Statistical Analysis Plan: ModPG3 Adult-Ped ISO 81060-2 Study

Study Title:	A Multi-person study to compare New Blood pressure algorithm to manual Blood pressure in pediatric and adult patients as defined in ISO 81060-2.
Study Number:	60115909
Study Design	This is a multi-person, non-randomized prospective, open label study to test the algorithms contained in the ModPG3 on adult subjects defined as greater than 12 years old and pediatric subjects defined as 3 to 12 years of age to determine if they meet the requirements of ISO 81060-2:2018+A1:2020 Non-invasive sphygmomanometers
Product Name:	ModPG3
Indication:	The ModPG3 will provide interfaces to allow the host to implement manual, long-term automated and short-term automated modes per ISO 80601-2-30 and to also provides patient modes that support pediatric and adult patients as defined in ISO 81060-2.
Statistician:	[redacted]
Sponsor:	Baxter Healthcare Corporation One Baxter Parkway Deerfield, Illinois 60015, USA
Responsible Medical Officer:	[redacted]
Final Date:	30 OCT 2023

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SIGNATURE PAGE

Study Title: A Multi-person study to compare New Blood pressure algorithm to manual Blood pressure in pediatric and adult patients as defined in ISO 81060-2

Protocol Number: 60115909 v. E

Statistician: [redacted]

I have read this report and confirm that to the best of my knowledge it accurately describes the planned analyses of the study.

Prepared by: [redacted] Date: [redacted]

Approved by: [redacted] Date: [redacted]

Approved by: [redacted] Date: [redacted]

[redacted]

REVISION HISTORY

Version	Revision Summary	Reason(s) for Revision
1.0	Initial release	N/A

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

α	Significance level
AE	Adverse Event
β	Probability of Type II error in any hypothesis test
BP	Blood Pressure
CRF	Case Report Form
DBP	Diastolic Blood Pressure
DUT	Device Under Test
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
ISO	International Organization for Standardization
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
R&D	Research & Development
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SS	Safety analysis set
UADE	Unanticipated Adverse Device Effects

1. STUDY DETAILS

This statistical analysis plan (SAP) is provided to describe the framework for the reporting, summarization, and statistical analysis methodology of the safety and efficacy parameters measured throughout the study. It is based on clinical trial protocol 60115909 Version E dated 12SEP2022.

1.1 Study Objectives

1.1.1 Primary Study Objective/Endpoint

The primary and only objective of this study is to collect a combination of non-invasive blood pressure readings using the ModPG3 investigational device and by trained clinicians using the auscultatory method. This data will be used to determine compliance of the ModPG3 with ISO 81060-2:2019/Amd 1:2020 on the adult and pediatric patient population.

1.2 Study Design

1.2.1 Study Design and Plan

This study is a multi-person, non-randomized study, prospective, single arm study. Data will be collected at all approved clinical sites. The study will be conducted in 2 parts.

- Part 1 will test subjects using the ModPG3 Investigational device with the SureBP algorithm enabled.
- Part 2 will test subjects using the ModPG3 Investigational device with the StepBP algorithm enabled.

Each part of the study will be run in 2 phases.

- Phase 1 will enroll a minimum of 30 subjects that meet the inclusion criteria. At least 20 adult and at least 10 pediatric subjects will be included. At the completion of phase 1 the data will be reviewed by the sponsor and the sponsor will decide whether to continue with phase 2.
- Phase 2 will enroll a minimum of 55 more qualified subjects.

The resulting dataset when combining phase 1 and phase 2 (for each Part of the study), at a minimum, will contain the following.

- At least 85 subjects (Maximum 150)
- At least 35 pediatric subjects (3 – 12 years old)
- At least 50 adult subjects (over 12 years old)

Patient selection is listed in the inclusion criteria.

The study requires three observers. The first two observers take auscultatory readings. The third observer checks that the systolic and diastolic blood pressure pairs are 4mmHg or less apart. If they are not, then the measurements are repeated. If they are, then the values are averaged to use as reference blood pressures. The third observer operates the ModPG3 investigational device and records the readings for that device. The two clinicians taking reference readings will be blinded to each other's readings and to the investigational device readings as required.

