurements beyond 10 valid measurements for each subject;
- Isolated premature ventricular contractions (PVC) will be addressed by removing the pressure associated with the PVC and the following compensatory beat. The PVC will be identified through analysis of the ECG waveform associated with the PVC and pulses. This is done during calculating IBPs from the IBP wave form, not in the statistical analysis.

9.4. Interim Analysis

No interim analysis is planned. As necessary for study conduct, engineering, and/or regulatory purposes, study data may be accessed and, if necessary, reported by the Sponsor prior to closure of the study.

9.5. Handling of Missing Data

Every effort will be made to obtain complete data. Data analysis will be based on collected data. Missing data will not be imputed using any imputation methods. Missing data is not expected for blood pressure values because up to 15 blood pressure determination procedures will be allowed, if necessary, to obtain 10 blood pressure recordings, thus minimizing the likelihood of missing data in IBP and NIBP blood pressure determination pairs. Any pair of blood pressure measurements with a missing value will be excluded from analysis.

9.6. Pass/Fail Criteria of the Study

The study will be considered to pass if a sufficient data set is collected to satisfy the requirements of ISO 81060-2:2013.

10. DEVIATIONS

10.1. Management of Protocol Deviations

Deviations to the protocol may occur when necessary to protect the life or physical well-being of a patient. Except in an emergency, prior approval by the Sponsor is required for changes in, or planned deviations from this protocol. If these changes affect the scientific soundness or the safety and welfare of the patient, prior EC/IRB approval is also required. Planned Protocol Deviation documentation must be filed in the Site Study Regulatory Binder.

There are two types of unplanned protocol deviations, critical deviations and non-critical deviations. All deviations must be documented and reported, the criticality of the deviation will determine the reporting path.

Critical Deviations: Deviations that significantly affect the safety, efficacy, integrity or conduct of the study. These deviations must be reported to the Sponsor no later than 5 working days from awareness of occurrence and reported to the EC/IRB per the deviation reporting policy.

If an Investigator uses a device without obtaining informed consent, the Investigator shall consider this a critical deviation and report the event to the Sponsor and the EC/IRB within 5 working days of the occurrence

Non-Critical Deviations: Protocol deviations that DO NOT significantly affect the safety, efficacy, integrity or conduct of the trial. These deviations must be documented on the Case Report Form Protocol Deviation page and will be reviewed by the study monitor.

11. COMPLAINT HANDLING AND ADVERSE EVENT REPORTING

11.1. Foreseeable Adverse Events and Device Effects

The study procedure requires adding NIBP measurements to a patient's procedure. While NIBP is non-invasive, there are some foreseeable risks associated with NIBP, as follows:

- slight discomfort upon inflation of the cuff,
- possible bruising,
- petechial rash

- discoloration of the skin beneath the cuff
- peripheral nerve injuries
- skin avulsion
- compartment syndrome
- ischemia

Whether or not the patient participates in the study, there are risks to having indwelling monitoring lines placed or having non-emergent aortic catheterization procedures with or without general anesthesia. To protect neonatal subjects, only subjects with existing indwelling monitoring lines will be enrolled, and no indwelling lines will be placed for study purposes. Foreseeable risks associated with these invasive procedures, as required for IBP, include:

- Bruising
- Bleeding
- Heart attack
- Stroke
- Damage to the artery where the catheter was inserted that may require additional attention (pseudoaneurysm), including shear damage
- Irregular heart rhythms (arrhythmias)
- Allergic reactions to the dye or medication
- Tearing the tissue of your heart or artery
- Kidney damage
- Infection
- Blood clots
- Ischemia
- Air embolism
- Potentially serious reactions to prescribed general anesthesia and/or sedatives

While general anesthesia is not a requirement of this study, it is foreseeable that some patients undergoing aortic catheterization procedures will be incidentally administered prescribed general anesthesia and/or other sedatives during the study. Though general anesthesia is widely considered safe for routine clinical use, it is known to be a potent neuromodulator with potentially serious documented side effects. [19, 20, 22, 23, 24, 25, 26] This research involves extension of the procedure by approximately 25 minutes to collect data, which may incidentally extend prescribed anesthesia and/or other medication administration. Though no definitive cumulative or long-term effects of general anesthesia are known with certainty, [25] to mitigate against these possible risks the study will not enroll subjects that have history of repeated recent anesthesia, and no subject will be allowed to participate more than once in the study. The risks associated with general anesthesia during this study are not expected to be significantly higher than those that the subject would have otherwise been exposed to had he or she not participated in this research.

11.2. Adverse Event Definitions

Adverse Event (AE): As defined by EN ISO 14155-2011: any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Serious Adverse Event (SAE): As defined by EN ISO 14155 – 2011: an adverse event that

(a) led to death;

(b) led to a serious deterioration in the health of the subject, that either resulted in:

(1) a life-threatening illness or injury, or

(2) a permanent impairment of a body structure or a body function, or

(3) in-patient or prolonged hospitalization, or

(4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function;

(c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Anticipated: Any adverse event and/or reaction, the specificity or severity of which is consistent with the EC/IRB approved informed consent, protocol, investigator brochure, or product labeling.

Unanticipated adverse device effect (UADE): As defined by 21 CFR 812.3: means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

11.3. Management of Adverse Event Reporting

Any adverse events will be recorded in the subjects study record and the Adverse Event Case Report Form. The following information should be obtained:

- Description of Event
- Date of onset and resolution
- Intensity (mild, moderate, severe)
  - **Mild**: Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
  - **Moderate**: Symptom(s) of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
  - **Severe**: Symptom(s) of a sufficient severity to cause the subject severe discomfort. Treatment for symptom(s) may be given.

- Serious (yes/no)
- Relationship to device (unrelated, possibly related, probably related)
  - **Unrelated**: The adverse event is reasonably expected to be related to (or caused by) a concurrent illness, effect of another device/drug or other cause, and is unlikely related to the investigational product
  - **Possibly related**: The adverse event is reasonably expected to be related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product
  - **Probably related**: There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or there is no other reasonable medical explanation for the event.
- Treatment given and/or action taken (procedure stopped, withdrawn from study, no action)
- Anticipated (yes/no)

Adverse events will be reported to the local EC/IRB per their policy.

11.4. Management of Serious Adverse Event and Unanticipated Adverse Device Effect Reporting

All SAEs and or UADEs will be documented as above and reported in writing to the Sponsor within 72 hours of knowledge of the event The Investigator shall submit the Adverse Event Case Report Form and GEHC_GQP_10.07.005_F002 Site Notification and Assessment of Serious and Unexpected Adverse Events (DOC0910335) with redacted supporting documentation to SAE mailbox. If the event resulted in the death of a subject, the event shall also be reported via telephone to the Sponsor within 24 hours of knowledge of the event. SAEs will be reported to the local EC/IRB per their policy.

The Sponsor's Medical Monitor (complete contact information listed in the Study Synopsis) should be contacted for SAEs and/or UADEs:

Fax: 800-888-3983
E-mail: SAE@ge.com

If additional information (i.e. outcome of event, date event resolved, additional treatments) is required to submit a follow-up report, the Investigator shall update the AE CRF and resubmit to Clinical Affairs. The Investigator shall submit the follow-up SAE and/or UADE report to the local EC/IRB per their policy.

11.5. Management of Device Complaints

Any complaints regarding the operation of the device or software or any malfunctions are to be reported to the Research Manager.

Sponsor contact for device complaints:

Stephanie Karwedsky, Clinical Affairs Project Manager

Telephone: +1 262 443 7008
E-mail: Stephanie.Karwedsky@ge.com

12. EARLY TERMINATION OR SUSPENSION

12.1. Criteria for Early Termination or Suspension

The study may be terminated early if the Sponsor determines that unanticipated adverse event(s) presents an unreasonable risk to subjects or for any other reason as Sponsor determines to be appropriate.

Termination shall occur no later than 5 working days after the sponsor makes the determination and no later than 15 working days after Sponsor first received notice of the effect.

The Sponsor will promptly notify the Investigators of any determination to terminate the study outside of the protocol timeframe. The Sponsor will provide each Investigator with written guidelines/instructions on termination processes and timelines.

The Investigator is responsible for reporting the early termination to their local EC/IRB.

12.2. Withdrawal of EC/IRB Approval

The Investigator is to notify the Sponsor of any withdrawal of EC/IRB approval within 5 working days of such occurrence. If the EC/IRB terminates or suspends its approval of the Study, the Investigator will promptly notify Sponsor and provide a detailed written explanation of the termination or suspension. Upon receipt, the sponsor will provide written guidelines/instructions on subject withdrawal/termination processes and timelines.

13. ETHICS COMMITTEE (EC) AND REGULATORY FILINGS

13.1. Regulatory Authority Approval Requirements (Global)

There are no applicable global regulatory authority approval requirements; however, this study will be conducted in accordance with ISO 81060-2:2013 standard requirements.

13.2. Ethics Committee Approval Requirements

This study is to be submitted to the EC/IRB for review and approval prior to enrolling subjects. The Investigator is responsible for keeping approval current and maintaining appropriate correspondence and reports. The study will be conducted in accordance with EC or IRB policy.

Copies of all EC/IRB applications, approval letters, Informed Consent Forms (ICF) and other correspondence are to be sent to the Sponsor, with originals kept in the Site Study Regulatory Binder.

13.3. Management of Protocol Revisions/Amendments

Any protocol revisions or amendments will be reviewed by the EC or IRB at the investigational site and approved by the Sponsor.

13.4. Informed Consent and Privacy Requirements

Informed consent will be obtained from all subjects prior to participation in the study, per the determination of the EC/IRB.

Institutional and national policies for informed consent and assent for minor patients will be followed throughout this study.

Informed consent will be documented in the source record of each subject. The Investigator or designee will consent the subject per regulatory guidelines which include that the subject has ample time to review the ICF and have all questions answered to their satisfaction; the subject may take the ICF home to review with family members or others prior to agreeing to participate in the study; upon agreeing to participate in the study, the subject signs and dates the document, and the person who consented the subject signs and dates the document.

Minor subjects are legally unable to provide informed consent. Therefore these study participants are dependent on their parent(s) or legal guardian to assume responsibility for their participation in clinical studies. Fully informed consent will be obtained from the legal guardian in accordance with applicable laws and regulations. All participants will be informed to the fullest extent possible about the study in language and terms they are able to understand.

Where appropriate, minor subjects will provide assent to enroll in a study (age of assent may be determined by IRB/EC or be consistent with local legal requirements). Participants of appropriate intellectual maturity should personally sign and date either a separately designed, written assent form, or the written informed consent. In all cases, participants should be made aware of their rights to decline to participate or to withdraw from the study at any time. Attention will be paid to signs of undue distress in patients who are unable to clearly articulate their distress, and a minor participant's wish to withdraw from a study will be respected unless special circumstances would, in the opinion of the investigator and parent(s) or legal guardian, negatively impact the welfare of a pediatric patient. In such a situation, continued parental or legal guardian consent should be sufficient to allow participation in the study. Emancipated or mature minors (defined by local laws) may be capable of giving autonomous consent.

The subject and/or, as applicable, their legally authorized representative, will be given a copy of the signed informed consent form and the original will be retained with study files.

14. DATA AND QUALITY MANAGEMENT

14.1. Management of Data

Both non-invasive and invasive blood pressure data will be collected from subjects enrolled in this study and labeled with de-identified subject identification designation (SID) that will not contain any identifiable personal information.

GE Healthcare may use patient data for future technology development, marketing purposes, publications or any other possible use. Specifically, the data obtained in this study may be used as part of a regulatory submission.

The approved Data Management Plan (DMP) will be located in the study's clinical history file maintained by the sponsor.

14.2. Subject De-identification

All subject data will be de-identified (coded) by the investigational site, and subjects will be assigned a unique identification number in the format provided by the Sponsor.

14.3. Completion of Case Report Forms (CRFs)

Data will be collected using paper CRFs and data collection system (DCS) data per the details of this protocol.

To ensure the quality and integrity of the data, it is the responsibility of the Principal Investigator or designee, in a timely manner, to complete a CRF for each subject who is enrolled to participate in this study. GEHC will provide CRFs and the instructions for their use. CRFs will be completed as information becomes available.

If errors or omissions are found in the course of a CRF audit or data review, *a Data Clarification Form (DCF)* will be generated and the error, omissions or clarifications will be corrected on these forms.

The Principal Investigator or a Sub-Investigator will sign and date the indicated places on the CRF. This signature will indicate that a thorough inspection of the data has been made and will thereby certify the contents of the form.

14.4. Record Retention at the Site

All records pertaining to the conduct of the study, including Case Report Forms, Informed Consent Forms, Ethics Committee (EC) or Institutional Review Board (IRB) correspondence, and other study documentation must be retained at the Site for inspection at any time by the GEHC Study Monitor or designee. These records will be maintained for a minimum of 5 years and thereafter will be handled according to GEHC Retention Policies. Elements should include the following:

- Subject Files – containing the completed patient CRFs
- Regulatory Binder – containing the protocol and amendments, EC/IRB submissions and approvals, (blank and signed/dated) Informed Consent Form(s), and Site study logs
- Reference Manuals – containing, as applicable, the following documents: resource list, responsibilities of the Investigator, Sponsor, adverse event and informed consent guidelines, study aids (training material, device screen shots), relevant central supplier instructions, and other pertinent documents.

No records will be destroyed without GE Healthcare notification and approval.

15. MONITORING PLAN

15.1. Brief Description

In collaboration with the site, the sponsor will ensure proper monitoring of the study to confirm that all the clinical requirements are met. Monitoring visits will ensure adherence to the protocol, completion of informed consents, IRB review of the study, maintenance of records, primary outcomes review and review of the CRFs and source documentation for accuracy and completeness.

15.2. Reference to Approved Monitoring Plan

The approved monitoring plan will be located in the study's clinical history file maintained by the sponsor.

16. PUBLICATION POLICY

All proposed publications using study data, in full or in part, will be subject to approval by the Sponsor prior to submission. The Investigator and Sponsor agree to act in good faith to consider the interests of each party in publication.

17. ADDITIONAL STUDY MATERIALS / ADDITIONAL COUNTRY-SPECIFIC REGULATORY REQUIREMENTS

The study will be conducted in accordance with all requirements of ISO 81060-2:2013. This study will be conducted in compliance with Good Clinical Practice, per international standards.

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APPENDIX A: AMENDMENT TO PROTOCOL VERSION 1.0

Purpose: This amendment document clarifies the inclusion criteria and minor issues (clarification related) in the procedure sections.

The following amendments were made to version 1.0 to produce version 2.0. Point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment for the previous version.

Item	Section	Revision or Clarification	Justification
1	Table 3	Updated Neonate III Weight to "≥ 2000g"	Consistent with ISO 81060-2:2013.
2	Section 6.4. Inclusion Criteria	5. Require non-emergent heart catheterization ~~(all subjects except neonates);~~; 6. ~~Neonates~~For neonates only ~~—~~, require non-emergent heart catheterization using the umbilical ~~arterial lines that have been placed for route care.~~line as access;	Clarified criteria for inclusion for neonates to ensure safety.
3	Section 7.1.1. Baseline Examination (all sites) (BS EN 1060-4:2004)	1. Demographics (~~Ageand~~Date of Birth and Gender)	Added requirement for collection of date of birth as evidence of age.
4	Section 7.1.3. Patient Procedure and Procedure-Specific Assessments (all sites)	Evaluation of the tested devices will be conducted during each patient's prescribed catheterization procedure by two trained observers and a supervisor. For each patient, the following procedure-specific information will be recorded on CRFs:	Clarified parties performing catheterization and evaluation.
5	Section 7.1.4. Static Calibration of the IBP System: Blood Pressure Assessments	2. Remove ~~the cuff~~existing cuffs from the patient.	Clarified that the referenced cuff is the existing cuff.

