CLINIMARK Test Plan

Multiparameter Monitor Non-Invasive Blood Pressure Validation Study

PR2019-329

COMMERCIAL SPONSOR:

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Document Ownership: Document is in accordance with CFR requirements for NSR Device Investigation and ISO14155 as appropriate

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Multiparameter Monitor Non-Invasive Blood Pressure Validation Study
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ETHICS COMMITTEE REVIEW:

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STUDY PROCEDURE:

Multiparameter Monitor Non-Invasive Blood Pressure Validation Study
Study ID#: PR-2019-329 Date: 10 APR 2019 Revision: 1

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Multiparameter Monitor Non-Invasive Blood Pressure Validation Study
PR2019-329

Synopsis

Purpose/ Objectives of the Clinical Investigation Plan

The purpose of this study is to provide supporting documentation for accuracy claims for the Vital Detect blood pressure monitor on the intended adult population. A modified same arm sequential method with dual observer auscultation will be used to collect data.
The procedure, data collection methods and data analysis that are outlined in this protocol follow

- **International Standard ISO 81060-2:2018** Non-invasive sphygmomanometers — Part 2: Clinical investigation of automated measurement type

The end goal is to provide Non-invasive Blood Pressure (NIBP) accuracy data to support validation of the Vital Detect blood pressure monitor.

Background

Automated blood pressure cuff measurement is the standard in numerous medical settings today. Oscillometric devices using deflation algorithms estimate the amplitude of pressure changes as the cuff deflates from above the systolic pressure. The amplitude suddenly increases as the pulse breaks through the occlusion of the artery. As the cuff pressure decreases further, the pulsations increase in amplitude, reaching a maximum level (which approximates the mean pressure), and then diminishes. Studies show that, especially in critical cases (arrhythmia, vasoconstriction, hypertension, shock), oscillometric devices are more accurate and consistent than devices using other non-invasive measuring techniques.

This study is designed to assess the accuracy of the Vital Detect blood pressure monitor with an adult population using a modified same arm sequential dual observer auscultation method and is considered investigational for this evaluation.

Summary Overview

The Vital Detect blood pressure monitor will be evaluated in two phases, Phase 1 and Phase 2. Phase 1 will consist of 30 subjects that will approximate the distribution of blood pressures as outlined in **ISO 81060-2:2018**. Upon completion of Phase 1, an interim analysis will be performed to determine whether or not to proceed with Phase 2. Phase 2 will test a minimum of 55 additional subjects to achieve a minimum of 85 subjects. The maximum number of subjects enrolled will not exceed 150 subjects.

Two trained observers, typically a Registered Nurse (RN) or Licensed Practical Nurse (LPN), will observe (listen to) the Korotkoff sounds at the brachial artery of the arm. The reference blood pressure measurements by the nurses will be performed sequentially with the device under test. The nurses will complete 1 or 2 initial baseline auscultatory reference blood pressure measurements and device under test measurements. This is followed by 3 to 8 valid paired blood pressure readings of auscultatory reference blood pressure measurements alternated with device under test measurements. For accuracy claims, the test device measurements will be compared to those made by the reference device. The data for the final analysis will contain no fewer than 85 subjects with a minimum of 255 valid paired observations. At least 90% of the subjects will contribute 3 paired observations. In this case, additional subjects shall be used to complete the minimum number of paired observations.

Subject Inclusion to the study:

- Subjects must be able to provide an informed consent or have legally authorized representative consent to participate.

- Subject must be willing and able to comply with the study procedures.
- Subject must be ≥ 18
- Subject or legally authorized representative must be able to read or write in English.
- Subjects with a finger circumference < 8.3 cm.
- At least 30% of subjects shall be male and at least 30% of subjects shall be female

Subject exclusion to the study:

- Lack of Informed consent.
- Subjects with deformities or abnormalities that may prevent proper application of the device under test.
- Subject is evaluated by the investigator or clinician and found to be medically unsuitable for participation in this study.
- Subjects with known heart dysrhythmias
- Subjects with compromised circulation or peripheral vascular disease.
- Subjects with clotting disorders or taking prescribed blood thinners.
- Subjects that cannot tolerate sitting for up to 1 hour.
- Subject with a blood pressure demographic that has already been filled.

It is expected that the data collection will take up to 1 hour per subject and approximately 1-6 weeks to complete the evaluations. There is no additional follow-up required for the investigation.