1.2.2 Determination of Sample Size

The total sample size will be a minimum of 170 subjects (a minimum of 85 subjects per algorithm). A sample size of 85 subjects per algorithm was chosen in compliance with ISO 81060-2:2019 / Amd. 1:2020. The following is an excerpt of the justification from Annex A of the guidance:

> *The sample size of 85 was determined from the statistics for a normal distribution. A 98% confidence interval ($\alpha = 0,02$) and a statistical power of 95% ($\beta = 0,05$) yield a sample size requirement of 85 subjects. This requirement originated from the early work of the AAMI blood pressure committee dating from 1987.*
>
> *Additionally, a sample size of 85 can be determined from the statistics for a t-distribution. A 95% confidence interval ($\alpha = 0,05$) and a statistical power of 98% ($\beta = 0,02$) yield a sample size of 85 subjects.*

1.2.3 Randomization Procedure

There is no randomization for this study.

1.2.4 Blinding

This is an open label study. However, there will be three observers to limit bias between blood pressure measurements. The first two observers take auscultatory readings that are averaged to use as reference blood pressures. The third observer operates the ModPG3 investigational device and records the readings for that device.

The two clinicians taking reference readings will be blinded to each other's readings and to the investigational device readings as required by section 5.2.2 of ISO 81060-2:2019/Amd 1:2020.

1.3 Analysis Populations

Two main analysis populations will be used for this study. These two populations will be determined by study part, which is differentiated by the two algorithms being tested.

1.3.1 Definition of Analysis Populations

Full analysis set (FAS): all subjects meeting inclusion/exclusion criteria and all ISO requirements who have at least one valid paired blood pressure measurement defined as having 2 auscultatory measurements (to be averaged) and a ModPG3 measurement.
The following criteria will result in a single measurement being excluded from the FAS:

- The subject is experiencing a significantly irregular heart rhythm at the time of measurement.
- The pair of observers' systolic and diastolic blood pressure values for the auscultatory reference measurements have a difference greater than 4 mmHg.
- The first pair of auscultatory reference measurements and first DUT measurement for all subjects will not be included in analysis. If repeat(s) auscultatory measurements were performed prior to the first DUT measurement, all pairs of auscultatory measurements prior to the first DUT measurement will be excluded.

The following criteria will result in an entire subject being removed from the FAS:

- There is evidence that the subject's auscultatory or DUT measurements were not collected in accordance with ISO requirements (e.g., not having 3 observers in the room, observers 1 and 2 not blinded to other's measurements).
- Any 2 auscultatory systolic measurements from one subject differ by more than 12 mmHg (this does not include any measurements excluded based on the above criteria).
- Any 2 auscultatory diastolic measurements from one subject differ by more than 8 mmHg (this does not include any measurements excluded based on the above criteria).
- If 9 or more auscultatory measurements were required.

Safety analysis set (SS): the set of all subjects who were connected to the auscultatory equipment or DUT, regardless of whether a valid blood pressure measurement was obtained.

1.3.2 Protocol Deviations

Protocol deviations will be summarized for all subjects in the FAS by part (i.e., algorithm group). Patient counts will be presented for minor protocol deviations, major protocol deviations, and for each category of major protocol deviation.

Protocol deviations will also be listed for the FAS. The listing will include patient id, age, sex, date deviation occurred, the assigned category of protocol deviation, verbatim comments (which may include a description of the circumstances surrounding the event and any action taken), assigned category of actions taken, and major/minor status.

1.4 Efficacy and Safety Variables

1.4.1 Efficacy Variables

Paired systolic and diastolic blood pressure measurements from the ModPG3 investigational device and the auscultatory reference readings will be collected.

1.4.2 Safety Variables

Adverse events and unanticipated adverse device effects will be collected.

1.5 Quality Check

An informal interim analysis is planned after approximately 30 subjects enrolled (20 adult and 10 pediatric) for each algorithm group. This will serve as an internal quality check to potentially stop the study for futility. More details on this can be found in Section 2.6.

2. ANALYSIS METHODS

2.1 General Principles

Unless otherwise specified, summary statistics (n, mean, standard deviation [SD], median, minimum, and maximum values) will be presented for continuous variables. Counts and, if relevant, percentages will be presented for categorical variables.

Unless otherwise specified, data listings will include patient ID, sex, and age at screening (rounded down to the nearest whole number).