APPENDIX B: AMENDMENT TO PROTOCOL VERSION 2.0

Purpose: This amendment document describes in detail the changes made to the study protocol to allow to make procedural clarifications and to add additional safeguards for neonate populations beyond the scope of the original procedure for neonate subjects. Additionally, it removes the requirement to adhere to all data collection elements of BS EN 106004:2004, due to incompatibility of aspects of this standard with ISO 81060-2-2013.

The following amendments were made to version 2.0 to produce version 3.0. Point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment for the previous version.

Item	Section	Revision or Clarification	Justification
6	Investigator Signature page	~~have read this protocol and study related documents and agree to conduct this study in full accordance with the stipulations of the protocol described herein, and any subsequent amendments.~~ I hereby agree to: (i) Conduct the investigation in accordance with the agreement, the investigational plan, FDA or applicable government regulations, and conditions of approval imposed by the reviewing Ethics Committee, IRB or governing regulatory body; (ii) Supervise all testing of the device involving human subjects; and (iii) Ensure that the requirements for obtaining informed consent are met.	Updated per Sponsor's internal procedures.
	Abbreviations	AAMI Association for Advancement of Medical Instrumentation BP BP DCS Data collection system ECG Electrocardiogram LCS Life Care Solutions IABP Intra-arterial blood pressure IBP Invasive blood pressure ISO International Standards Organization MAA Maximum amplitude algorithm MAP Mean blood pressure NIBP Noninvasive blood pressure PAD Peripheral Artery Disease PDM Patient Data Module (for CARESCAPE B650) PSM Patient Side Module (for CARESCAPE B650) P_{sys} Systolic pressure P_t Target pressure	
7	Study Synopsis: Brief Description of Study Purpose	This study is required to demonstrate that the non-invasive blood pressure (NIBP) measurement algorithms on two commercially available multifunction hemodynamic acquisition modules, the Patient Data Module (PDM) equipped with the DINAMAP® SUPERSTAT algorithm ("PDM-SUPERSTAT") and the Patient Side Module (PSM) equipped with Datex-Ohmeda GE algorithm ("PSM-Datex-Ohmeda"), provide accurate NIBP measurements in accordance with the guidelines provided by the most recent International Organization for Standardization (ISO) 81060-2:2013~~requirements relevant to Unites~~	Removed the requirement to adhere to all data collection elements of BS EN 106004:2004, due to incompatibility of aspects of this standard with ISO 81060-2-2013.

Item	Section	Revision or Clarification	Justification
		~~States devices and the BS EN 1060-4:2004 standard widely recognized in Europe~~.	
8	Study Synopsis: Investigator Names	**Investigator Names:** David Scott Marks, MD MBA Professor and Vice Chair of Medicine and Radiology Director of Cardiac Catheterization Laboratories and Clinical Trials Froedtert Hospital/Medical College of Wisconsin Jeffrey Garland, MD Director of Perinatal Research Wheaton Franciscan Healthcare – St. Joseph's~~Susan Foerster, MD Pediatric Cardiologist Assistant Professor, Medical College Member, Children's Specialty Group Children's Hospital of Wisconsin~~ **Address:** 9200 West Wisconsin Avenue Milwaukee, WI 53226 **Telephone:** 414-805-0579 **E-mail:** dmarks@mcw.edu **Address:** 5000 West Chambers Street Milwaukee, WI 53210 ~~9000 West Wisconsin Avenue Milwaukee, WI 53226~~ **Telephone:** 414- 447-2663 ~~414-266-2884~~ **E-mail:** jsgarland@hotmail.com ~~SFoerster@chw.org~~	Updated site and investigator information.
9	Study Synopsis: Device/Product Description	(~~DSC~~DCS) for storage and analysis purposes	Typographical correction.
10	Study Synopsis: Regulatory Status	Pre-Market ☒ *The commercial DASH® 4000 patient monitor (control system) equipped with GXP validated non-commercial DC-COLLECTOR and DC-Edit software programs for data collection is considered investigational. The acquisition modules PDM-SuperSTAT and PSM-Datex-Ohmeda -with the ~~above identified~~PSM-Datex-Ohmeda and PDM-SuperSTAT algorithms and used on the CARESCAPE Monitor B650 and accessories are commercially available. Though pre and post market devices are utilized, all aspects of the study will be considered investigational.~~The commercial DASH® 4000 patient monitor (control system) equipped with GXP validated non-commercial DC-COLLECTOR and DC-Edit software programs for data collection is considered investigational~~* Post-Market ☐☒ ~~*Devices under study (Acquisition modules PDM-SuperSTAT and PSM-Datex-Ohmeda used on the CARESCAPE Monitor B650) are currently commercial devices in the US*~~	Updated the study regulatory status to more clearly indicate the investigational devices. This is a clarification to original intent.

Item	Section	Revision or Clarification	Justification
11	Study Synopsis: Medical Monitor Name	**Medical Monitor Name:** Ron Von Jako, MD~~Olli Vaisanen, MD~~ **Address:** 301 Ballardvale St., Suite 4 Wilmington, MA 01887-4405~~Kuortaneenkatu 2 00510 FI~~ **Telephone:** +1 781 262 5579~~+358 40 652 9662~~ **E-mail:** Ron.VonJako@med.ge.com~~Olli.Vaisanen@ge.com~~	Updated Medical Director name and contact information.
12	Section 2.1. Literature Review	The basis of this standard ~~if~~ is… ~~**BS EN 1060-4:2004**~~ ~~The BS EN 1060-4:2004 standard for determining the overall system accuracy of non-invasive sphygmomanometers is a similar British-adopted standard required by many regulatory bodies in the United Kingdom and worldwide. The BS EN 1060-4:2004 standard was developed under a mandate given the European Committee for Standardization (CEN) by the European Commission and the European Free Trade Association to provide a means of conforming to the Essentials Requirements of the New Approach Directive 93/42/EC Medical Devices.~~[4] ~~In many areas in Europe, satisfaction of the BS EN 1060-4:2004 is requisite to determining the clinical suitability of NIBP devices for use in routine clinical practices. Furthermore, satisfaction of this standard may also be a first step to achieving 'Grade A' rating according to the British Hypertension Society (BHS) in the United Kingdom.~~[5] ~~Thus, it is critical that devices used in both America and Europe comply with both ISO 81060-2:2013 and BS EN 1060-4:2004 guidelines.~~	Typographical correction. Removed background relating to the requirement to adhere to all data collection elements of BS EN 106004:2004, due to incompatibility of aspects of this standard with ISO 81060-2-2013.
13	Section 2.3. Device Risk Analysis	Participation in this study has no direct benefit to participants; however, participants may benefit from more reliable assessment of blood pressure readings during their procedure due to the use of multiple devices and multiple recordings for blood pressure measurement. Participation in this study will not alter the prescribed cardiac catheterization procedure recommended by the patient's physician, though the duration of the procedure may be slightly increased by a period of time not expected to exceed 20 minutes (1-2 minutes per NIBP measurement). For neonatal patients, risk will be minimized by the inclusion of neonate patients that are being catheterized using routine umbilical line catheterization, which has been shown to have a minimal complication rate even during longer procedures when performed by experienced physicians. [7] Neonatal patients may participate for up to three days, taking ~~a~~as few determinations as necessary to accomplish research objectives each day ~~at the~~under the supervision of a medically qualified investigator ~~discretion~~.	Clarified neonatal risk statement.

Item	Section	Revision or Clarification	Justification
14	Section 4.1. Hypothesis	This is a study conducted to satisfy ~~both~~ the ISO 81060-2:2013 ~~and BS EN 1060-4:2004~~ standard~~s~~ for two NIBP devices (PSM-Datex-Ohmeda and PDM-SuperSTAT) and, as such, does not require a statistical hypothesis. The Pass/Fail criteria for this study are set forth in **Section 9.5 - Pass/Fail Criteria of the Study**.	Removed the requirement to adhere to all data collection elements of BS EN 106004:2004, due to incompatibility of aspects of this standard with ISO 81060-2-2013.
15	Section 4.2.1. Primary Objective:	The primary objective of the study is to determine if the PSM-Datex-Ohmeda and PDM-SuperSTAT NIBP measurement devices provide accurate blood pressure measurements in all indicated patient populations (neonates, children, pediatrics, adolescents and adults, and special populations) according to the definitions set forth by ISO 81060-2:2013~~ and BS EN 1060-4:2004~~ .	Removed the requirement to adhere to all data collection elements of BS EN 106004:2004, due to incompatibility of aspects of this standard with ISO 81060-2-2013.
16	Section 4.3.1. Primary endpoints:	For NIBP only: • Accuracy, determined according to ISO 81060-2:2013 ~~and BS EN 1060-4:2004~~	Removed the requirement to adhere to all data collection elements of BS EN 106004:2004, due to incompatibility of aspects of this standard with ISO 81060-2-2013. Corrected typographical error.
17	Section 6.1.1. Number of Subjects	The total minimum enrollment for both algorithm arms is ~~100~~ 83 total evaluable patients. Non-evaluable patients, as determined by the Sponsor per the ISO 81060-2:2013 ~~and BS EN 1060-4:2004~~ standard~~s~~, will not be counted towards the minimum quota requirements. Enrollment will continue until the minimum evaluable patient enrollment ~~are met~~ and ~~the patient~~ distribution requirements of the ~~both~~ ISO 81060-2:2013 ~~and BS EN 1060-4:2004~~ standard~~s~~ are met. Total patient enrollment in both arms will not exceed ~~140~~ 200 patients. The two NIBP measurement arms in this study are: 1. **PDM-SuperSTAT Arm** (minimum of ~~55~~ 45 evaluable patients): GE DINAMAP® SuperSTAT algorithm delivered by the PDM acquisition module connected to the CARESCAPE Monitor B650 2. **PSM-Datex-Ohmeda Arm** (minimum of ~~45~~ 38 evaluable patients): Datex-Ohmeda delivered by the PSM acquisition module connected to the CARESCAPE Monitor B650	Adjusted number of subjects to reflect necessary population to satisfy the ISO 81060-2-2013 requirement.
18	Section 6.1.2. Summary of Patient Stratification Requirements	**PDM-SuperSTAT Arm** Minimum of ~~55~~ 45 evaluable subjects, including: • ~~≥20~~ 15 adults and adolescents >12 years old ~~▪ 15 adults ≥50 years old~~ ~~▪ 5 adults ≥18 to <50 years old~~ ~~• ≥5 adolescents (≥12 to <18 years old)~~ • ≥5 pediatric (≥3 to ~~<~~≤12 years old), • ≥7 Atrial Fibrillation Patients ~~(≥18 years old)~~ ~~▪ 4 adults ≥50 years old~~ ~~▪ 3 adults ≥18 to <50 years old~~	Adjusted number of subjects to reflect necessary population to satisfy the ISO 81060-2-2013 requirement.

Item	Section	Revision or Clarification	Justification
		• ≥18 neonates(≤28 days) and infants/children (≥29 days to <3 years old) • ~~≥18 neonates/infants (≥29 days <3 years old)~~ ~~We~~This study intends ~~intend~~ to collect 10 paired measurements (NIBP and IBP) per patient, and will collect a minimum of: • ≥~~370~~ 270 valid blood pressure measurement pairs should be obtained for patients ≥3 years old • ≥~~180~~ 150 valid blood pressure measurement pairs should be obtained for patients <3 years old **PSM-Datex-Ohmeda Arm** Minimum of ~~45~~ 38 evaluable subjects, including: • ≥15 adults and adolescents >12 years old ~~• 15 adults ≥50 years old~~ ~~• 5 adults ≥18 to <50 years old~~ ~~• ≥5 adolescents (≥12 to <18 years old)~~ • ≥5 pediatric (≥3 to ≤~~<~~12 years old), • ≥ ~~15~~ 18 ~~neonates/~~infants/children (<3 years old and weighing >5 kg) This study intends ~~We intend~~ to collect 10 paired measurements (NIBP and IBP) per patient, and will collect a minimum of: • ≥~~300~~ 200 valid blood pressure measurement pairs should be obtained for patients ≥3 years old • ≥150 valid blood pressure measurement pairs should be obtained for patients <3 years old weighing >5 kg (approximately 11 lbs)	
19	Section 6.3.1. Enrollment Strategy for Stratification Groups	Patients will be consecutively enrolled until each stratification quota reaches its minimum quota for enrollment per study arm. When the minimum number of patients is enrolled, enrollment will end on a per-strata basis. When all strata have reached their minimum enrollment targets, additional patients may be consecutively enrolled that meet any stratification criteria in order to reach the target total patient enrollment number described in Section 6.1 – Number of Subjects, and to meet the patient distribution requirement set forth in the ISO 81060-2:2013 ~~and BS EN 1060-4:2004~~ standard~~s~~.	Removed BS EN 106004:2004 requirements.
20	Section 6.3.2 Minimum Patient Numbers and Cuff Sizes	~~Requirements of the BS EN 1060-4:2004 Standard~~ ~~There are no specific cuff size requirements for the BS EN 1060-4:2004 standard. The patient numbers are in accordance with the percentage values required by both standards.~~	Removed BS EN 106004:2004 requirements.
21	Section 6.3.3. Stratification of Adult Patients	**6.3.3 Stratification of Adult Patients ~~(Adult Site)~~** Enrollment of adult patients ~~and~~will be the same in both study arms (PSM-Datex-Ohmeda and PDM-SuperSTAT) except that additional special population patients (chronic atrial fibrillation patients) will be ~~stratified~~included in the PDM-SuperSTAT stratification groups by age and gender ~~(~~, as shown in Table 1~~)~~. ***[Updated Table 1]***	Removed BS EN 106004:2004 requirements and outdated site names.
22	Section 6.3.4. Stratification of Pedeatrics	**6.3.4 Stratification of Pediatric~~, Children, Infant, and Neonatal Patients (*Children's Site*)~~**	Removed BS EN 106004:2004

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		The enrollment of pediatric patients (aged ≥3 AND ≤12 years) will be the same in both study arms (PSM-Datex-Ohmeda and PDM-SuperSTAT), as described in Table 2. ~~The enrollment of adolescent and pediatric patients will be the same in both study arms (PSM-Datex-Ohmeda and PDM-SuperSTAT), as described in Table 2.~~ ~~Enrollment of adolescent (aged ≥12 and ≤18 years) and pediatric (aged ≥3 AND <12 years) will be stratified by age and gender (Table 2).~~ **Table 2** –~~-~~ ~~Adolescent and~~ Pediatric Enrollment Stratification by Age and Gender ***[Revised Table 2]*** *Abbreviations*: M = male; F = female; *n*, number of patients ***Note***: # 30% of population to be male and 30% of population to be female	requirements and outdated site names.
23	Section 6.3.5. Stratification of Children, Infant, and Neonatal Patients	**6.3.5. Stratification of Children, Infant, and Neonatal Patients** The enrollment of children < 3 years of age will be the different in each study arm (PDM-SuperSTAT and PSM-Datex-Ohmeda), as described in Tables 3 and 4, respectively. There will be no stratification by gender. The neonates will not be evaluated by the PSM-Datex-Ohmeda module.~~The enrollment of adolescent and pediatric patients will be the different in each study arm (PDM-SuperSTAT and PSM-Datex-Ohmeda), as described in Tables 3 and 4, respectively.~~ ***[Revised Tables 3 and 4]***	Removed BS EN 106004:2004 requirements and outdated site names.
24	Section 6.3.6. Additional Requirements:	Additional requirements ~~on~~ for patient distribution required by ISO 81060-2:2013 ~~and/or BS EN 1060-4:2004~~ are listed below: ~~***Age >50 years (BS EN 1060-4:2004)***~~ ~~Among adult, adolescent and children over 3 years old, 50%-75% shall be older than 50 years. For PDM-SuperSTAT, at least 19 patients should be older than 50; and for PSM-Datex-Ohmeda, at least 15 patients should be older than 50.~~ ***Limb Size Distribution (ISO 81060-2:2013)*** Among adult, adolescent and children over 3 years old, a minimum of 10% patients will be examined using each of the 5 cuff sizes for children and adults. For PDM-SuperSTAT, at least ~~4~~ 3 patients for each cuff; and for PSM-Datex-Ohmeda, at least ~~3~~ 2 patients for each cuff. ***Blood Pressure Distribution (ISO 81060-2:2013)*** Among adult and adolescent patients, at least 10% patients will be in each of the following four BP groups: • 10% systolic BP ≤100 mmHg • 10% systolic BP ≥160 mmHg • 10% diastolic BP ≤ 70 mmHg • 10% diastolic BP ≥ 85 mmHg ~~• **systolic BP ≤100 mmHg,**~~ ~~• **systolic BP ≥160 mmHg,**~~ ~~• **diastolic BP ≤ 70 mmHg, and**~~ ~~• **diastolic BP ≥ 85 mmHg.**~~ ***Note***: Neonates, infants, and children ~~between 3~~less than ~~and~~ 12 years old are exempt from this requirement. The	Removed BS EN 106004:2004 requirements.