Purpose / Objectives of the Clinical Investigation Plan

The primary purpose of this study is to provide supporting documentation for the Vital USA blood pressure monitor on an adult population using a modified same arm sequential, dual observer auscultation method. There are no risks or adverse device effects expected. There are no contraindications for use in the proposed study or study population.

Identification and description of the investigational device

The devices under test will be built according to the Vital USA design control processes.

The devices will include the Vital USA Vital Detect multiparameter platform with finger cuff.

Vital Detect Multiparameter Platform Monitor

Firmware	**Version Number**
NIBP (Non-Invasive Blood Pressure) Firmware	V10.0.15-48
Main	V5.0.3-1
Display	V1.0.11-20

The Vital Detect blood pressure monitor is an investigational device. Device model numbers, serial numbers, date(s) of use, subject ID number(s) will be recorded on the Case Report Forms. A Device Accountability Log will be maintained for the sponsor's equipment documenting date of receipt, and date of return for used and unused product.

The intended purpose of the test is to evaluate the Vital Detect blood pressure monitor to **ISO 81060-2:2018.** The intended use for these products are manual and automatic Non-Invasive Blood Pressure monitoring on adults age 18 and older.

All appropriate testing has been performed and demonstrates safety and efficacy for use in human studies prior to Clinimark's receipt of the devices. Such documentation resides in the Design History Files at Vital USA. The device under test, the Vital Detect blood pressure monitor with finger cuff, is the only component expected to come in contact with the subjects.

The manufacturing of the device followed the good manufacturing practice regulation as identified in 21 CFR 820.

Instructions for installation, use, storage and handling can be found in the Vital Detect Manual.

Vital USA staff will train the Clinimark staff on the instructions for set up and use of the Vital Detect blood pressure monitor prior to start of the study.

Reference Study Equipment

Reference Sphygmomanometer

The reference sphygmomanometer will be the Crystal Digital Sphygmomanometer. The device will be supplied by Clinimark to use for the duration of the study. The reference sphygmomanometer used in this study does comply with the requirements of ISO 81060-1, additionally the maximum error will be $\pm$ 1 mmHg per NIST traceable calibration verification.

Reference cuffs:

A released cuff (based on bladder size selection such as Baumanometer Calibrated V-Lok Cuff or Critikon Dura-Cuf or other.

The selection of the Reference cuff shall have a bladder length of 75% to 100% of the upper arm circumference and a bladder width of 37% to 50% of the upper arm circumference. If there is no reference cuff design that meets this requirement for an individual subject, a cuff that most closely meets these parameters will be selected.

Pulse Oximeter

GE 3900 TruTrak+ / OXYTip+ OXY-F-UN Sensor & Oxy-OL3 cable (cleared device K102426)

Stethoscope

3M Littman dual Auscultatory stethoscope or equivalent will be used in the study.

Preliminary Investigations and Justifications of the Study

In review of the literature, **ISO 81060-2:2018** clearly defines the accepted guideline for conduct, documentation and evaluation of the accuracy of non-invasive automated measurement sphygmomanometer systems. This study is a full validation on the Vital Detect blood pressure monitor in an adult population following the guideline as appropriate for the **ISO 81060-2:2018**.

No Previous testing in the Clinimark laboratories were performed on the USA Vitals Multiparameter Monitor

Risks and benefits of the Investigational device and clinical investigation

Currently the FDA defines blood pressure devices as Class II devices CFR Section: 21 CFR §870.1130, Noninvasive Blood Pressure Measurement System. – Cardiovascular Diagnostic Devices. **The devices under test in this study are thereby considered non-significant risk devices.**

The device and use of the device under test does not meet the definition of significant risk device under 21 CFR 812.3(m)

For the purpose of this study:

It is not intended as an implant.

- The cuff is applied to the bicep and is removed following data collection, typically less than 1 hour

It is not purported or represented to be for use in supporting or sustaining human life

- These devices are not used to support or sustain human life.

It is not used for use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health

- They are not used to diagnose, cure mitigate or treat disease.

The device as used in this investigation does not present a serious risk to the health, safety, or welfare of a subject.

- See below for discussion of risk associated with the device and use of the device.

There are no anticipated risks or adverse device effects to be assessed. There are no contraindications for use in the proposed study / study population (See description of Study Population below). There may be other risks to the subject associated with the device or procedure that are unforeseeable at this time.