Unless otherwise noted, all analyses will be performed using SAS/Graph® 9.4 software, SAS/STAT® 15.1 software or higher, and BaseSAS® 9.4. Copyright © 2016, SAS

Unless otherwise specified, the estimated mean and median for a set of values will be displayed to 1 more significant digit than the original values, standard deviations will be displayed to 2 more significant digits, and minimum and maximum values will be displayed with the same number of significant digits as the original values. If an original value has more than 2 decimal places, the significant digits will be counted as if there are 2 decimal places. All percentages will be displayed with 1 decimal place unless more decimal places are needed to show 1 significant digit (i.e. a percentage of 0.01 will be shown as 0.01 as opposed to 0.0).

2.1.1 Definition of Baseline

No baseline measurements are being recorded for this study.

2.1.2 Completion and Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the patient has, or is presumed to have, completed all study procedures according to the protocol. The Investigator may terminate a patient's study participation at any time during the study if he/she judges it to be in the patient's best interest.

If a patient is withdrawn from the study, the study monitor must be informed in the shortest possible time, regardless of the reason for withdrawal. In addition, a patient or the patient's legally authorized representative may discontinue his or her participation at any time during the study. If a patient's participation is discontinued, the reason(s) must be recorded in the source documents and on the CRFs.

If a patient is prematurely removed from the study, all data prior to discontinuation should be recorded in the CRF and all available data will be included in the statistical analyses.

2.2 Patient Disposition

Patient disposition will be summarized by algorithm group and will include:

- Number of subjects who signed informed consent (enrolled)
- Number of subjects who met inclusion/exclusion criteria and are eligible for study measurements to be taken

- Number of subjects treated with at least one study device (Safety Set)
- Number of subjects in the Full Analysis Set
- Number of paired measurements in the Full Analysis Set
- Number of subjects who completed the study
- Number of subjects who discontinued (withdrew early) from the study. These subjects will also be summarized by primary reason for withdrawal from the study. The percentages associated with each reason for early withdrawal will have the total number of subjects who withdrew early as the denominator.

Subjects who withdraw early from the study will be listed, and the listing will include all reasons for withdrawal.

The patient overview table will include all subjects who have been enrolled in the study. The patient disposition table will include subjects in the FAS only. Listings will be based on the set of all subjects who have been enrolled in the study.

2.3 Demographics and Other Baseline Characteristics

Demographics (age, sex, and race) and other baseline characteristics (height, weight, limb used, arm length, arm circumference, limb circumference group and octal, FlexiPort size, and auscultatory cuff size) will be summarized descriptively by algorithm group for the FAS population. A listing will also be provided for this population.

2.4 Efficacy Analyses

2.4.1 Primary Efficacy Analysis

The primary efficacy analysis will be carried out on the FAS. The primary efficacy endpoint measurements and analyses described below will be completed for each of the two algorithms being tested: StepBP and SureBP.

2.4.1.1 Derivation of the Primary Endpoint

The primary efficacy endpoint measurements described below will be completed separately for each of the two algorithms being tested (Part 1: SureBP Algorithm/Part 2: StepBP Algorithm).

The auscultatory measurements from the two observers will be averaged to create the reference blood pressure value using the following formula for both systolic and diastolic blood pressure, separately:

$$p_{REFi} = \frac{p_{REFi,1} + p_{REF\,i,2}}{2} \qquad (1)$$

where

i is the observation number

$p_{REF_{i,1}}$ is the blood pressure determined by Observer 1 for the i[th] observation

$p_{REF_{i,2}}$ is the blood pressure determined by Observer 2 for the i[th] observation

For each ModPG3 measurement, the paired reference measurement will be an average of the auscultatory measurement directly proceeding the ModPG3 measurement and the one directly after the ModPG3 measurement:

$$p_{REF-sqi} = \frac{p_{REFi} + p_{REFi+1}}{2} \qquad (2)$$

The mean difference of all paired observations will then be calculated for both systolic and diastolic blood pressure separately using the following formula:

$$\bar{x}_n = \frac{1}{n}\sum_{i=1}^{n}(p_{SUTi} - p_{REF-sqi}) \qquad (3)$$

where

n is the total number of paired observations,

i is the index for the paired observation, and

p_{SUTi} is the measurement from the ModPG3 device under test.

The standard deviation of the differences will be calculated as follows:

$$s_n = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x}_n)^2} \qquad (4)$$

where

n is the total number of paired observations,

i is the index for the paired observation, and

x_i is the paired difference $(p_{SUTi} - p_{REF-sqi})$ for observation *i*.