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		mean of the reference invasive systolic and diastolic blood pressure measurements taken during the study will be used in calculation. ~~***Blood Pressure Distribution (BS EN 1060-4:2004)***~~ ~~– Among adult, adolescent, and children over 3 years old, at least 10% patients will be in each of the following four BP groups:~~ ~~• systolic BP ≤110 mmHg,~~ ~~• systolic BP ≥160 mmHg,~~ ~~• diastolic BP ≤ 70 mmHg, and~~ ~~• diastolic BP ≥ 100 mmHg.~~ ~~*Note*: children between 3 and 12 years old are included. The first valid reference invasive systolic and diastolic blood pressure measurement taken during the study will be used in calculations.~~ ~~**Modification of Stratification Quotas to Meet Standard Requirements**~~ ~~The specific quotas in this study have been designed by the Sponsor as a Good Faith representation of calculated values for patient and procedure numbers provided in the ISO 81060-2:2013 and BS EN 1060-4:2004 standards. Due to the complexity of these standards, unexpected changes in patient enrollment, accrual of evaluable data pairs (NIBP and IBP), and device type may require modification to the stratification quota during the course of the study.~~ ~~If the Sponsor conducts a review during this study that indicates a total patient enrollment in any stratification group that meets or exceeds the number required to satisfy the ISO 81060-2:2013 and BS EN 1060-4:2004 standards, the Sponsor may discontinue or continue enrollment in any stratification group. Continuation and discontinuation of enrollment in any stratification group will be made at the discretion of the Sponsor, and the Investigator will be notified by the Sponsor upon such a determination.~~	
25	Section 6.5. Inclusion Criteria	Subjects will be included that: 1. Require non-emergent heart catheterization, if greater than 3 years of age; subjects less than 3 years of age will be assessed using indwelling radial/femoral/pedal or umbilical arterial monitoring lines; ~~2. Require non-emergent heart catheterization (all subjects except neonates);~~ ~~3. Neonates only – umbilical arterial lines that have been placed for route care.~~ 2. Have an upper limb (right OR left side) that fits a cuff size of the device (circumference ranging 3 cm to 40 cm) **OR** have a thigh (right OR left side) that fits a cuff size of the device (circumference ranging 38 to 50 cm);	Revised to safeguard subjects.

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		3. ~~Is~~ Are willing and able to provide blood pressure measurements using both IBP and NIBP; 4. ~~Is~~ Are able and willing to provide written informed consent or ~~has~~have a legally authorized representative that is willing to provide written informed consent with assent from minor patients, if required by IRB policy; ~~5. If informed consent is provided by a legally authorized representative on the patient's behalf, the subject is willing to provide assent to study participation, if capable of providing assent in the opinion of the investigator.~~	
26	Section 6.6. Exclusion Criteria	Subjects will be excluded that: ~~9. Do not meet the stratification quota set forth in Tables 1 and 2;~~ 1. Exhibit signs or symptoms or have a current diagnosis of peripheral vascular disease in either upper AND/OR lower limbs; 2. Have current, uncontrolled circulatory shock; 3. Exhibit injuries, deformities, intravenous lines, or other abnormalities that, in the opinion of the investigator, may prevent proper cuff application or functioning; 4. Are currently pregnant, suspect that they are pregnant, or are currently lactating; 5. ~~Have contraindications to standard BP measurements;~~ 6. Have any other condition that makes the subject unable to tolerate 4 fast flushes (adult, adolescent, or pediatric) or 1 fast flush (neonates and children <3 years of age) for dynamic calibration without posing a risk to the patient's physiological stability. 7. Are under general anesthesia.	Revised to safeguard subjects.
27	Section 7.1.1. Baseline Examination (all sites) (BS EN 1060-4:2004)	**7.1.1 Baseline Examination (all sites) ~~(BS EN 1060-4:2004)~~** For enrolled patients that have provided informed consent the following baseline information will be collected on CRFs after informed consent requirements have been satisfied and before the procedures are performed: 1. Demographics (Ageand Gender) 2. Height and Body Weight 3. Relevant Medical History ~~4. Cardiovascular condition(s)~~ 5. Physiological Condition (Stable/Unstable) 6. Urine pregnancy test, if applicable (females of childbearing potential) 7. Arm or Thigh Circumference (cm) 8. Appropriate Cuff Brand (Critikon® Soft-Cuf or Classic-Cuf) and Size	Removed BS EN 106004:2004 requirements

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		9. Baseline Non-Invasive Blood Pressure (NIBP), consisting of systolic blood pressure (SBP) and diastolic blood pressure (DBP) 10. Location of NIBP Measurement (Arm/Thigh) and measuring circumstance 11. Mean Arterial Pressure (MAP) 12. Current medications 13. Pulse rate	
28	Section 7.1.2. Required Setup Procedures	**7.1.2. Required Setup Procedures** ~~for all Subject Stratifications (all sites)~~	Removed for consistency with subject stratification changes.
29	Section 7.1.3 Patient Procedure and Procedure-Specific Assessments	**7.1.3 Patient Procedure and Procedure-Specific Assessments** ~~**(all sites)**~~ For each patient, the following procedure-specific information will be recorded on CRFs: 1. Model and serial number for the DASH® 4000 2. Model and serial number for CARESCAPE B650 3. Model and serial number for the PSM or PDM acquisition module used 4. Catheter cross-section, length, and trade name 5. Trade name of pressure transduce 6. Site/artery used for IBP measurements ~~7.~~ Monitor filter settings and recording settings, if applicable 8. ~~Measuring circumstance (at rest OR during or immediately following exercise; if at rest, record whether the patient is sitting or lying down)~~ 9. Identification of the observer making the recordings (name and position) 10. Details of any special circumstances during measurement 11. Pulse rate at the start of device evaluations 12. Time and date of last manometer calibration **ECG Placement and Setup** Three ECG sensors will be placed on patients aged ≥29 days, with leads on the left and right arm and left leg connected to the DASH® 4000. No ECG will be captured for subjects aged <29 days. ~~Three ECG sensors will be placed on the patient, with leads on the left and right arm and left leg connected to the DASH® 4000.~~	Removed for consistency with subject stratification changes and made changes to safeguard subjects.
30	Section 7.1.4. Arterial Catheterization	Dynamic calibration will be performed in the beginning of each procedure according to the "Dynamic Calibration" section of the *Device Set-Up Manual* provided by the Sponsor. A maximum of 1 flush is to be conducted for patients aged <3 years. A maximum of 4 flushes may be conducted for patients aged ≥3 years. During calibration, values will be recorded for: 4. Number of fast flushes 5. Damping coefficient 6. Natural frequency ~~Dynamic calibration will be performed throughout each procedure as IBP records continuously rather than at discreet intervals like NIBP~~	Added safeguards for subjects.

Item	Section	Revision or Clarification	Justification
		~~("Dynamic Calibration" section of the *Device Set-Up Manual* provided by the Sponsor).~~	
31	Section 7.1.5. Blood Pressure Assessments	NIBP will be measured using the CARESCAPE Monitor B650 patient monitor equipped with an acquisition module (either PDM-SuperSTAT or PSM-Datex-Ohmeda, determined by study arm). IBP will be measured using the DASH® 4000 plus DC-COLLECTOR and DC-EDIT software. During the blood pressure assessments, values will be recorded for: 6. Treatment Arm 7. Time of first and last blood pressure measurement 8. Systolic, Diastolic, Mean, Test Duration 9. If the prescribed wait time was taken between tests 10. Any measurements with no determination **Table 5 –** Number of Blood Pressure Assessments Population / Maximum Number of Blo Pressure Determinatio ≥ 3 years old / 15 < 3 years old to > 29 days old / 15 ‹ 29 days old / 5-10 ~~NIBP will be measured up to 15 times for each patient using the CARESCAPE Monitor B650 patient monitor equipped with an acquisition module (either PDM-SuperSTAT or PSM-Datex-Ohmeda, determined by study arm) to obtain a minimum of 5, maximum of 10 valid NIBPs per patient. For adults, adolescents and children older than 3, all valid NIBPs should be taken within 60 minutes; and for neonates, infants and children under 3 years, at least 3 valid NIBPs should be taken within 60 minutes. IBP will be measured using the DASH® 4000 plus DC-COLLECTOR and DC-EDIT software.~~ Both NIBP and IBP assessments will be conducted simultaneously, with IBP data collected on the DCS and NIBP data recorded by hand onto a paper Case Report Form (CRF). If necessary, assistance will be provided by other study staff to ensure that accurate and simultaneous blood pressure data is recorded. IBP data will be continuously collected throughout the study and NIBP data will be recorded according to the following procedure: 7. Use the patient monitor equipped with either PDM-SuperSTAT or PSM-Datex-Ohmeda according to the patient's study arm to determine the patient's blood pressure. ~~8. Remove the cuff from the patient.~~ 9. Clear the patient monitor memory of the previous determination and wait at least 3 min *Note*: For the CARESCAPE Monitor B650, the memory can only be cleared by discharging the case (with acquisition module attached) 10. Have the observers using the reference IBP monitoring equipment (DASH® 4000) and the	Added safeguards for subjects.

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		NIBP monitoring equipment (CARESCAPE Monitor B650 with either PSM or PDM) simultaneously record and determine the patient's blood pressure, as follows. ~~a. Select the appropriate patient monitors based on study arm~~ ~~b. Put on correctly sized cuffs~~ c. Start continuous collection on the IBP DCS system at the same time as recording of NIBP begins d. Collect each NIBP measurement from the CARESCAPE Monitor B650 e. Discharge the patient monitor to clear the memory of the previous NIBP determination after each determination. *Note*: Because the discharge will erase the data from the previous NIBP measurement, record all necessary values before discharging the 11. Wait ~~at least 60 s~~the following amount of time (Table 6) between determinations or, for neonatal patients, 3 min. **Table 6 –** Minimum Time between Determinations **[Added Table 6]** Population Age / Minimum Wait Period ≥ 3 years / ≥60 seconds > 29 days old to 3 years / ≥60 seconds ‹ 29 days / ≥3 minutes (variable)* *Wait period is based on the investigator's discretion of patient health status of the patient. It is, however, suggested that a 20 minute wait period may be appropriate between 3 determinations obtained within a 2 hr window OR 4 determinations obtained within a 3 hr window. 6. Repeat steps 4, 5, and 6 until ~~10~~ the target number of recordings and determinations have been performed. In the event that any blood pressure determination is not successful, the procedure may be repeated to achieve ~~10~~ the target number of successful blood pressure determinations. No more than ~~15~~ the maximal number of total blood pressure determinations as specified ~~above~~in Table 5 will be performed on any patient. ***Neonates Only***: Neonatal patients may participate for up to three days, taking an average of 3-4 determinations each day at the investigator's discretion.	
32	Section 7.3. Withdrawal and Discontinuation Criteria	If the Sponsor conducts a review during this study that indicates a total patient enrollment in any stratification group that meets or exceeds the number required to satisfy the ISO 81060-2:2013 ~~and BS EN 1060-4:2004~~ standard~~s~~s, the Sponsor may discontinue or continue enrollment in any stratification group. Continuation and discontinuation of enrollment in any stratification group will be made	Removed BS EN 106004:2004 requirements

Item	Section	Revision or Clarification	Justification
		at the discretion of the Sponsor, and the Investigator will be notified by the Sponsor upon such a determination.	
33	Section 9.1.1. Analysis Populations	Separate analysis will be performed for PSM-Datex-Ohmeda and the PDM-SuperSTAT arms per requirements of the ISO 81060-2:2013 ~~and BS EN 1060-4:2004~~ standard~~s respectively~~. Analyses will be conducted for the following ~~-~~populations: • adults, adolescents, and pediatric patients, who are >= 3 years old and atrial fibrillation patients (PDM-SuperSTAT arm) • adults, adolescents and pediatric patients, who are ≥3 years old (PSM-Datex-Ohmeda arms) • neonates and children <3 years of age (PDM-SuperSTAT arm) • children <3 years of age and weigh over 5 kg (11 lbs) (PSM-Datex-Ohmeda arm) If deemed necessary by the Sponsor, when the measurement accuracy is compromised in a sub-population, affected sub-populations may be excluded from analysis ~~adults, adolescents, and pediatric patients (both arms),~~ ~~neonates and children <3 years of age (PDM-SuperSTAT arm),~~ ~~children <3 years of age and weigh over 5 kg (11 lbs) (PSM-Datex-Ohmeda arm),~~ ~~adults, adolescents, and pediatric patients and atrial fibrillationpatients (PDM-SuperSTAT arm)~~	Removed BS EN 106004:2004 requirements
34	Section 9.2 Determining Reference Invasive Blood Pressure Per ISO 81060-2:2013	**9.2 Determining Reference Invasive Blood Pressure Per ISO 81060-2:2013** First, the mean and the standard deviation of the invasive blood pressures derived from the IBP wave recordings during a NIBP determination will be calculated; and the range of reference invasive blood pressure will be determined as mean ±1 standard deviation (SD) of the IBPs. The same method will be used for both systolic and diastolic blood pressures. Calculation of reference IBP from IBP wave recordings is not part of the statistical analysis. All data from a subject will be excluded for analysis, when the range of invasive systolic BP is wider than 20 mmHg or when the range of invasive diastolic BP is wider than 12 mmHg. ~~Per BS EN 1060-4:2004~~ ~~The range of reference invasive blood pressure will be determined using the minimum and maximum of IBPs derived from the IBP wave recordings during NIBP determinations. The same method will be used for both systolic and diastolic blood pressures. Calculation of reference IBP from IBP wave recordings is not part of the statistical analysis. All data from a patient with less than 5 NIBP determinations will be excluded for analysis.~~	Removed BS EN 106004:2004 requirements
35	Section 9.2.9.3. Analysis of Subject Characteristics	The following subject characteristics data will be summarized using descriptive statistics if applicable per standard requirements for each analysis population by study arm. Continuous variables will be described using mean, standard deviation, median, minimum and maximum. Categorical variables will be described using count and percentage.	Removed BS EN 106004:2004 requirements