Blood Pressure Cuff

The reported risks associated with NIBP include: A) slight discomfort upon inflation of the cuff; B) possible bruising; C) petechial rash; and D) discoloration of the skin beneath the cuff. In rare instances the reported risks associated with NIBP include: A) peripheral nerve injuries; B) skin tear; and C) compartment syndrome (swelling of muscles in the limb causing the reduction of the blood supply to the muscle).

More than 3,946 adults, children, and newborn babies have had their blood pressures taken repeatedly in 104 studies using similar equipment. In these previous studies, the complications of taking repeated blood pressures were temporary and involved either bruising/rash; for example, petechiae rash (less than 2.2%), skin redness/lines (0.8%), or tingling/discoloration in the extremity wearing the cuff while the cuff is inflated (0.1%).[1,2,3,4,5,6]

It is possible that the test subject may experience an allergic reaction to the material in the cuff. The Vital USA finger cuff in this trial utilize standard material that has undergone skin sensitivity testing.

ECG Electrodes

Materials (such as the adhesives and/or gel contact) used in the electrodes may cause some skin irritation in some subjects. Typical skin irritations present with redness of skin and in some cases of sensitivity is an allergic reaction. Biocompatibility testing for surface contact electrodes is a requirement of the international Standards Organization (ISO) 10993- Biological Evaluation of Medical Devices. The risk in the use of ECG electrodes is believed to be minimal.

Pulse Oximetry Sensor

Pulse Oximetry Sensor placement involves positioning pulse oximetry sensors on the volunteer subject in the same manner that is used on hospitalized patients. The sensors may be warm to the touch. Under normal operating conditions, (no fault conditions), the sensors are not expected to

overheat. If the sensors are too warm, they will be removed immediately. Clip on sensors exert a minimal amount of pressure. They should not cause discomfort. If the sensors are too uncomfortable, they will be removed immediately. Adhesive sensors or tape may cause some irritations to the skin in some subjects. Every effort will be made to minimize products with natural rubber or latex. Products containing natural rubber or latex will be identified. The risk in the use of pulse oximetry sensors is believed to be minimal.

General Electrical Equipment

Electrical hazards are a potential risk with all electrical equipment. The equipment used in this study has been designed to meet applicable safety standards. The equipment will be safety and functionally tested by the sponsor and institution (as indicated) prior to patient use. The possibility of any electrical hazard is extremely remote.

Benefits

The benefits to the study are to the advancement of non-invasive medical monitoring of patients by improving Accuracy and performance of non-invasive blood pressure measurements. The only alternative to this study is to NOT participate.

Design of the Clinical Investigation

Method

The Vital Detect blood pressure monitor will be evaluated as a comparative, single center, non-randomized, study in a minimum of 30 subjects, conducted in 2 phases. The maximum number of subjects enrolled is 150 for both phases, to achieve 85 valid data sets. Each subject test is expected to take up to 1 hour. The overall data collection process is expected to be completed across 6 weeks.

The Auscultator will have a normal audiogram before the study begins. All experimenters will review the protocol prior to test.

Each subject or his/her legally authorized representative will be provided an IRB approved Informed Consent. As applicable, subjects will be told about any new information that might change their decision to participate. Subjects who have completed the informed consent and health questionnaire form and meet inclusion/exclusion criteria will be enrolled in the study if they meet desired blood pressure demographics. The study will be explained within his/her ability to understand.

Phase 1 will enroll a minimum of 30 qualified subjects into the study. Two trained observers will listen to the Korotkoff sounds at the brachial artery of the arm. The reference blood pressure measurements by the observers will be performed sequentially with the device under test. The device under test memory will be cleared prior to the next determination. In some cases, this may mean powering down the device to clear the previous readings. The observers will complete 1 or 2 initial baseline blood pressure measurements and then 3 to 8 paired NIBP measurements to be collected for the Accuracy evaluation will follow. Any pair of observers' determinations with a difference greater than 4 mmHg shall be excluded. If any determinations are excluded, additional pair(s) of determinations shall be taken to ensure that the needed number of valid test-reference pairs is collected (up to a maximum of 8 paired readings). In some cases, it may be that only 2 valid paired readings are achieved. This protocol allows for up to 10% of the subjects to have 2 valid paired observations (90% or more will contribute 3 paired observations). In this case, additional subjects shall be used to complete the minimum number of paired observations. A minimum of 85 valid paired NIBP measurements is needed for the final Accuracy analysis. The blood pressure measurements will be such that reference cuff measurements will be alternated with the device under test measurement. The auscultator will wait a minimum of 60 seconds between each blood pressure determination. Each observer's recording of observations of the reference sphygmomanometer shall not be visible to the other observer. The observers will record the exact measurement heard during auscultation and will not round the blood pressure readings. The readings of the sphygmomanometer-under-test shall not be visible to either of these observers. Each subject test is expected to take up to 60 minutes for the enrollment / data collection process.