In addition, both the mean and the standard deviation of the averaged paired measurements per subject will be calculated as follows:

$$x_j = \frac{1}{d}\sum_{k=1}^{d}(p_{SUT\,j,k} - p_{REF-sqj,k}) \qquad (5)$$

$$s_m = \sqrt{\frac{1}{m-1}\sum_{j=1}^{m}\left(x_j - \bar{x}_n\right)^2} \qquad (6)$$

where

[redacted]

m is the number of subjects in the study,
j is the index for the individual subject,
x_j is the ModPG3 device error,
d is the number of measurements per subject, and
k is the index for the individual measurement.

2.4.1.2 Analysis of Primary Efficacy Assessment

The ModPG3 blood pressure measurements (p_{SUTi}) and the reference blood pressure measurements ($p_{REF\text{-}sqi}$) will be summarized descriptively using n, mean, standard deviation, minimum, median, and maximum for each systolic and diastolic blood pressure by algorithm.

The distribution of reference blood pressure measurements will also be summarized descriptively using frequencies and percentages of measurements in the following groups by algorithm:

- Systolic less than or equal to 100 mmHg.
- Systolic greater than or equal to 160 mmHg.
- Systolic greater than or equal to 140 mmHg.
- Diastolic less than or equal to 60 mmHg.
- Diastolic greater than or equal to 100 mmHg.
- Diastolic greater than or equal to 85 mmHg.

In addition, the mean difference ($\bar{x}_n$) and standard deviation of the differences (s_n) will be calculated as above and displayed per algorithm.

The acceptance criteria is as follows and will be analyzed and accepted separately for each systolic and diastolic blood pressures and by algorithm:

- Criteria 1: $\bar{x}_n$ (Formula 3) shall be within or equal to ±5.0 mmHg and s_n (Formula 4) shall be no greater than 8.0 mmHg.
- Criteria 2: s_m (Formula 6) shall meet the values listed in the table below:

$\bar{x}_n$	Maximum permissible standard deviation, S_m, as a function of, $\bar{x}_n$ mmHg									
	0.0	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**
±0	6.95	6.95	6.95	6.95	6.93	6.92	6.91	6.90	6.89	6.88
±1	6.87	6.86	6.84	6.82	6.80	6.78	6.76	6.73	6.71	6.68
±2	6.65	6.62	6.58	6.55	6.51	6.47	6.43	6.39	6.34	6.30
±3	6.25	6.20	6.14	6.09	6.03	5.97	5.89	5.83	5.77	5.70
±4	5.64	5.56	5.49	5.41	5.33	5.25	5.16	5.08	5.01	4.90
±5	4.79	–	–	–	–	–	–	–	–	–

Both criteria 1 and criteria 2 must be met for both systolic and diastolic blood pressures in order for a particular algorithm to declare acceptance.

Plots of reading error versus arm circumference will be provided for systolic and diastolic blood pressures separately by algorithm. Reading error will be calculated as the difference between the DUT and reference blood pressure values. The borders of each cuff will be indicated with vertical lines.

2.5 Safety Analyses

All safety analyses will be presented on the Safety Set by algorithm and in total.

2.5.1 Derivation of Adverse Events, Unanticipated Adverse Device Effects, and Unanticipated Problems

The number of events per subject will be calculated as follows for each algorithm:

$$\frac{Number\ of\ Total\ Events}{Number\ of\ Subjects\ in\ Safety\ Set}$$

And as

$$\frac{Number\ of\ Total\ Events}{Number\ of\ Subjects\ in\ both\ Safety\ Sets}$$

for the total group.

2.5.2 Analysis of Adverse Events and Unanticipated Adverse Device Effects

An AE overview summary table will be prepared to include the number of subjects, the percentage of subjects (%), the number of events, and the number of events per patient, for the following categories:

1. Any adverse event
2. Non-serious AEs

3. Serious AEs (SAEs)
4. Adverse events related to the study device
5. Unanticipated Adverse Device Effects (UADEs)
6. AEs leading to withdrawal

Additional listings and tables on the above categories will be given by SOC and PT. For SAE listings, the seriousness criteria will be included in the listing.

2.5.3 Analysis of Unanticipated Problems

An unanticipated problems overview summary table will be prepared to include the number of subjects, the percentage of subjects (%), the number of events, and the number of events per patient by algorithm group and overall. The listing will include patient ID, age, sex, algorithm group, measurement start time, time of unanticipated problem, unanticipated problem information, and action taken.