Item	Section	Revision or Clarification	Justification
		• Number of Adult/adolescents/children/atrial fibrillation patients • Number of patients <1000g, 1000-2000g,>2000g in weight • Number of patients <29 days, ≧~~≥~~29 days and < 1 year of age, ≧~~≥~~ 1 year and < 3 years of age, ≧~~≥~~ 3 year and < 12 years of age • Number of patients over 5 kg (11 lbs) and meet one of the following: ⩾29 days and < 1 year of age~~, ⩾ 1 year and < 2 years of age~~, ≧~~≥~~ 2 year and < 3 years of age • Gender • Height and weight • Arm Size • Age • ~~Number of patients older than 50 years~~ • Adult and adolescent subjects with mean invasive systolic blood pressure ⩾ 160 mmHg • Adult and adolescent subjects with mean invasive systolic blood pressure ⩽ 100 mmHg • Adult and adolescent subjects with mean invasive diastolic blood pressure ≧~~≥~~85 mmHg • Adult and adolescent subjects with mean invasive diastolic blood pressure ≦~~≤~~ 70 mmHg • ~~Adults, adolescents and children over 3 years old with 1st invasive systolic blood pressure ⩾ 160 mmHg~~ ~~Adults, adolescents and children over 3 years old with 1st invasive systolic blood pressure ⩽ 110 mmHg~~ ~~Adults, adolescents and children over 3 years old with 1st invasive diastolic blood pressure ⩾ 100 mmHg~~ • ~~Adults, adolescents and children over 3 years old with 1st invasive diastolic blood pressure ⩽ 70 mmHg~~ • Number of subjects tested on each cuff size • Arterial sites where IBP was taken • Heart rate	
36	Section 9.3.1. Data Exclusion	The following NIBP data will be excluded from analysis: • NIBP data from a subject if the range of reference systolic blood pressure is more than 20mmHg or the range of reference diastolic blood pressure is more than 12 mm Hg, per ISO 81060-2:2013 standard; • ~~NIBP data from a subject if the number of NIBPs taken is less than 5, per EN 1060-4:2004 standard;~~ • Measurements beyond 10 valid measurements for each subject; • Isolated premature ventricular contractions (PVC) will be addressed by removing the pressure associated with the PVC and the following compensatory beat. The PVC will be	Removed BS EN 106004:2004 requirements

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		identified through analysis of the ECG waveform associated with the PVC and pulses. This is done during calculating IBPs from the IBP wave form, not in the statistical analysis.	
37	Section 9.5. Handling of Missing Data	Every effort will be made to obtain complete data. Data analysis will be based on collected data. Missing data will not be imputed using any imputation methods. Missing data is not expected for blood pressure values because up to 15 blood pressure determination procedures will be allowed, if necessary, to ~~achieve~~ obtain 10 blood pressure recordings, thus minimizing the likelihood of missing data in IBP and NIBP blood pressure determination pairs. Any pair of blood pressure measurements with a missing value will be excluded from analysis.	Grammatical correction.
38	Section 9.6.Pass/Fail Criteria of the Study	The study will be considered to pass if a sufficient data set is collected to satisfy the requirements of ISO 81060-2:2013~~ and BS EN 1060-4:2004~~.	Removed BS EN 106004:2004 requirements
39	Section 11.4. Management of Serious Adverse Event and Unanticipated Adverse Device Effect Reporting	**Sponsor contact for SAEs and/or UADEs:** Ron Von Jako, MD *Telephone*: +1 781 262 5579 ~~*Mobile: +1 617 669 3200*~~ *Email*: Ron.VonJako@med.ge.com ~~Olli Vaisanen, MD~~ ~~Telephone: +358 40 652 9662~~ ~~olli.vaisanen@ge.com~~ Fax: 800-888-3983 E-mail: SAE@ge.com	Updated Medical Director name and contact information.
40	Section 13.1. Regulatory Authority Approval Requirements (Global)	There are no applicable global regulatory authority approval requirements; however, this study will be conducted in accordance with ISO 81060-2:2013 ~~and BS EN 1060-4:2004~~ standard requirements.	Removed BS EN 106004:2004 requirements
41	Section 13.4. Informed Consent and Privacy Requirements	Informed consent will be documented in the source record of each subject. The Investigator or designee will consent the subject per regulatory guidelines which include the subject has ample time to review the ICF and have all questions answered to their satisfaction; the subject may take the ICF home to review with family members or others prior to agreeing to participate in the study; upon agreeing to participate in the study, the subject signs and dates the document ~~while initialing each page~~, and the person who consented the subject signs and dates the document.	Clarified that initials are not required on each page per the Sponsor's current global template.
42	Section 18. ADDITIONAL COUNTRY-SPECIFIC REGULATORY REQUIREMENTS	The study will be conducted in accordance with all requirements of ISO 81060-2:2013~~ and BS EN 1060-4:2004.~~. This study will be conducted in compliance with ~~BS EN ISO 14155:2011~~ Good Clinical Practice, per international standards. ~~The results of~~	Removed BS EN 106004:2004 requirements
43	References	***[Removed references 4 and 5 related to deleted sections]***	Removed BS EN 106004:2004 requirements

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44	Footer	DOC1466558	Added Sponsor MWS DOC to footer.
45	throughout	***[Updated bullets, section heading, page numbering, dates, and versions throughout]***	Standard documentation and style practices.

APPENDIX C: AMENDMENT TO PROTOCOL VERSION 3.0

Purpose: This amendment document describes in detail the changes made to the study protocol to make procedural clarifications and to add additional safeguards for neonate populations beyond the scope of the original procedure. Additionally, this amendment clarifies discrepancies and simplifies presentation of the risks associated with incidental medications and/or general anesthesia administration during study procedures where these concomitant medications are clinically indicated outside of the study.

The following amendments were made to version 3.0 to produce version 4.0. Point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment for the previous version.

Item	Section	Revision or Clarification	Justification
46	Study Synopsis	**Study Title**: Measurement of NonInvasive Blood Pressure with DINAMAP SuperSTAT and Datex-Ohmeda with Intra-arterial Blood Pressure in Neonates through Adults and Special Populations (MISSION Trial) **Study Number:** 123.04-2013-GES-0008 **Research Type:** Clinical (human) ☒ Pre-Clinical (animal) ☐ External Bench ☐ ~~**Study Number:** 123.04-2013-GES-0008~~ ~~**Research Type:**~~ ~~Clinical (human) ☒~~ ~~Pre-Clinical (animal) ☐~~ ~~External Bench ☐~~	Adjusted formatting for clarity and spacing (no change in content).
47	Study Synopsis	Jeffrey Garland, MD Director of Perinatal Research *Wheaton Franciscan Healthcare – St. Joseph's* **Address:** 5000 West Chambers Street Milwaukee, WI 53210 **Telephone:** 414- 447-2663 **E-mail:** jsgarland@hotmail.com Russel Hirsch, MD Associate Professor of Pediatrics Director, Cardiac Catheterization Laboratory Director, Pulmonary Hypertension Service *Cincinnati Children's Hospital Medical Center (CCHMC)* **Address:** 3333 Burnet Avenue Cincinnati, OH 45229 **Telephone:** 515-636-7072 **E-mail:** Russel.hirsch@cchmc.org	Updated Sponsor Medical Monitor identity and contact information.

Item	Section	Revision or Clarification	Justification
		Medical Monitor Name: Helena Haukilehto, MD ~~Ron Von Jako, MD~~ **Address:** Kuortaneenkatu 2, Helsinki, 00510 FI ~~301 Ballardvale St., Suite 4 Wilmington, MA 01887-4405~~ **Telephone:** +358-103943609~~+1 781 262 5579~~ **E-mail:** ~~Ron.VonJako@med.ge.com~~ helena.haukilehto@ge.com	
48	Section: 2.1. - Literature Review	Accurate blood pressure measurement is essential to providing optimal care in hospitals and other clinical settings, and non-invasive blood pressure (NIBP) has overwhelmingly become the contemporary clinical standard for blood pressure measurement. [11] Accurate blood pressure (BP) measurement is dependent on a trained observer using validated, calibrated, and properly maintained equipment, which has led to increasing emphasis on adherence of commercial NIBP devices to validated standards for accuracy and reliability. [2 2] While previous studies ~~having~~ have shown that arterial waveforms can be accurately and reproducibly reconstructed using oscillometric algorithms, such as the DINAMAP® SUPERSTAT and Datex-Ohmeda GE algorithms studied in this trial, the accuracy of these NIBP measurement algorithms has also been shown to have high variability in patients with variant age and cardiac disease status. [3] Thus, there is a need to evaluate these algorithms against a validated clinical standard applicable to commercial sphygmomanometers. .... **Oscillometric NIBP Measurement** The basic physiological principles that underlie NIBP technologies were first documented in the mid-1970s, and significant improvements have since been made in the algorithms that drive NIBP assessment. [6] In the past decade, there has been increasing theoretical discourse regarding the optimal methods for evaluation of arterial mechanical properties and blood pressure pulse using noninvasive oscillometric maximum amplitude algorithm (MAA) estimates of the mean blood pressure obtained with air-filled occlusive cuffs. [7] These data, once collected, can be mathematically extrapolated from experimental IBP measurements and waveform simulations and then recorded as exponential models. Most recently, automatic NIBP measurement systems have come to market that use highly specialized software algorithms to account for cuff pressure oscillations caused by the peripheral flow of ~~blow~~ blood either as discrete intervals or areas under a curve, allowing greater accuracy to be achieved using NIBP monitoring methods. [8] As a result, modern NIBP algorithms are generally more accurate than their predecessors. [7]	Corrected typographical error.

Item	Section	Revision or Clarification	Justification
49	Section 2.2. - Pre-Clinical (animal) Trials and Previous Clinical (human) Experience	Previous study has indicated that the GE DINAMAP® SuperSTAT algorithm on the GE CARESCAPE Patient Monitor Series or DASH® Monitor Series is accurate in adult, children, and neonate patients, including hypotensive and hypertensive patients. [12]	Added upper limit for hypertensive patients for clarity and consistency, as already specified in subsequent document sections.
50	Section 2.3. - Device Risk Analysis	Participation in this study has no direct benefit to participants; however, participants may benefit from more reliable assessment of blood pressure readings during their procedure due to the use of multiple devices and multiple recordings for blood pressure measurement. ~~Participation in this study will not alter the prescribed cardiac catheterization procedure recommended by the patient's physician, though the duration of the procedure may be slightly increased by a period of time not expected to exceed 20 minutes (1-2 minutes per NIBP measurement). For neonatal patients, risk will be minimized by the inclusion of neonate patients that are being catheterized using routine umbilical line catheterization, which has been shown to have a minimal complication rate even during longer procedures when performed by experienced physicians.~~ [5] ~~Neonatal patients may participate for up to three days, taking as few determinations as necessary to accomplish research objectives each day under the supervision of a medically qualified investigator.~~ The NIBP device does not pose additional risks to patients, but there are risks associated with the additional IBP comparator procedures above the required clinical care for participating subjects. Use of existing indwelling lines in very young patients is designed to minimize additional disruption of care in pediatric patients.	Clarifications to pediatric risk.
51	Section 2.3. - Device Risk Analysis	2.3.1 Risk Analysis for Subjects with Indwelling Lines (≤29 days of age) Eligible subjects aged 29 days or less will be recruited only if they currently have, or are scheduled to have, an indwelling femoral or umbilical arterial monitoring line placed, which has been shown to have a minimal complication rate even during longer procedures when performed by experienced physicians. [5]. For these subjects, NIBP measurements will be taken in a minimally disruptive manner in these patients in order to minimize possible interruption in their care. No additional lines will be placed for study purposes. These patients may participate for up to three days, taking as few determinations as necessary to accomplish research objectives each day under the supervision of a medically qualified investigator. There is not expected to be a significant risk to subjects based on placement of measurement devices in this study. 2.3.2 Risk Analysis for Subjects undergoing Non-Emergent Aortic Catheterization (aged >29 days to adult) Patients aged 29 days or older having prescribed non-emergent aortic catheterization procedures will be enrolled. Typical catheterization procedures in pediatric patients involve the use of general anesthesia for the duration of the clinically indicated procedure. The risks associated with general anesthesia are well documented and are widely considered safe when prudently administered. [15, 16, 17] Due to study participation, the duration of general anesthesia may be slightly	Additional clarifications by population group are added for clarity.

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		increased by a period of about 25 minutes (1-2 minutes for each study NIBP measurement), after which no further research procedures will be performed. General anesthesia is widely recognized as a neuromodulator with potential neurotoxic effects; [18, 19, 20, 21, 22, 23] however, it is widely believed that prudent use of general anesthesia in pediatric patients does not pose significant acute or chronic risks to patients at routine clinical dosages and non-repeating administrations. [18, 24, 25] As used in this study, the devices and study procedures are not expected to pose significant risks to participating subjects beyond those of their clinically indicated catheterization procedure. 2.3.3 General Controls and Risk Mitigations (all subjects) No medicinal agents, including anesthesia and sedatives, are specifically required by the study; however, being in the study will not prevent subjects from receiving medications that are otherwise prescribed for their procedure. Extension of administration of general anesthesia consisting of approximately 25 minutes is foreseeable. Because repeat anesthesia administration has been identified as a central risk factor, particularly amongst pediatric subjects, [24] the study will not enroll any subject aged greater than 29 days but less than 12 years of age that has recently received anesthesia outside of the study within the last 3 months. Additionally, no subject will be allowed to participate more than once to mitigate any possible risks associated with repeat anesthesia administrations.	
52	Section 3.1.1.1 - Patient Data Module (PDM) with DINAMAP® SuperSTAT Algorithm (PDM-SUPSERSTAT)	~~This is accomplished through the use~~Use of various signal quality measures~~, which~~ is used to reduce the impact of noise	Typographic correction.
53	Section 3.3. - Risk Category/Rationale (US Only)	The CARESCAPE Monitor B650, acquisition modules (PDM and PSM), and peripheral cuffs and hoses used in this study are cleared for commercial use and will be used as intended in their labeling. All commercial devices are considered to be IDE Exempt per 21 CFR 812.2(c)(2). The DASH® 4000 is a commercial device; however, when equipped with the GxP validated non-commercial DC-EDIT and DC-COLLECTOR tools for data output it is to be used for research purposes only. DC-EDIT and DC-COLLECTOR tools are not expected to impact the function of the DASH® 4000 device. When equipped with DC-EDIT and DC-COLLECTOR, the DASH® 4000 ~~is~~and algorithms investigated in this research study are considered a non-significant risk device per the 21 CFR 812.3 definition:	Clarification of original text.
54	Section 4.1. - Hypothesis	This is a study conducted to satisfy the ISO 81060-2:2013 standard for two NIBP devices (PSM-Datex-Ohmeda and PDM-SuperSTAT) and, as such, does not require a statistical hypothesis. The Pass/Fail criteria ~~for this study~~ are ~~set forth~~described in **Section 9.5 - Pass/Fail Criteria**.	Updated Section reference.
55	Section 4.3.1. - Primary endpoints:	~~Per patient, NIBP and IBP endpoints will be collected for:~~ ~~• Systolic BP (mmHg)~~ ~~• Diastolic BP (mmHg)~~ ~~• NIBP and IBP Mean Arterial Blood Pressure (MAP)~~	Adjusted formatting of primary endpoint for pagination purposes (no change to content).