After data collection has taken place on a minimum of 30 subjects, an interim analysis will be performed. At this point Vital USA will have the option to continue with Phase 2 of the study, as long as no changes were made to the device. Phase 2 will be conducted in the same manner as Phase 1 (as outlined above), enrolling a minimum of 55 additional subjects for a total of at least 85 subjects.

There are no deviations expected from this investigation plan, should deviations be needed, discussions will be conducted with the sponsoring company, Principal investigator and the IRB will be notified per their requirements. Deviations from the study protocol will be disclosed in the final report.

Endpoint / Comparator

The primary objective of this study is to provide a validation to **ISO 81060-2:2018** for non-invasive blood pressure measurement accuracy for the Vital Detect blood pressure monitor on the intended population. The Vital Detect blood pressure will be compared to the Reference Sphygmomanometer via a modified same arm sequential method with dual auscultators.

The final analysis will contain no fewer than 85 qualified subjects to achieve approximately 255 paired observations. The end goal is to pass the Criterion 1 and Criterion 2 of **ISO 81060-2:2018.**

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Criterion 1

Mean Error of individual paired determinations ≤ ±5.0 mmHg
Standard Deviation of determination ≤ 8.0mmHg

Criterion 2

Standard Deviation of the average paired determinations must meet criteria in Table 1 below (page 12).

Study Population

The study population for phase 1 will include a minimum of 30 qualified adult subjects. Phase 2 will include a minimum of 55 additional subjects for a total of 85 subjects for the study. The subject or legally authorized representative must understand the study and provide consent for participation by signing the Informed Consent Form. The subject shall also be informed about the clinical investigation within his/her ability to understand

Subject enrollment is based on meeting the inclusion criteria and none of the exclusion criteria and the subject and data demographics needed for the study.

Subject Inclusion to the study:

- Subjects must be able to provide an informed consent or have legally authorized representative consent to participate.
- Subject must be willing and able to comply with the study procedures.
- Subject must be ≥ 18
- Subject or legally authorized representative must be able to read or write in English.
- Subjects with a finger circumference < 8.3 cm
- At least 30% of subjects shall be male and at least 30% of subjects shall be female

Subject exclusion to the study:

- Lack of Informed consent.
- Subjects with deformities or abnormalities that may prevent proper application of the device under test.
- Subject is evaluated by the investigator or clinician and found to be medically unsuitable for participation in this study.
- Subjects with known heart dysrhythmias

- Subjects with compromised circulation or peripheral vascular disease.
- Subjects with clotting disorders or taking prescribed blood thinners.
- Subjects that cannot tolerate sitting for up to 1 hour.
- Subject with a blood pressure demographic that has already been filled.

Limb size distribution:

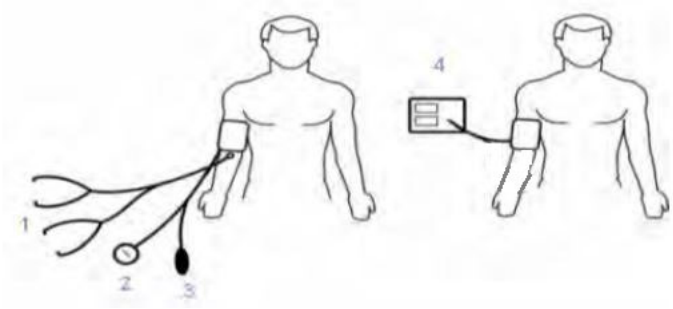
Since this is not a standard cuff configuration, the subjects will only be selected to show a distribution across the range of finger sizes.

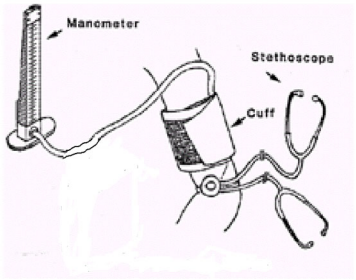
Duration of Clinical Investigation

Each subject, and therefore use of the device, is expected to take up to 1 hour. The study is expected to take approximately 1-6 weeks to complete for this subject population.