2.6 Quality Check Methods

An informal interim analysis/quality check will be performed by the R&D group after 30 subjects from each algorithm have enrolled. This is a non-statistically based interim analysis with the potential to stop for futility. R&D will receive the blood pressure measurements for this check. There are no formal statistical hypotheses being tested. The check is purely descriptive in nature.

2.7 Other general principles

2.7.1 Adjustment for covariates

There are no adjustments for covariates in this study.

2.7.2 Handling of Dropouts or Missing data

All data collected up to the point where the patient drops out will be used for analyses. No missing data will be imputed for this study.

2.7.3 Multicenter Studies

This study was conducted in approximately 2 sites. Data from all sites will be pooled together for analyses.

2.7.4 Multiple Comparison/Multiplicity

No formal statistical tests are calculated for this study, so no multiplicity adjustments are needed.

2.7.5 Use of an "efficacy subset" of subjects

There are no plans to use an efficacy subset of subjects for this study.

2.7.6 Rounding and Decimal Places

The estimated mean and median for a set of values will be displayed to 1 more significant digit than the original values, standard deviations will be displayed to 2 more significant digits, and minimum and maximum values will be displayed with the same number of significant digits as the original values. All percentages will be displayed out to 1 decimal place.

3. CHANGES FROM ANALYSIS PLANNED IN PROTOCOL

There are no planned changes in analyses from the protocol.

4. REFERENCES

1. ISO 81060-2:2019/Amendment 1:2020, *Non-Invasive sphygmomanometers – Part 2: Clinical investigation of intermittent automated measurement type – Amendment 1*

5. APPENDIX

5.1 Appendix 1: List of Tables, Listings, and Figures

Table Number	Analysis Population	Table Name
14.1.1	N/A	Subject Overview
14.1.2	FAS	Subject Disposition
14.1.3	FAS	Protocol Deviations
14.1.4	FAS	Categorical Demographics and Baseline Characteristics
14.1.5	FAS	Continuous Demographics and Baseline Characteristics
14.2.1	FAS	Efficacy Assessment: Statistics for Criterion 1 and Criterion 2 Assessment.
14.2.2	FAS	Efficacy Assessment: Summary statistics for blood pressure measurements by algorithm group and measurement type.
14.2.3	FAS	Efficacy Assessment: Distribution of reference blood pressure measurements by algorithm group.
14.3.1.1.1	SS	Summary of Adverse Events
14.3.1.1.2	SS	Adverse Events by SOC and Preferred Term
14.3.1.1.3	SS	Serious Adverse Events by SOC and Preferred Term
14.3.1.1.4	SS	Non-Serious Adverse Events by SOC and Preferred Term
14.3.1.1.5	SS	Adverse Events Related to Study Device by SOC and Preferred Term

14.3.1.1.6	SS	Unanticipated Adverse Device Effects by SOC and Preferred Term
14.3.1.1.7	SS	Adverse Events Leading to Withdrawal by SOC and Preferred Term
14.3.1.1.8	SS	Adverse Events Leading to Death by SOC and Preferred Term
14.3.5	SS	Summary of Unanticipated Problems

Listing Number	**Analysis Population**	**Listing Name**
16.2.1	N/A	Subject Disposition
16.2.2	FAS	Protocol Deviations
16.2.3	SS	Subjects Excluded from the Full Analysis Set
16.2.4	FAS	Demographic and Baseline Characteristics
16.2.5	FAS	Device Exposure
16.2.6.1	FAS	Efficacy data measurements for blood pressure
16.2.6.2	FAS	Pulse rate data measurements
16.2.7.1.1	SS	Adverse Events
16.2.7.1.2	SS	Adverse Events Related to Study Device
16.2.7.1.3	SS	Unanticipated Adverse Device Effects
16.2.7.1.4	SS	Adverse Events Leading to Withdrawal
16.2.7.1.5	SS	Adverse Events Leading to Death
16.2.7.1.6	SS	Serious Adverse Events
16.2.9.1	SS	Unanticipated Problems

Figure Number	**Analysis Population**	**Figure Name**
14.2.3.1	FAS, SureBP Algorithm	SureBP Algorithm: Reading Error vs. Arm Circumference
14.2.3.2	FAS, StepBP Algorithm	StepBP Algorithm: Reading Error vs. Arm Circumference