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		~~For NIBP only:~~ ~~• Accuracy, determined according to ISO 81060-2:2013~~ Per patient, NIBP and IBP endpoints will be collected for: • Systolic BP (mmHg) • Diastolic BP (mmHg) • NIBP and IBP Mean Arterial Blood Pressure (MAP) Per patient, for NIBP only: • Accuracy, determined according to ISO 81060-2:2013	
56	Section 5.1. - Type of Research Study	Open-Label ☒ *Patients or patients' legal representatives and investigators will have knowledge of all treatments* Blinded ☐ Double-Blinded ☐ Single-site ☐ Multi-site ☒ *The study will be conducted at ~~two (2~~three (3) sites* Randomization Procedure: Not randomized ☒ *Patients will consecutively assigned to PDM-SuperSTAT or PSM-Datex-Ohmeda groups based on demographics-based stratification ~~quotas, starting with the PDM-SuperSTAT group~~* Single arm ☐ Comparator ☐ Parallel ☐ Crossover ☒ *~~Patient~~Patients will receive NIBP and IBP assessments, with NIBP type (PDM-SuperSTAT or PSM-Datex-Ohmeda) determined by ~~treatment~~study arm. Each patient will act as their own control for ~~the purpose of~~ NIBP vs. IBP comparisons* Prospective ☒ *Patients are enrolled and then undergo study procedures.*	Updated to reflect additional site.
57	Section 6 – Study Subjects	6.1 Subject Population~~Number of Subjects~~ The study will include neonates with indwelling femoral or umbilical arterial monitoring lines and infant, pediatric, adolescent, and adult	Removed tables and captions for Tables 1-4 and replaced with a single table and brief summary

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		subjects requiring non-emergent surgery involving aortic catheterization (including chronic atrial fibrillation patients among adults and adolescents). ~~The total minimum enrollment for both algorithm arms is 83 total evaluable patients. Non-evaluable patients, as determined by the Sponsor per the ISO 81060-2:2013 standard, will not be counted towards the minimum quota requirements. Enrollment will continue until the minimum evaluable patient enrollment and distribution requirements of the ISO 81060-2:2013 standard are met. Total patient enrollment in both arms will not exceed 200 patients.~~ ~~The two NIBP measurement arms in this study are:~~ ~~**PDM-SuperSTAT Arm** (minimum of 45 evaluable patients): GE DINAMAP® SuperSTAT algorithm delivered by the PDM acquisition module connected to the CARESCAPE Monitor B650~~ ~~**PSM-Datex-Ohmeda Arm** (minimum of 38 evaluable patients): Datex-Ohmeda delivered by the PSM acquisition module connected to the CARESCAPE Monitor B650~~ ~~Each patient may only be included in one study arm. No patients will be treated with more than one NIBP device. These stratification quotas are fully described along with additional standard-specific requirements in Tables 1 to 4.~~ 6.12 Summary of Patient Stratification Requirements ~~Patient enrollment is summarized in the following sections by study arm; however, full details on patient enrollment requirements, including gender and health condition requirements, are found in Tables 1 to 4.~~ ~~PDM-SuperSTAT Arm~~ ~~Minimum of 45 evaluable subjects, including:~~ ~~This study intends to c≥15 adults and adolescents >12 years old~~ ~~≥5 pediatric (≥3 to ≤12 years old),~~ ~~≥7 Atrial Fibrillation Patients~~ ~~≥18 neonates(≤28 days) and infants/children (≥29 days to <3 years old)~~ ~~ollect 10 paired measurements (NIBP and IBP) per patient, and will collect a minimum of:~~ ~~≥270 valid blood pressure measurement pairs should be obtained for patients ≥3 years old~~ ~~≥150 valid blood pressure measurement pairs should be obtained for patients <3 years old~~ ~~PSM-Datex-Ohmeda Arm~~ ~~Minimum of 38 evaluable subjects, including:~~ ~~≥15 adults and adolescents >12 years old~~ ~~≥5 pediatric (≥3 to ≤12 years old),~~ ~~≥ 18 infants/children (<3 years old and weighing >5 kg)~~ ~~This study intends to collect 10 paired measurements (NIBP and IBP) per patient, and will collect a minimum of:~~ ~~≥200 valid blood pressure measurement pairs should be obtained for patients ≥3 years old~~ ~~≥150 valid blood pressure measurement pairs should be obtained for patients <3 years old weighing >5 kg (approximately 11 lbs)~~	for clarity. No change in intended target population. Section 6.2 and Table 1 replace all prior text.

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		Adolescent and/or adult, pediatric, and neonatal patients and special patients with chronic atrial fibrillation that require prescribed heart catheterization will be enrolled according to the inclusion/exclusion and stratification criteria on a quota block basis. For the purposes of this study, chronic atrial fibrillation will be defined as persistent or sustained atrial fibrillation which does not stop spontaneously. 6.3.1 Enrollment Strategy for Stratification Groups ~~The stratification quotas set forth in the following sections should be individually met for both the PSM-Datex-Ohmeda and PDM-SuperSTAT study arms.~~ ~~Patients will be consecutively enrolled until each stratification quota reaches its minimum quota for enrollment per study arm. When the minimum number of patients is enrolled, enrollment will end on a per-strata basis. When all strata have reached their minimum enrollment targets, additional patients may be consecutively enrolled that meet any stratification criteria in order to reach the target total patient enrollment number described in Section 6.1 – Number of Subjects, and to meet the patient distribution requirement set forth in the ISO 81060-2:2013 standard.~~ 6.3.1 Minimum Patient Numbers and Cuff Sizes ~~Both the PDM-SuperSTAT and PSM-Datex-Ohmeda arms are required to individually fulfill the requirements of ISO 81060-2:2013, including that the minimum number of patients is a function of the number of available cuff sizes, according to the equation for the percentage of total evaluable patients. In this study, a total of 6 (5 arm cuffs including on for infants and 1 thigh cuff) GE Critikon SOFT-CUF® occlusive blood pressure cuff sizes will be investigated in infants through adults and 5 GE Critikon CLASSIC-CUF® occlusive blood pressure cuff sizes will be investigated in neonates. Per ISO81060-2:2013, for a sphygmomanometer intended for use with multiple cuff sizes, at least $\frac{1}{2\times n}$ of the subjects shall be tested with each cuff size, where *n* is the number of cuff sizes; and neonates, infants and children <3 years of age are exempt from this requirement. Thus, *n* equals 5 for this study for patients ≥3 years of age, and each cuff size should be tested in at least 10% of those patients.~~ ~~Based on this requirement and additional ISO 81060-2:2013 guidelines for patient characteristics by demographic group, the minimum patient requirements for this study are described in detail in Tables 1-4.~~ 6.3.3 Stratification of Adult Patients ~~Enrollment of adult patients will be the same in both study arms (PSM-Datex-Ohmeda and PDM-SuperSTAT) except that additional special population patients (chronic atrial fibrillation patients) will be included in the PDM-SuperSTAT stratification groups by age and gender, as shown in Table 1.~~ ~~**Table 1** – Summary of Adult and Adolescent Patient Enrollment Stratification by Age and Gender~~ ~~*Abbreviations*: M = male; F = female; *n*, number of patients~~	

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		~~***Note***: #30% of population to be male and 30% of population to be female~~ ~~* chronic atrial fibrillation patients will be included only in the PDM-SuperSTAT arm~~ Stratification of Pediatrics ~~The enrollment of pediatric patients (aged ≥3 AND ≤12 years) will be the same in both study arms (PSM-Datex-Ohmeda and PDM-SuperSTAT), as described in Table 2.~~ ~~**Table 2** – Pediatric Enrollment Stratification by Age and Gender~~ ~~*Abbreviations*: M = male; F = female; *n*, number of patients~~ ~~***Note***: #30% of population to be male and 30% of population to be female~~ Stratification of Children, Infant, and Neonatal Patients ~~The enrollment of children < 3 years of age will be the different in each study arm (PDM-SuperSTAT and PSM-Datex-Ohmeda), as described in Tables 3 and 4, respectively. There will be no stratification by gender. The neonates will not be evaluated by the PSM-Datex-Ohmeda module.**3 – PDM-SuperSTAT arm**: Pediatric and Neonatal Enrollment Stratification by Age and Weight~~ ~~* infant and child patients under 3 years of age will be examined using one of 6 GE Critikon SOFT-CUF® occlusive blood pressure cuffs~~ ~~#*Abbreviations*: M = male; F = female; *n*, number of patients~~ ~~**Table 4 – PSM-Datex-Ohemda:** Infants and Children under 3 years of age and weighing >5 kg (approximately 11 lbs)* infant, and children patients under 3 years of age will be examined using one of 6 GE Critikon SOFT-CUF® occlusive blood pressure cuffs~~ ~~Abbreviations: M = male; F = female; n, number of patients# Only patients weighing >5 kg (approximately 11 lbs) can be examined with PSM-Datex-Ohemda under the current FDA-approved labeling~~ ~~**Additional Requirements:**~~ ~~Additional requirements for patient distribution required by ISO 81060-2:2013 are listed below:~~ ~~Limb Size Distribution (ISO 81060-2:2013)~~ ~~Among adult, adolescent and children over 3 years old, a minimum of 10% patients will be examined using each of the 5 cuff sizes for children and adults. Enrollments for PDM-SuperSTAT will include at least 3 patients for each cuff; and enrollments for PSM-Datex-Ohmeda will include at least 2 patients for each cuff.~~ ~~Blood Pressure Distribution (ISO 81060-2:2013)~~ ~~Among adult and adolescent patients, at least 10% patients will be in each of the following four BP groups:~~ ~~– 10% systolic BP ≤100 mmHg~~ ~~– 10% systolic BP ≥160 mmHg~~ ~~– 10% diastolic BP ≤ 70 mmHg~~ ~~– 10% diastolic BP ≥ 85 mmHg~~ ~~Note: Neonates, infants, and children less than 12 years old are exempt from this requirement. The mean of the reference invasive~~	

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		~~systolic and diastolic blood pressure measurements taken during the study will be used in calculation.~~ ~~....~~ 6.3 Number of Subjects The total minimum enrollment for the two study arms is 83 total evaluable patients (maximum of 200 patients), as follows: 3. **PDM-SuperSTAT Arm** (***N***$_{PDM}$): 45 evaluable patients with GE DINAMAP® SuperSTAT algorithm (PDM Module) on CARESCAPE Monitor B650, to achieve a total target of ≥270 BP data pairs in patients ≥3 years old (up to 10 paired measurements per subject) and ≥150 BP data pairs in patients <3 years old (up to 10 total paired measurements per subject, up to one per hour). 4. **PSM-Datex-Ohmeda Arm** (***N***$_{PSM}$): 38 evaluable patients with Datex-Ohmeda algorithm (PSM module) on CARESCAPE Monitor B650, to achieve a total of ≥200 BP data pairs in patients ≥3 years old (up to 10 paired measurements per subject) and ≥150 BP data pairs in patients <3 years old (up to 10 total paired measurements per subject, up to one per hour). 6.3.1 Stratification of Subjects Subject enrollment will be stratified based on prospective criteria to ensure diversity in the population, as described in ISO 81060-2:2013 and set forth in Table 1. Patients will be enrolled concurrently in both arms until all minimum quotas are reached, and thereafter up to the maximum enrollment for the study. Incomplete/non-evaluable datasets, as determined by the Sponsor, will not be considered to satisfy minimum requirements in Table 1. Additionally, multiple cuff sizes will be used, including a minimum of 1/(2 x n) per stratification group , where n is the total within a stratification group able to be tested using the cuff in accordance with its labeling (Table 1) **Table 1** – Summary of Patient Enrollment Stratification by Characteristics [Added Table 1]	
58	Section 6.2 - Protection of Vulnerable Subjects	The information collected in this study could not have been obtained in a less vulnerable, consenting population, necessitating the use of minor patients. Adolescent, pediatric, and neonatal patients will be recruited and enrolled according to all US FDA, ~~ICH E6~~ISO 14155:2011 GCP, and ~~GLP~~other applicable local requirements for protection of vulnerable subjects. Special measures will be taken to protect the rights of these vulnerable study participants and to shield them from undue risk. ~~These patients~~Study procedures for neonate subjects will be modified to minimize interruption in normal medical care, including limiting sampling to once per hour. ~~will be recruited without undue or inappropriate inducements to the parent or legal guardian, and informed consent and assent, when appropriate, will be collected as described in Section 13.4 Informed Consent and Privacy Requirements. For patients capable of providing assent, assent will be required for~~	Updated standards to make corrections and added detail about pediatric patient risk mitigations, and to limit redundancy.

Item	Section	Revision or Clarification	Justification
		~~participation in this study in addition to informed consent from parent(s) or legal guardian(s).Inclusion Criteria~~	
59	Section 6.3. Number of Subjects	The total minimum enrollment for the two study arms is 83 total evaluable patients (maximum of 200 patients), as follows: **1. PDM-SuperSTAT Arm (N_{PDM})**: 45 evaluable patients with GE DINAMAP® SuperSTAT algorithm (PDM Module) on CARESCAPE Monitor B650, to achieve a total target of ≥270 BP data pairs in patients ≥3 years old (up to 10 paired measurements per subject) and ≥150 BP data pairs in patients <3 years old (up to 10 total paired measurements per subject, up to one per hour). 2. **PSM-Datex-Ohmeda Arm (N_{PSM})**: 38 evaluable patients with Datex-Ohmeda algorithm (PSM module) on CARESCAPE Monitor B650, to achieve a total of ≥200 BP data pairs in patients ≥3 years old (up to 10 paired measurements per subject) and ≥150 BP data pairs in patients <3 years old (up to 10 total paired measurements per subject, up to one per hour).	Simplified the presentation of requirements, for clarity to investigators. No change in total enrollment.
60	Section 6.3.1. - Stratification of Subjects	Subject enrollment will be stratified based on prospective criteria to ensure diversity in the population, as described in ISO 81060-2:2013 and set forth in Table 1. Patients will be enrolled concurrently in both arms until all minimum quotas are reached, and thereafter up to the maximum enrollment for the study. Incomplete/non-evaluable datasets, as determined by the Sponsor, will not be considered to satisfy minimum requirements in Table 1. Additionally, multiple cuff sizes will be used, including a minimum of 1/(2 x *n*) per stratification group (except for the children/infants/neonates group) , where *n* is the total within a stratification group able to be tested using the cuff in accordance with its labeling (Table 1). [Revision to Table 1]	Simplified the presentation of requirements, for clarity to investigators. No change in total enrollment. Combined multiple tables in Table 1 to one table for clarity. There are modifications to the presentation of stratification groups designed to aid in enrollment.
61	Section 6.4. - Inclusion Criteria	Subjects will be included that: 1. ~~Require non-emergent heart catheterization, if greater than 3 years of age; subjects less than 3 years of age will be assessed using indwelling radial/femoral/pedal or umbilical arterial monitoring lines;~~ Are aged >29 days requiring clinically indicated non-emergent heart catheterization OR aged ≤29 days with placed or scheduled placement of an indwelling femoral or umbilical arterial monitoring line; 2. side) that fits a cuff size of the device (circumference ranging 3 cm to 40 cm) OR have a thigh (right OR left side) that fits a cuff size of the device (circumference ranging 38 to 50 cm); 3. Are ~~willing and~~expected to be able to provide blood pressure measurements using both IBP and NIBP; 4. Are able and willing to provide written informed consent or have a legally authorized representative willing to provide written informed consent with assent from minor patients, ~~if~~as required by IRB policy.	Revised to clearly indicate requirements for neonates as well as other populations. Notably, special controls for neonatal subjects are in place, including only use of existing indwelling lines.