Modified Same arm Sequential Method

Equipment Set Up:





Equipment Key"

1 Dual stethoscope
2 reference sphygmomanometer display
3 reference sphygmomanometer hand pump
4 sphygmomanometer under test

Procedure

1. Set up all equipment prior to start of study.
2. Explain the procedure to the subject. Have the subject or authorized representative read the Informed Consent Form and review the information answering all questions. Once all questions have been answered, have the subject or authorized representative sign the form. Have the subject or authorized representative complete the Health Assessment Short Form. Review the study with the subject or authorized representative to make sure he / she wants to participate. Each subject / representative will be given a copy of the consent form prior to release.
3. Measure the subjects finger circumference and ensure that it within the acceptance criteria and measure the forearm length from the location on the arm where the stethoscope is placed to the base of the index finger and record these values. The forearm length is for reference only.
4. Prepare the subject for the study.
   3.1 The subjects should be asked to empty their bladders prior to sitting down.
   3.2 The subject will be positioned such that the subject:
   - is seated comfortably with legs uncrossed and feet flat on the floor.
   - has the back, elbow and forearm supported;
   - has the middle of cuff site at the level of the left ventricle of the heart.

   3.3 Recommend that the subject be as relaxed as possible and that they avoid talking during the entire procedure.
   3.4 The cuff should be applied on the bare arm and there shall be no arm compression proximal to the cuff

3.5 Before the first reading is taken, 5 min should elapse.

5. Apply the pulse oximeter to the subject as a secondary review for a regular rhythm and to provide the heart rate values. Apply the 3-lead ECG only if needed to confirm normal sinus rhythm.
6. Record subject initials, subject number and demographics information onto the Case Report Form.
7. Review the Health assessment short form, if the subject meets the inclusion / exclusion criteria to the study then accept into the study, and continue otherwise the subject is considered not enrolled.
8. Record device information for tracking. (manufacturer, model #, serial or lot, hardware / software control info) on the Case Report Form (CRF).
9. Measure the circumference of the upper arm at the midpoint and place the appropriate sized reference blood pressure cuff on the bicep of the subject.
10. Attach the reference sphygmomanometer to the connector hose on the appropriate port on the reference blood pressure cuff.
11. Make sure the observers for the reference sphygmomanometer are positioned at a height level with the center of the manometer and within 15^{o} from the centerline of the mercury tube (if used) so that parallax errors are avoided.
12. Both observers shall make an initial baseline reference blood pressure determination using a dual stethoscope. The last audible Korotkoff sound, fifth phase or K5, will be used for the diastolic blood pressure determination. Record which Korotkoff sound was used on the CRF. Record the baseline reference blood pressure reading on the CRF.
13. Apply the device under test on the subjects finger and follow the Instructions For Use (IFU).
14. Wait at least 60 seconds and then take the initial baseline device-under-test blood pressure determination. A third observer will record the data for the device-under-test and the reference values from the auscultators insuring that no pair differ more than 4 mmHg. These baseline data points shall not be used in the accuracy determination.
15. Make sure the previous reading of the device-under-test is cleared prior to the next reading.
16. For each subsequent blood pressure determination, wait at least 60 seconds between the readings.
17. The observers will start with the reference sphygmomanometer, then device-under-test, alternating until three valid paired blood pressure determinations are completed. The final reading should be on the reference sphygmomanometer. Make sure to wait at least 60 seconds between each of the readings.
18. The reference blood pressure determinations prior to the test device and post the test device will be averaged for the actual reference blood pressure determination of comparison.
19. Record each blood pressure determination and the pulse rate on the Case Report Form.
20. A maximum number of attempts for the subject is 8 paired determinations.
21. After three valid test-reference pairs are completed, the cuff will be removed.
22. The auscultator will monitor the subject's comfort level and the cuff test site throughout the duration of the study and upon removal of the cuff.
23. The subject will be advised during the study that he/she may stop the test at any time.
24. All equipment will be removed from the subject.
25. The observers will record any final notes on the Case Report Form. The subject will be released with no follow-up required.

Statistical Considerations

There will be an interim statistical analysis following the data collection of the first 30 subjects. The final analysis for the Vital Detect blood pressure monitor will contain no fewer than 85 subjects resulting in a minimum of 255 paired observations.

All data from a subject shall be excluded if any two reference systolic blood pressure determinations differ by more than 12 mmHg or if any two reference diastolic blood pressure determinations differ by more than 8 mmHg. If an individual subject is unstable during the period of the test, two valid consecutive determination pairs may be used. No more that 10% individual subjects may have fewer than three valid

determinations. Therefore at least 90% of the subjects will contribute 3 paired observations, if necessary the balance of the data will be added from additional subjects.

Data analysis and demographics will be presented in the final report

The sphygmomanometer-under-test shall meet the following two criteria.

a) Criterion 1
For systolic and diastolic blood pressures, the mean error of determination, x_n, of the n individual paired determinations of the sphygmomanometer-under-test and the reference sphygmomanometer for all subjects shall be ≤ ±5,0 mmHg, with a standard deviation, s_n, ≤8,0 mmHg when calculated according to Equation (1) and Equation (2):

The observers' individual values of each determination shall be averaged to create the reference blood pressure determination.

$$\bar{x}_n = \frac{1}{n} \times \sum_{i=1}^{n} (p_{sut_i} - p_{ref-sq_i}) \quad (1)$$

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

where
x_n is the mean error;

$p_{sut_i} - p_{ref-sq_i} = x_i$ difference between the i_{th} paired blood pressure determination (sphygmomanometer-under-test – reference sphygmomanometer);

n is the number of determinations.

i is the index of the individual element

p_{ref-sq_i} is the REFERENCE BLOOD PRESSURE for the ith DETERMINATION as calculated according to Formula (3);

$\bar{x}_n$ and s_n shall be calculated and expressed to at least 0.1 mmHg (0.01 kPa).

The REFERENCE BLOOD PRESSURE, $_{ref\ sq_i}p$ – , (the observers' DETERMINATIONS with the REFERENCE SPHYGMOMANOMETER) shall be the average of the preceding and following REFERENCE BLOOD PRESSURES.

$$p_{\text{ref}-\text{sq}_i} = \frac{1}{4} \times (p_{\text{ref}_{i,1}} + p_{\text{ref}_{i,2}} + p_{\text{ref}_{i+1,1}} + p_{\text{ref}_{i+1,2}}) \quad (3)$$

where
$_{ref_{i,1}}p$ is the BLOOD PRESSURE determined by observer 1 for the ith DETERMINATION;
$_{ref_{i,2}}p$ is the BLOOD PRESSURE determined by observer 2 for the ith DETERMINATION.

EXAMPLE n = 255 for paired blood pressure measurements for a 85 subject study.

b) Criterion 2
For the systolic and diastolic blood pressures for each of the m subjects, the standard deviation, s_m, of the averaged paired determinations per subject of the sphygmomanometer-under-test and of the reference

sphygmomanometer, shall meet the criteria listed in Table 1 when calculated according to Equation (4).

$$s_m = \sqrt{\frac{1}{m-1} \times \sum_{j=1}^{m} (x_j - \bar{x}_n)^2} \quad (4)$$

where
x_n is the mean error over all subjects (see Equation 1);

m is the number of subjects;

j is the index for the individual element

x_j is calculated from Equation (4).

$$x_j = \frac{1}{d} \times \sum_{k=1}^{d} (p_{sut_{j,k}} - p_{ref-sq_{j,k}}) \quad (5)$$

where
d is the number of determinations per subject.

k is the index for the individual elements

$p_{ref-sq_{j,k}}$ is the REFERENCE BLOOD PRESSURE calculated according to Formula (6)

$$p_{ref-sq_{j,k}} = \frac{1}{4} \times (p_{ref_{j,k,1}} + p_{ref_{j,k,2}} + p_{ref_{j,k+1,1}} + p_{ref_{j,k+1,2}}) \quad (6)$$

EXAMPLE m =85 for a sphygmomanometer intended for use in participants (an 85 subject study).

Table 1 — Averaged subject data acceptance (criterion 2)

$\bar{x}_n$	Maximum permissible standard deviation, s_m, as function of mean error, $\bar{x}_n$ 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	—	—	—	—	—	—	—	—	—
EXAMPLE For mean error of ± 4,2, the maximum permissible standard deviation is 5,49.										