Item	Section	Revision or Clarification	Justification
62	Section - 6.5 Exclusion Criteria	Subjects will be excluded that: 1. Have previously participated in this study (no subject may participate more than once). 2. Exhibit signs or symptoms or have a current diagnosis of peripheral vascular disease in ~~either~~ upper AND/OR lower limbs; 3. Have current, uncontrolled circulatory shock; 4. Exhibit injuries, deformities, intravenous lines, or other abnormalities that, in the opinion of the investigator, may prevent proper cuff application or functioning; 5. ~~Are~~ For women of child-bearing potential, are currently pregnant, ~~suspect that they are~~ suspected to be pregnant, or are currently lactating; 6. ~~Have any other condition that makes the subject unable to tolerate 4 fast flushes (adult, adolescent, or pediatric) or 1 fast flush (neonates and children <3 years of age) for dynamic calibration without posing a risk to the patient's physiological stability;~~ Have any condition that could interfere with the subjects ability to tolerate the procedure, including having a maximum of 4 fast flushes (adult, adolescent, or pediatric patients aged >29 days) or 1 fast flush (neonates aged <29 days); ~~7. Are under general anesthesia.~~ 7. If aged greater than 29 days but less than 12 years of age, have previously had any clinical or research procedure requiring general anesthesia in the last 3 month period; 8. If aged greater than 29 days but less than 12 years of age, are expected to require more than three (3) total hours of continuous general anesthesia for the scheduled procedure (including clinically necessary anesthesia and anticipated 25 minute extension for study purposes).	Specified than no subject may participate more than once as an additional protection. Clarified that pregnancy testing is only required for potentially child-bearing subjects (not children/neonates). Added additional protections for pediatric and neonatal subjects.
63	Section 6.6. -Screening Subjects for Enrollment	**6.6 Screening Subjects for Enrollment** There are three (3) investigational clinical sites involved in this clinical trial. Patients will be screened for enrollment by the investigational site according to their standard procedure, in accordance with IRB policy. All patients will be consecutively screened and enrolled first into the PDM-SuperSTAT group if eligible. Remaining patients will then be screened for the PSM-Datex-Ohmeda group. All patient enrollment will be conducted according to the stratification criteria and inclusion/exclusion criteria.	Added third site. Removed incomplete description of population, which is presented in greater detail in the added sections above to avoid possible confusion between populations under study.
64	(*moved*) Section 7.1.1. - Baseline Examination (all sites)	**7.2.1. Baseline Examination** ~~For enrolled patients that have provided informed consent the following baseline information will be collected on CRFs after informed consent requirements have been satisfied and before the procedures are performed:~~ ~~1. Demographics (Ageand Gender)~~ ~~2. Height and Body Weight~~ ~~3. Relevant Medical History~~ ~~4. Physiological Condition (Stable/Unstable)~~ ~~5. Urine pregnancy test, if applicable (females of childbearing potential)~~ ~~6. Arm or Thigh Circumference (cm)~~	Moved section to 7.2.1, for clarity.

Item	Section	Revision or Clarification	Justification
		~~7. Appropriate Cuff Brand (Critikon® Soft-Cuf or Classic Cuf) and Size~~ ~~8. Baseline Non-Invasive Blood Pressure (NIBP), consisting of systolic blood pressure (SBP) and diastolic blood pressure (DBP)~~ ~~9. Location of NIBP Measurement (Arm/Thigh) and measuring circumstance~~ ~~10. Mean Arterial Pressure (MAP)~~ ~~11. Current medications~~ ~~12. Pulse rate~~	
65	Section 7.1 - Setup Procedures	**7.1 ~~Required~~ Setup Procedures** **7.1.1 IBP Data Collection on the Data Collection System (DCS)** IBP and ECG data will be collected using a DASH® 4000 patient monitor with the hardware and software tools to connect to a computerized data collection system (DCS) housed on a Sponsor-provided laptop computer. One DCS (laptop) will be connected to the DASH® 4000 via a serial cable from the DASH to the DCS laptop. The investigator is responsible for setting up the DCS for collection of IBP data according to the "Setup of Data Collection" section of the *Device Set-Up Manual* provided by the Sponsor. The control panel for the DASH® 4000 patient monitor is shown in the "DASH® 4000 Control Panel" section of the section of the *Device Set-Up Manual* provided by the Sponsor, which provides details on user setup and operation of the DASH® 4000 patient monitor. The patient procedure for IBP setup is shown in the "IBP Setup" section of the *Device Set-Up Manual* provided by the Sponsor.	Added reference to manual.
66	Section 7.1.2. - NIBP Data Collection	NIBP will be recorded on a commercial CARESCAPE Monitor B650 with most recent commercial software version installed. NIBP data will be transcribed by hand from the display of the CARESCAPE B650 monitor onto the Sponsor-provided Case Report Form (CRF). For patients in the PDM-SuperSTAT arm of the study, NIBP will be measured with a CARESCAPE Monitor B650 equipped with a PDM acquisition module. For patients in the PSM-Datex-Ohmeda arm of the study, NIBP will be measured with a CARESCAPE Monitor B650 equipped with a PSM acquisition module. ~~Each patient may only be included in one study arm. No patients will be treated with more than one NIBP device.~~	Removed duplicate.
67	Section 7.2.2 - Before the Procedure	**7.2.2 Before the Procedure ~~and Procedure-Specific Assessments~~** For each patient, the following procedure-specific information will be recorded on CRFs:	Clarified section title.
68	Section 7.2.2 - Before the Procedure	Static Calibration of the IBP System ~~Static response (ability of the monitoring~~Three ECG sensors will be placed with leads on the left and right arm and left leg connected to the DASH® 4000. Before each patient procedure, static calibration will be conducted for the IPB system to ~~accurately determine constant pressure) and dynamic response (accurately reproducing rapid changes in pressure) affect IBP~~ensure measurement accuracy~~. Therefore, static calibration (~~" according to the "Static Calibration" section of the *Device Set-Up*	Clarified language to improve clinical readability.

Item	Section	Revision or Clarification	Justification
		Manual provided by the Sponsor~~) will be performed prior to each patient procedure.~~ .Each system will be calibrated at 5 static pressures spread across the working range of the device to be tested~~. During calibration, values will be~~, recorded ~~for~~as: 1. Pressure for each of the 5 calibration static pressures tested 2. Calibration completion status (success/fail) 3. Descriptions of any errors during any static calibration procedure ECG Placement and Setup Three ECG sensors will be placed on patients aged ≥29 days, with leads on the left and right arm and left leg connected to the DASH® 4000. No ECG will be captured for subjects aged <29 days.Arterial Catheterization	
69	Section 7.2.3. - Patient Procedures	7.2.3 Patient Procedures Each patient will undergo intra-arterial aortic catheterization according to the standard of care at the investigational site. All tubing, transducers, and stopcocks will be filled with fluid and purged of all bubbles prior to data recording for IBP or NIBP in this study. If general anesthesia and/or other medicinal products are prescribed outside of the study, they will be administered according to the local standard of care prior to study measurements.~~The patient procedure for IBP setup is shown in the "IBP Setup" section of the *Device Set-Up Manual* provided by the Sponsor.~~ Dynamic Calibration of the IBP System -Dynamic calibration will be performed in the beginning of each procedure according to the "Dynamic Calibration" section of the *Device Set-Up Manual* provided by the Sponsor. For patients that the procedure will extended beyond one day, dynamic calibration will be conducted once each day prior to determinations. A maximum of 1 flush is to be conducted for patients aged <~~3 years.~~29 days. A maximum of 4 flushes may be conducted for patients aged ≥~~3~~ 29 days~~years~~. During calibration, values will be recorded for: 1. Number of fast flushes 2. Damping coefficient 3. Natural frequency For subjects less than 29 days of age, care will be taken to minimize disruption of care, and, when possible, procedures will be performed during times when feeding or other care is provided.	Added section heading, and clarified and separate patient procedural information.
70	Section 7.2.4 - Blood Pressure Assessments	7.2.4 Blood Pressure Assessments NIBP will be measured using the CARESCAPE Monitor B650 patient monitor equipped with an acquisition module (either PDM-SuperSTAT or PSM-Datex-Ohmeda, determined by study arm). IBP will be measured using the DASH® 4000 plus DC-COLLECTOR and DC-EDIT software. During the blood pressure assessments, values will be recorded for: 11. Study Arm	Consolidated information into a single table for clarity (new Table 2). This reduces the number of tables to make the protocol easier to follow.

<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td></td><td></td><td>
12. Time of first and last blood pressure measurement
13. Systolic, Diastolic, Mean, Test Duration
14. If the prescribed wait time was taken between tests
15. Any measurements with no determination
Both NIBP and IBP assessments will be conducted simultaneously, with IBP data collected on the DCS and NIBP data recorded by hand onto a paper Case Report Form (CRF). If necessary, assistance will be provided by other study staff to ensure that accurate and simultaneous blood pressure data is recorded.
IBP data will be continuously collected throughout the study and NIBP data will be recorded according to the following procedure:
12. Use the patient monitor equipped with either PDM-SuperSTAT or PSM-Datex-Ohmeda according to the patient's study arm to determine the patient's blood pressure.
13. Clear the patient monitor memory of the previous determination and wait at least 3 min
~~*Note:* For the CARESCAPE Monitor B650, the memory can only be cleared by discharging the case (with acquisition module attached)~~
14. Have the observers using the reference IBP monitoring equipment (DASH® 4000) and the NIBP monitoring equipment (CARESCAPE Monitor B650 with either PSM or PDM) simultaneously record and determine the patient's blood pressure, as follows.
a. Start continuous collection on the IBP DCS system at the same time as recording of NIBP begins
b. Collect each NIBP measurement from the CARESCAPE Monitor B650
~~c. Discharge the patient monitor to clear the memory of the previous NIBP determination after each determination.~~
~~*Note:* Because the discharge will erase the data from the previous NIBP measurement, record all necessary values before discharging the~~
~~15. Wait the following amount of time (Table 6) between determinations or, for neonatal patients, 3 min.~~
~~16. **Table 6 –** Minimum Time between Determinations~~
<table>
<tr><th>~~Population Age~~</th><th>~~Minimum Wait Period~~</th></tr>
<tr><td>~~≥ 3 years~~</td><td>~~≥60 seconds~~</td></tr>
<tr><td>~~> 29 days old to 3 years~~</td><td>~~≥60 seconds~~</td></tr>
<tr><td>~~‹ 29 days~~</td><td>~~≥3 minutes (variable)*~~</td></tr>
</table>
~~*Wait period is based on the investigator's discretion of patient health status of the patient. It is, however, suggested that a 20 minute wait period may be appropriate between 3 determinations obtained within a 2 hr window OR 4 determinations obtained within a 3 hr window.~~
17. Wait the appropriate amount of time between determinations (as defined in Table 2).
18. Repeat steps ~~4, 5, and 6~~3 and 4 adhering to the requirements in Table 2 until the target number of recordings and determinations have been performed or the subject leaves the study. In the event that any blood pressure determination is not successful,
</td><td></td></tr>
</table>

<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td></td><td></td><td>the procedure may be repeated to achieve the target number of successful blood pressure determinations. No more than the maximal number of total blood pressure determinations as specified in Table ~~5~~ 2 will be performed on any patient.
~~***Neonates Only***: Neonatal patients may participate for up to three days, taking an average of 3-4 determinations each day at the investigator's discretion.~~
19. When all NIBP measurements are complete, stop the IBP data collection.

Table 2 – Number of Blood Pressure Assessments and Frequency
<table><tr><th>Population</th><th>Maximum Number of BP Determinations</th><th>Target Number of Valid BP Determinations</th><th>Frequency of Determinations</th></tr><tr><td>Pediatric, Adolescents, and Adults (aged ≥ 3 years)</td><td>15 max attempts</td><td>10 determinations</td><td>At least 60 s between determinations</td></tr><tr><td>Children & Infants (<3 years old to >29 days old)</td><td>10 max attempts</td><td>10 determinations</td><td>At least 60 s between determinations</td></tr><tr><td>Neonates (‹ 29 days old)</td><td>10 max attempts</td><td>5-10 determinations</td><td>At least 3 minutes between determinations (over max of 72 hours)</td></tr></table></td><td></td></tr>
<tr><td>71</td><td>Section 7.4 - Withdrawal and Discontinuation Criteria</td><td>The patient may withdraw from study participation at any time, for any reason without consequence. The Investigator may withdraw a patient at any time for any reason. The reasons for withdrawal and discontinuation for any patient shall be recorded. These will be reported to the Sponsor. The EC/IRB should be notified per their notification of patient withdrawal policy.
~~If the Sponsor conducts a review during this study that indicates a total patient enrollment in any stratification group that meets or exceeds the number required to satisfy the ISO 81060-2:2013 standards, the Sponsor may discontinue or continue enrollment in any stratification.~~ Data collected up until the time of withdrawal ~~-~~may still be disclosed to the Sponsor as part of this study to ensure the integrity of research data.
Continuation and discontinuation of enrollment in any stratification group will be made at the discretion of the Sponsor in the context of applicable regulatory and standards requirements, and the</td><td>Clarified criteria for withdrawal and discontinuation.</td></tr>
</table>

Item	Section	Revision or Clarification	Justification
		Investigator will be notified by the Sponsor upon such a determination.	
72	Section 9.1.1. - Analysis Populations	Separate analysis will be performed for PSM-Datex-Ohmeda and the PDM-SuperSTAT arms per requirements of the ISO 81060-2:2013 standard. Analyses will be conducted for the following populations: • adults, adolescents, and pediatric patients, who are ≥ 3 years old and chronic atrial fibrillation patients (PDM-SuperSTAT arm)	Added term for consistency of terminology.
73	Section 11.1 - Foreseeable Adverse Events and Device Effects	~~Foreseeable~~The study procedure requires adding NIBP measurements to a patient's procedure. While NIBP is non-invasive, there are some foreseeable risks associated with NIBP ~~include~~, as follows: • slight discomfort upon inflation of the cuff, • possible bruising, • petechial rash • discoloration of the skin beneath the cuff • peripheral nerve injuries • skin avulsion • compartment syndrome • ischemia ~~Foreseeable risks associated with IBP include:~~ Whether or not the patient participates in the study, there are risks to having indwelling monitoring lines placed or having non-emergent aortic catheterization procedures with or without general anesthesia. To protect neonatal subjects, only subjects with existing indwelling monitoring lines will be enrolled, and no indwelling lines will be placed for study purposes. Foreseeable risks associated with these invasive procedures, as required for IBP, include: • Bruising • Bleeding • Heart attack • Stroke • Damage to the artery where the catheter was inserted that may require additional attention (pseudoaneurysm), including shear damage • Irregular heart rhythms (arrhythmias) • Allergic reactions to the dye or medication • Tearing the tissue of your heart or artery • Kidney damage • Infection • Blood clots • Ischemia • Air embolism • Potentially serious reactions to prescribed general anesthesia and/or sedatives While general anesthesia is not a requirement of this study, it is foreseeable that some patients undergoing aortic catheterization procedures will be incidentally administered prescribed general anesthesia and/or other sedatives during the study. Though general anesthesia is widely considered safe for routine clinical use, it is known	Updated to reflect the Sponsor's review of the literature, which includes addressing risks of possible concomitant general anesthesia in subjects of this study.

Item	Section	Revision or Clarification	Justification
		to be a potent neuromodulator with potentially serious documented side effects. [18, 21, 22, 23, 24, 25, 19] This research involves extension of the procedure by approximately 25 minutes to collect data, which may incidentally extend prescribed anesthesia and/or other medication administration. Though no definitive cumulative or long-term effects of general anesthesia are known with certainty, [24] to mitigate against these possible risks the study will not enroll subjects that have history of repeated recent anesthesia, and no subject will be allowed to participate more than once in the study. The risks associated with general anesthesia during this study are not expected to be significantly higher than those that the subject would have otherwise been exposed to had he or she not participated in this research.	
73	Section 11.4. - Management of Serious Adverse Event and Unanticipated Adverse Device Effect Reporting	Helena Haukilehto, MD ~~Ron Von Jako, MD~~ *Telephone*: +358-103943609~~+1 781 262 5579~~ ~~*Email*: Ron.VonJako@med.ge.com~~ *Email*: helena.haukilehto@ge.com	Updated Sponsor medical director name and contact information.
74	Section 17. ADDITIONAL STUDY MATERIALS / ADDITIONAL COUNTRY-SPECIFIC REGULATORY REQUIREMENTS	17. Additional Study Materials / Additional Country-Specific Regulatory Requirements	Combined supplementary section headings and placed references at end of document.

APPENDIX D: AMENDMENT TO PROTOCOL VERSION 4.0

Purpose: This amendment document describes in detail the changes made to the study protocol to make procedural clarifications and to clarify additional safeguards and reporting for neonate populations. Additionally, this amendment corrects formatting and wording issues to ensure clarity and consistency within the document and between the document and applicable standards.

The following amendments were made to version 4.0 to produce version 5.0. Point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment for the previous version.

Item	Section	Revision or Clarification	Justification
75	Study Synopsis	**Medical Monitor Name:** Helena Haukilehto, MD **Address:** Kuortaneenkatu 2 Helsinki, 00510 FI **Telephone:** +358-103943609 **E-mail:** ~~h~~Helena.~~haukilehto~~Haukilehto@ge.com	Typographical correction in email (capitalization only). Corrections in spacing are made to ensure consistency of the display of the synopsis for screen and print viewing.
76	Section 2.3.1. Risk Analysis for Subjects with Indwelling Lines (≤29 days of age)	For these subjects, NIBP measurements will be taken in a minimally disruptive manner ~~in these patients~~ in order to minimize possible interruption in their care.	Typographical correction to remove repeated phrase appearing twice in this sentence.
77	Section 6.2. Protection of Vulnerable Subjects	The information collected in this study could not have been obtained in a less vulnerable, consenting population, necessitating the use of minor patients. Adolescent, pediatric, and neonatal patients will be recruited and enrolled according to all US FDA, ISO 14155:2011 GCP, and other applicable local requirements for protection of vulnerable subjects. Special measures will be taken to protect the rights of these vulnerable study participants and to shield them from undue risk. ~~Study procedures for neonate subjects will be modified to minimize interruption in normal medical care, including limiting sampling to once per hour.~~ Study procedures for pediatric and neonate subjects will be modified to minimize interruption in normal medical care, which includes additional limitations on sampling frequency beyond the minimums suggested by ISO 81060-2:2013 (as shown in Table 2) for the general population. This is done to ensure minimal risk for participating subjects.	Table 2 was added in the prior amendment to detail requirements for sampling per population. The risk section is revised to reflect that a detail of risks is now included in Table 2 (referenced to Table 2 to clarify this). Note, these requirements are still in addition to the minimums posed by the standard, and there is no intended change in risk based on this revision, which is intended to clarify the document.
78	Section 6.3. Number of Subjects	The total minimum enrollment for the two study arms is 83 total evaluable patients (maximum of 200 patients), as follows: **1. PDM-SuperSTAT Arm** (N_{PDM}): 45 evaluable patients with GE DINAMAP® SuperSTAT algorithm (PDM Module) on CARESCAPE Monitor B650, to achieve a total target of ≥~~270~~ 150 BP data	Subject populations are updated for consistency with the standard and to reflect the addition of sampling limitations per population in Table 2 (as

<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td></td><td></td><td>pairs in patients ≥3 years old (up to 10 paired measurements per subject) and ≥150 BP data pairs in patients <3 years old (~~up to 10 total paired measurements per subject, up to one per hour~~as described in Table 2).
2. PSM-Datex-Ohmeda Arm (***N*_{PSM}**): 38 evaluable patients with Datex-Ohmeda algorithm (PSM module) on CARESCAPE Monitor B650, to achieve a total of ≥~~200~~ 150 BP data pairs in patients ≥3 years old (up to 10 paired measurements per subject) and ≥150 BP data pairs in patients <3 years old (up to 10 total paired measurements per subject~~, up to one per hour)~~ (as described in Table 2).</td><td>described in Amendment 78).</td></tr>
<tr><td>79</td><td>Section 6.3.1. Stratification of Subjects</td><td>Table 1 – Summary of Patient Enrollment Stratification by Characteristics
<table>
<tr><th>Enrollment Stratification</th><th>Minimum Total in PDM-SuperSTAT arm</th><th>Minimum Total in PSM-Datex-Ohmeda arm</th><th>Age (years) requirement</th><th>Weight (g) requirement</th><th>Gender (M/F)</th><th>Minimum number of patients (n)</th></tr>
<tr><td>Adults and Adolescents (General population) [b]</td><td>15 total patients</td><td>15 total patients</td><td>>12 yr</td><td rowspan="5">(no weight requirement)</td><td>F#</td><td>n ≥ 5</td></tr>
<tr><td></td><td></td><td></td><td>>12 yr</td><td>M#</td><td>n ≥ 5</td></tr>
<tr><td>Adults and Adolescents Chronic Atrial Fibrillation [b]</td><td>7 total patients</td><td>-</td><td>>12 yr</td><td>M or F#</td><td>n ≥ 7</td></tr>
<tr><td>Pediatrics</td><td>5 total patients</td><td>5 total patients</td><td>≥3 AND <12 yr</td><td>F#</td><td>n ≥ 2</td></tr>
<tr><td></td><td></td><td></td><td>≥3 AND <12 yr</td><td>M#</td><td>n ≥ 2</td></tr>
<tr><td rowspan="5">Children/Infants/ Neonates</td><td rowspan="3">18 total patients</td><td rowspan="3">-</td><td>≥1 yr AND <3 yr</td><td></td><td>M or F</td><td>n ≥ 3</td></tr>
<tr><td>>29 days AND <1 yr</td><td></td><td>M or F</td><td>n ≥ 3</td></tr>
<tr><td>(no age requirement)*</td><td>< 1000 g
1000-2000 g
>2000 g</td><td>M or F
M or F
M or F</td><td>n ≥ 3
n ≥ 3
n ≥ 3</td></tr>
<tr><td rowspan="2">-</td><td rowspan="2">18 total patients</td><td>≥1 yr AND <3 yr</td><td>>5 kg (~11 lbs) [a]</td><td>M or F</td><td>n ≥ 3</td></tr>
<tr><td>>29 days AND <1 yr</td><td>>5 kg (~11 lbs) [a]</td><td>M or F</td><td>n ≥ 3</td></tr>
<tr><td></td><td></td><td></td><td>(no age requirement)*</td><td>≥5 kg (~11 lbs) [a]</td><td>M or F</td><td>n ≥ 3</td></tr>
<tr><td>TOTAL</td><td>45 TOTAL</td><td>38 TOTAL</td><td colspan="4"></td></tr>
</table>
Abbreviations: M = male; F = female; *n*, number of patients
* No age requirement within the children/infant/neonates category ma include subjects aged birth to <3 yrs
# Investigators should equitably represent male and female patients, which must each make up a minimum of 30% of the final population upon completion (i.e. at least 30% male and 30% female, the remaining 30% may be either male or female based on enrollment).
***Important*: Additional Stratification requirements**
[a] Only patients weighing >5 kg (approximately 11 lbs) can be examined PSM-Datex-Ohemda under the current labeling
[b] Among adults~~/~~ and adolescents, at least 10% should have baseline sys of ≤100 and ≥160 as well as diastolic BP of ≤ 70 and ≥ 85 mmHg</td><td>Added clarification that subjects ages <29 days may be included in the children/Infants/Neonates stratification group, up to the allowable total patient number per PDM/PSM module. This reflects the original intent of this table and clarifies the original study intent.</td></tr>
<tr><td>80</td><td>Section 7.2.1. Baseline Examination</td><td>For enrolled patients that have provided informed consent the following baseline information will be collected on CRFs after informed consent requirements have been satisfied and before the procedures are performed:
1. Demographics (Age and Gender)
2. Gestational Age at Birth (*for Neonates only*)</td><td>Added collection of age AND gestational age at birth for neonates only.</td></tr>
</table>

Item	Section	Revision or Clarification	Justification
81	Section 9.4. Interim Analysis	No interim analysis is planned. As necessary for study conduct, engineering, and/or regulatory purposes, study data may be accessed and, if necessary, reported by the Sponsor prior to closure of the study.	Clarified that unplanned interim analyses may be conducted.
82	Footer	DOC1466558, ~~Rev~~Version 4.0~~5.0~~	Per current Sponsor documentation standards, the footer is updated to reflect the document "Version" rather than "Rev" (an internal IT system marker not synonymous with protocol revision/version).

APPENDIX E: AMENDMENT TO PROTOCOL VERSION 5.0

Purpose: This amendment document describes in detail the changes made to the study protocol to reflect that both the DASH®4000 and CARESCAPE B650 may be equipped with GxP-validated tools designed to assist in research data capture. These tools are not intended for commercial release, and devices equipped with these tools will be used for investigational use only as described in this protocol. The addition of GxP tools for the CARESCAPE B650 (which were originally only available for DASH®4000 as described in prior versions of this protocol) is intended to simplify data collection and reduce the frequency of errors or biases potentially encountered in manual data transcription from the study devices.

The following amendments were made to version 5.0 to produce version 6.0. Point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment for the previous version.

Item	Section	Revision or Clarification	Justification
83	Abbreviations	GEHC GE Healthcare GxP Good Processing Tools (validated research tools, not for commercial use)	Added additional abbreviation definitions, as used in the body of the protocol.
84	Study synopsis: Device Description	The control used in this study is gold standard aortic invasive blood pressure (IBP). Data may be collected on the DASH® 4000 patient monitor equipped with the non-commercial GEHC DC-EDIT and GEHC DC-COLLECTOR GxP software that can be compared with data either manually collected from the NIBP CARESCAPE Monitor B650 monitor, or data may be collected using the GxP-validated GEHC PDM Data Collection Module, which is capable of collecting electronic data typically displayed using patient monitors~~d, which~~. The GxP-validated systems used in this study serve the sole function of enabling the device to directly output data such as blood pressure waveforms ~~data~~ and parameters to the computerized data collection system (DCS) for storage and analysis purposes.	Added additional information about the GxP processing tools used in the study.
85	Study Synopsis: Regulatory Status	*H® 4000 patient monitor (control system) equipped with GxP validated non-commercial DC-COLLECTOR and DC-Edit software programs for data collection is considered investigational. The acquisition modules PDM-SuperSTAT and PSM-Datex-Ohmeda with the PSM-Datex-Ohmeda and PDM-SuperSTAT algorithms and used on the CARESCAPE Monitor B650 and accessories are commercially available. The PDM is considered investigational when GxP-validated PDM Data Collection Module is used, which functions in the same manner as the PDM but with additional ability to collect research data typically displayed on a patient monitor. Though pre- and post- market devices are utilized, all aspects of the study will be considered investigational.*	Added additional information about the GxP processing tools used in the study.
86	Section 2.3 Device Risk Analysis	The NIBP measurement (PDM-SuperSTAT and PSM-Datex-Ohmeda) devices and all patient monitors used in this study under	Added additional information about the GxP

Item	Section	Revision or Clarification	Justification
		study are commercially available, and all devices will be used according to their labeling. The GxP-validated GEHC PDM Data Collection ~~GxP~~Module ~~software that enabled~~may, when possible, be used to enable digital export of research data typically displayed on patient monitors.~~,~~ The GxP-validated GEHC PDM Data Collection module works in the same way as the commercially available PDM module, but also has software to enable digital export of the data for research use. The validated non-commercial DC-EDIT and DC-COLLECTOR equipment for the DASH® 4000 and GEHC PDM Data Collection Module ~~serves~~ as a data output connections only and ~~is~~ are not expected to impact the clinical function of the device. Participation in this study is not expected to impact patient management, clinical diagnosis, or treatment strategy compared to that which would be determined by the standard of care outside of this study.	processing tools used in the study.
87	Section 3.1.1.1. Patient Data Module (PDM) with DINAMAP® SuperSTAT Algorithm (PDM-SUPSERSTAT)	The Patient Data Module (PDM) is a high-acuity mobile hemodynamic acquisition module designed to help eliminate gaps and ECG resets when moving patients. The device can interface with the Solar® and CARESCAPE module patient monitors at the bedside and can quickly snap into and provide power for a Transport Pro® monitoring device. The detachable PDM docking station interfaces to the module frame flex board, and the 10-pin connector provides the VSYS ePort supply voltage and the Ethernet communication lines to the PDM module. The PDM includes GE's clinical algorithms, including 12SL™ 12-lead ECG, 12RL™ derived 12-lead ECG, GE EK-Pro four-lead arrhythmia analysis, GE DINAMAP® SuperSTAT non-invasive blood pressure, and Masimo® SET® or Nellcor® OxiMax® SpO_2. PDM uses the DINAMAP® SuperSTAT NIBP measurement algorithm. The GxP-validated GEHC PDM Data Collection Module, which enables the digital collection of research data typically manually transcribed from the patient monitor may also be used in the procedure. The modified GEHC PDM Data Collection Module used the same technology as the commercial PDM module, but has additional GxP-validated data collection features that are intended for research use only (serving to minimize potential errors or biases due to manual transcription from the patient monitor) to allow data output. This software program is not otherwise expected to produce any change in function of the commercially marketed patient module.	Added additional information about the GxP processing tools used in the study.
88	Section 3.1.2.1. CARESCAPE Monitor B650	The CARESCAPE Monitor B650 combines the strong clinical heritage of Datex-Ohmeda anesthesia and Marquette Electronics cardiac expertise, providing a significant level of backwards compatibility that allows hospitals to leverage prior technology and training. While the CARESCAPE Monitor B650 equipped with the DASH® 4000 may be used in the study, use of these patient monitoring devices will~~may~~ not be required for procedures conducted using the GxP-validated GEHC PDM Data Collection Module, which enables the digital collection of research data typically manually transcribed from the patient monitor. ~~The modified GEHC PDM Data Collection Module used the same technology as the~~	Added additional information about the GxP processing tools used in the study.

Item	Section	Revision or Clarification	Justification
		~~commercial PDM module, but has additional GxP-validated data collection features that are intended for research use only (serving to minimize potential errors or biases due to manual transcription from the patient monitor).~~	
89	Section 3.2. Regulatory Status	The PSM and PDM acquisition modules and CARESCAPE B650 used in this study are commercialized in the United States and have been cleared by the US FDA. Because the PSM module is not currently cleared for using in neonates or infants under 5 kg (approximately 11 lbs.), no patients in this age range will be examined with PSM in this study. The PDM device is cleared for use in patients of all ages. When possible, sites may also use the modified GxP-validated GEHC PDM Data Collection module, which uses the same technology as the commercially available PDM module with additional features to enable digital collection of research data. The GxP-validated PDM Data Collection Module is considered a pre-market device used for research purposes only, and is not intended to be commercialized. The DASH® 4000 patient monitors are commercialized; however, when the Good Processing Tools (~~GXP~~GxP) validated DC-EDIT and DC-COLLECTOR are equipped on the DASH®4000 the device is considered non-commercial (investigational) and is to be used for research purposes only. Notably, DC-EDIT and DC-COLLECTOR have been validated for use in clinical data collection for the purpose of regulatory submissions. The results of the current study may be used as part of regulatory submissions to the US FDA or other global regulatory bodies to support the use of the investigational NIBP software algorithms with other patient monitoring systems.	Added additional information about the GxP processing tools used in the study.
90	Section 3.3. Risk Category/Rationale (US Only)	The CARESCAPE Monitor B650, acquisition modules (PDM and PSM), and peripheral cuffs and hoses used in this study are cleared for commercial use and will be used as intended in their labeling. All commercial devices are considered to be IDE Exempt per 21 CFR 812.2(c)(2). The DASH® 4000 is a commercial device; however, when equipped with the GxP validated non-commercial DC-EDIT and DC-COLLECTOR tools for data output it is to be used for research purposes only. Similarly, the GxP-validated PDM Data Collection Module used in place of manual transcription from patient monitors is intended for research use only. DC-EDIT and DC-COLLECTOR (for DASH®4000) as well as the PDM Data Collection Module ~~-~~tools are not expected to impact the function ~~of the DASH® 4000 device~~of other devices or the integrity of the study, but instead are intended solely to enable digital collection of study data while minimizing biases associated with manual transcription of data. When ~~equipped with~~using a DASH® 4000 equipped with DC-EDIT and DC-COLLECTOR~~, the DASH® 4000~~ or the PDM Data Collection Module in place of manual data transcription from patient monitors, the ~~and~~ devices ~~algorithms~~ investigated in this research study are considered~~a~~ non-significant risk devices per the 21 CFR 812.3 definition:	Added additional information about the GxP processing tools used in the study.
91	Section 3.4. Device/Product	The PSM acquisition module (using Datex-Ohmeda GE for NIBP assessment) is cleared for commercial use under US FDA 510(k)	Added additional information about the GxP

Item	Section	Revision or Clarification	Justification
	Classification and Rationale	K062576 (2006), and the PDM acquisition module (using DINAMAP® SuperSTAT for NIBP assessment) is cleared for commercial use under US FDA 510(k) K071073 (2007) as a non-invasive blood pressure measurement system (DXN) under CFR 870.1130. When available, the pre-market PDM Data Collection GxP Module may be used in place of manual transcription from patient monitors using the commercial PDM module, enabling research data to be collected digitally. The PDM Data Collection GxP Module has been qualified per Good Processing Tools (GxP) by GE Healthcare for collection of ECG, ~~and~~ blood pressure~~arterial~~ data in clinical settings, ~~settings (GEHC Internal Book Numbers DOCXXXXXXX and DOCXXXXXXX), and~~ is considered investigational and intended for research use only. The CARESCAPE Monitor B650 is a Class II medical device classified as a Patient Physiological Monitor (with arrhythmia detection or alarms) by the US FDA and cleared under 510(k) K131223 (2013). The most recent FDA cleared software version for the CARESCAPE Monitor B650 at the time of the study will be used on the CARESCAPE Monitor B650. The DASH® 4000 patient monitor is a Class II medical device classified as a Patient Physiological Monitor by the US FDA and cleared under 510(k) K073462 (2008). Non-commercial DC-EDIT and DC-COLLECTOR tools used on the DASH®4000 have been qualified per Good Processing Tools (~~GXP~~GxP) by GE Healthcare for collection of ECG and arterial data in clinical settings ~~(GEHC Internal Book Numbers DOC0610288 and DOC0609984~~). When equipped with these tools, the DASH® 4000 patient monitor will be considered investigational.	processing tools used in the study. Corrects/removed outdated DOC references.
92	Section 3.5. Device/Product Issuance and Replacement	• PSM and PDM acquisition modules for the CARESCAPE Monitor B650 with appropriate software versions already installed, or, based on availability, the PDM Data Collection Module- labeled as investigational (for research purposes only).	Added additional information about the GxP processing tools used in the study.
93	Section 6.3. Number of Subjects	5. **PSM-Datex-Ohmeda Arm** (***N*PSM**): 29~~38~~ evaluable patients with Datex-Ohmeda algorithm (PSM module) on CARESCAPE Monitor B650, to achieve a total of ≥150 BP data pairs in patients ≥3 years old (up to 10 paired measurements per subject) and ≥150 BP data pairs in patients <3 years old (as described in Table 2). [correction is also reflected in Table 1]	Corrects typographical error in number of subjects. This correction is also reflected in Table 1.
94	Section 7.1.1. IBP Data Collection on the Data Collection System (DCS)	The PDM Data Collection Module may be used to collect research data (based on availability) for PDM procedures, else IBP and ECG data will be collected using a DASH® 4000 patient monitor with the hardware and software tools to connect to a computerized data collection system (DCS) housed on a Sponsor-provided laptop computer. ~~One~~ A ~~DCS (laptop)~~laptop will be connected for electronic data capture, when GxP-validated data capture tools are used ~~to the DASH® 4000 via a serial cable from the DASH to the DCS laptop~~. The investigator is responsible for setting up the ~~DCS for~~ data collection ~~of IBP data~~ according to the "Setup of Data Collection" section of the *Device Set-Up Manual* provided by the Sponsor. For applicable procedures, the~~The~~ control panel for the	Added additional information about the GxP processing tools used in the study, which utilize the DCS system to collect additional data compared to the previous GxP tool.

Item	Section	Revision or Clarification	Justification
		DASH® 4000 patient monitor is shown in the "DASH® 4000 Control Panel" section of the section of the *Device Set-Up Manual* provided by the Sponsor, which provides details on user setup and operation of the DASH® 4000 patient monitor. The patient procedure for IBP setup is shown in the "IBP Setup" section of the *Device Set-Up Manual* provided by the Sponsor. Similarly, the *Device Set-Up Manual* provides instructions for setup and use of the PDM Data Collection Module for electronic data capture during PDM procedures.	
95	Section 7.1.2. NIBP Data Collection	NIBP will be recorded on a commercial CARESCAPE Monitor B650 with most recent commercial software version installed. NIBP data will be transcribed by hand from the display of the CARESCAPE B650 monitor onto the Sponsor-provided Case Report Form (CRF) when the PDM Data Collection Module is not available. When the PDM Data Collection Module is available, data collection may be performed electronically using this tool. For patients in the PDM-SuperSTAT arm of the study, NIBP will be measured with a CARESCAPE Monitor B650 equipped with a PDM acquisition module or the GxP PDM Data Collection Module. For patients in the PSM-Datex-Ohmeda arm of the study, NIBP will be measured with a CARESCAPE Monitor B650 equipped with a PSM acquisition module.	Added additional information about the GxP processing tools used in the study.
96	Section 7.2.2. Before the Procedure	For each patient, the following procedure-specific information will be recorded on CRFs: Model and serial number for the DASH® 4000 (if applicable) Model and serial number for CARESCAPE B650 (if applicable) Model and serial number for the PSM or PDM acquisition module used Catheter cross-section, length, and trade name Trade name of pressure transducer Site/artery used for IBP measurements Monitor filter settings and recording settings, if applicable Identification of the observer making the recordings (name and position) Details of any special circumstances during measurement Pulse rate at the start of device evaluations Time and date of last manometer calibration Three ECG sensors will be placed with leads on the left and right arm and left leg connected to the DASH® 4000 or the PDM Data Collection Module~~.~~	Corrected applicability of data collection elements.
97	Section 7.2.4. Blood Pressure Assessments	NIBP will be measured using the CARESCAPE Monitor B650 patient monitor equipped with an acquisition module (either PDM-SuperSTAT or PSM-Datex-Ohmeda, determined by study arm). ~~For PDM procedures where the PDM Data Collection Module is used for electronic data capture, this may be used in place of manual transcription from the patient monitor to paper CRFs.~~ IBP will be measured using the DASH® 4000 plus DC-COLLECTOR and DC-EDIT software. For PDM procedures where the PDM Data Collection Module is used for electronic data capture, this may be used in place of manual transcription from the patient monitor to paper	Clarified use of the PDM data collection module.

Item	Section	Revision or Clarification	Justification
		CRFs. During the blood pressure assessments, values will be recorded for: … Both NIBP and IBP assessments will be conducted simultaneously, ~~with IBP data collected on the DCS and NIBP data~~using either digital data recording tools (when available) or recorded by hand onto a paper Case Report Form (CRF). If necessary, assistance will be provided by other study staff to ensure that accurate and simultaneous blood pressure data is recorded. IBP data will be continuously collected throughout the study. For cases where manual data collection of ~~and~~ NIBP data is necessary, it will be recorded according to the following procedure: … When all NIBP measurements are complete, stop the IBP data collection. For PDM procedures where the PDM Data Collection Module is used, data may be captured electronically instead of using the manual procedure according to the following procedure: 1. Use the PDM Data Collection Module to determine the patient's blood pressure. 2. Wait at least 3 min. 3. Simultaneously record and determine the patient's blood pressure, as follows. 4. Start NIBP measurement from the PDM Data Collection Module 5. Wait the appropriate amount of time between determinations (as defined in Table 2). 6. Repeat steps 3 and 4 adhering to the requirements in Table 2 until the target number of recordings and determinations have been performed or the subject leaves the study. In the event that any blood pressure determination is not successful, the procedure may be repeated to achieve the target number of successful blood pressure determinations. No more than the maximal number of total blood pressure determinations as specified in Table 2 will be performed on any patient. 7. When all NIBP measurements are complete, stop the data collection. ~~For PDM procedures where the PDM Data Collection Module is used, data may be captured electronically instead of using the manual procedure. In this case, the user should conduct each determination using the laptop-based interface for the PDM Data Collection Module. After all determinations are completed using the laptop-based interface for the PDM Data Collection Module, the user should ensure that the files are stored and labeled as described in the *Device Set-Up Manual.*~~ The same number and type of determination should be performed whether the manual or digital PDM Data Collection Module is used.	
98	Section 7.3. Data Storage	All digitally recorded ~~IBP~~ data ~~from the DCS~~ will be saved from the DCS folder to a Sponsor-provided external media (e.g., flash drive	Clarified that using the new GxP module data

Item	Section	Revision or Clarification	Justification
		or CD), and the Investigator will confirm that all data is saved on flash drive or CD and stored in a secured area at the investigational site. When NIBP data ~~will be~~ is recorded on paper case report forms, it will be stored in a secure area at the investigational sites.	collection is not limited to IBP using the DCS.
99	Section 9.2. Determining Reference Invasive Blood Pressure Per ISO 81060-2:2013	First, the mean and the standard deviation of the invasive blood pressures derived from the IBP wave recordings during a NIBP determination will be calculated; and the range of reference invasive blood pressure will be determined as mean ±1 standard deviation (SD) of the IBPs. The same method will be used for both systolic and diastolic blood pressures. Calculation of reference IBP from IBP wave recordings is not part of the statistical analysis. ~~All data from a subject will be~~Data may be excluded for analysis~~,~~ when the range of invasive systolic BP is wider than 20 mmHg or when the range of invasive diastolic BP is wider than 12 mmHg, as such that analysis is performed in accordance with ~~or as specified per~~ ISO 81060-2:2013.	Clarified that analysis (including exclusion of some data) will be performed as detailed in ISO 81060-2-2013.
100	Section 9.3.1. Data Exclusion	• NIBP data from a subject if the range of reference systolic blood pressure is more than 20mmHg or the range of reference diastolic blood pressure is more than 12 mm Hg, or as specified per ISO 81060-2:2013 standard;	Clarified that analysis (including ranges of data) will be performed as detailed in ISO 81060-2-2013.
101	Section 13.4. Informed Consent and Privacy Requirements	Informed consent will be documented in the source record of each subject. The Investigator or designee will consent the subject per regulatory guidelines which include that the subject has ample time to review the ICF and have all questions answered to their satisfaction; the subject may take the ICF home to review with family members or others prior to agreeing to participate in the study; upon agreeing to participate in the study, the subject signs and dates the document, and the person who consented the subject signs and dates the document. Minor subjects are legally unable to provide informed consent. Therefore these study participants are dependent on their parent(s) or legal guardian to assume responsibility for their participation in clinical studies. Fully informed consent will be obtained from the legal guardian in accordance with applicable laws and regulations. All participants will be informed to the fullest extent possible about the study in language and terms they are able to understand.	Corrected typographical error.
102	Section 14.3. Completion of Case Report Forms (CRFs)	Data will be collected using paper CRFs and data collection system (DCS) data per the details of this protocol.	Corrected typographical error.

APPENDIX F: AMENDMENT TO PROTOCOL VERSION 6.0

Purpose: This amendment document describes in detail the changes made to the study protocol to clarify that subjects with radial lines are eligible to participate., in addition to the existing routes (umbilical and femoral) already specified in the protocol. All catheterization lines will be places as clinically indicated, and will not be altered for study purposes.

The following amendments were made to version 5.0 to produce version 6.0. Point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment for the previous version.

Item	Section	Revision or Clarification	Justification
103	Section 2.3.1 Risk Analysis for Subjects with Indwelling Lines (≤29 days of age)	Eligible subjects aged 29 days or less will be recruited only if they currently have, or are scheduled to have, an indwelling femoral, radial, or umbilical arterial monitoring line placed. The type of line places will be determined according to the site standard of care, and not altered based on participation in the study. While radial lines are the most commonly placed indwelling lines in neonates, femoral and umbilical lines share a similar safety profile and, in some cases, are preferred in order to preserve integrity of vessels when future interventions may be required.[15] Like radial and femoral line placements, umbilical lines have, ~~which has~~ been shown to have a minimal complication rate even during longer procedures when performed by experienced physicians.[5,15] For these subjects, NIBP measurements will be	Clarified that subjects with radial lines are eligible to participate. Notably, the type of indwelling line places is determined according to the standard of care and not influences by study participation. Added additional citation #15 to support the safety profile of radial lines.
104	Section 6.1 Subject Population	The study will include neonates with indwelling femoral, radial, or umbilical arterial monitoring lines and infant, pediatric, adolescent, and adult subjects requiring non-emergent surgery involving aortic catheterization (including chronic atrial fibrillation patients among adults and adolescents).	Clarified that subjects with radial lines are eligible to participate.
105	Section 6.4 Inclusion Criteria	1. Are aged >29 days requiring clinically indicated non-emergent heart catheterization OR aged ≤29 days with placed or scheduled placement of an indwelling femoral, radial, or umbilical arterial monitoring line;	Clarified that subjects with radial lines are eligible to participate.
106	Section 11.4 Management of Serious Adverse Event and Unanticipated Adverse Device Effect Reporting	All SAEs and or UADEs will be documented as above and reported in writing to the Sponsor within 72 hours of knowledge of the event The Investigator shall submit the Adverse Event Case Report Form and GEHC_GQP_10.07.005_F002 Site Notification and Assessment of Serious and Unexpected Adverse Events (DOC0910335) with redacted supporting documentation to SAE mailbox. If the event resulted in the death of a subject, the event shall also be reported via telephone to the Sponsor within 24 hours of knowledge of the event. SAEs will be reported to the local EC/IRB per their policy.	Removed redundant duplicate entry of the Medical Monitor's contact information, per Sponsor's internal best practices and templates. The contact information for the medical monitor is unchanged, and still remains in the early part

Item	Section	Revision or Clarification	Justification
		The Sponsor's Medical Monitor (complete contact information listed in the Study Synopsis) should be contacted for SAEs and/or UADEs: ~~Helena Haukilehto, MD~~ ~~*Telephone*: +358 103943609~~ ~~*Email*: helena.haukilehto@ge.com~~ Fax: 800-888-3983 E-mail: SAE@ge.com	of the protocol "study synopsis" section.
107	References	15. Sabourdin N, Louvet N, Constant I. Selection of Anesthesia Techniques for the Neonate. In: Lerman J, ed. *Neonatal Anesthesia*. New York, NY: Springer; 2014.	Added additional citation #15 to support the safety profile of radial lines.

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