Monitoring Arrangements

A Clinimark Independent Monitor (Louisville, CO USA) will provide all monitoring. The Monitor shall be responsible for maintaining a record of the findings, conclusions and actions taken from the results of monitoring the study ensuring that:

The monitoring requirements for an NSR device study is identified in 21 CFR 812.2(b) *Abbreviated requirements.* For monitoring an NSR device investigation, the requirement is to comply with 21 CFR 812.46 with respect to monitoring investigations: (a) Securing Compliance, (b) Unanticipated adverse device effects, (c) Resumption of terminated studies

- Compliance to the signed agreement between the Investigator and sponsor
- The study follows the protocol and any amendments that apply
- Compliance to any conditions of the approval imposed by the IRB or FDA

Additionally:

- The conditions for the study continue to be acceptable
- Accurate, complete, and current records are maintained and required reports are written
- Any adverse effects are documented and reported to the Sponsor and IRB as appropriate
- Monitor activities may include for example: performing source data verification and requesting corrections to feedback forms where potential inconsistencies or missing values are identified.
- Findings of non-compliance or required modifications are reviewed with the investigator and the Sponsor, and is presented in a written report to both
- Providing a Monitoring Report at the end of the Clinical Investigation

Monitoring Plan:

1) Informed Consent
    - Verify that the consent form was signed prior to any study procedures being conducted
    - Verify that the staff conducting the consent is listed for approval on the Delegation of Authority Log
    - Ensure that the consent process is documented.
2) Subject Eligibility
    - Verify that the subject meets the inclusion criteria and none of the exclusion criteria.
3) Baseline Data
    - Verify demographic information with the health assessment short form
    - Check that informed consent time and date is prior to start of the procedure
4) Verify all CRFs are completed
5) Adverse Events
    - Verify that Adverse Events and Serious Adverse Events / UADEs are being reported accordingly to the IRB and Sponsor in the required timeframe and their respective reporting requirements.
6) Protocol Deviations
    - Verity that Protocol Deviations are being reported accordingly to the IRB and Sponsor in the required timeframe and their respective reporting requirements.
7) Device Deficiencies
    - Verify that Device Deficiencies are being documented and reported accordingly to the IRB and Sponsor in the required timeframe and their respective reporting requirements.
8) Ensure the Trial Master File is complete.

Data and Quality Management / Confidentiality

A checklist will be maintained identifying the contents of the Project folder PFC#2019-329
The subject's name and signature will be recorded on the Informed Consent, Health Assessment Form, Assent Form (if applies) and a subject participation list. The data collection form will only use a

subject number and initials for the day of the test along with subject demographics. A name will not be recorded on the data collection form.

Records identifying the subject's name will be kept in a secured location with either a locked file or locked door. Access to these files will be on a limited basis. Potential reviewers of this information include: Clinimark representatives collecting the information and conducting the study, Medical Director for Clinimark, the U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, Governmental agencies in other countries, Salus Institutional Review Board and representatives of the sponsor. This group may use the information to conduct independent audits and reviews to verify compliance of the regulatory requirements for these studies but not copy the information.

Data files stored electronically will be associated with a subject based off of subject #, date and by filename recorded on the data collection forms. The original device electronic data files will be preserved in its original form. Data analysis will be performed as a separate electronic file.

Data files, data collection records with subject demographics and subject number may be additionally copied, reviewed and supplied to the commercial sponsor for the study or Contractors associated with Clinimark for data analysis purposes.

There is no current plan to publish this research in scientific journals or present at medical meetings. The subject identity will not be disclosed if the decision to publish is reversed.

All study records will be stored for at least 2 years post the release of the product or project cancelations.

Records - Study Documentation

Study procedure

PR2019-329– IRB Approved Study protocol

Subject Documents

IRB Approved Informed Consent Form (Adult)
Health Form (Clinimark Control # F2000-001-040 REV 1)- Health Assessment-Short Form

Study Conduct Documents

CRF2019-329– Case Report Forms

Case Report Forms

To ensure the quality and integrity of the data, it is the responsibility of the Investigator(s) or designee to complete the Case Report Forms (CRFs) for each subject who is enrolled to participate in this study.
In some cases the CRFs will also be the source document for some information that is not directly collected in the Health Assessment Form. The following information will be recorded on the CRF as appropriate:

- Study date, Subject ID#, Subject Initials, and Relevant Subject Demographics,
- Evidence that informed consent was signed and dated prior to the subject participating in the study
- Information for Subject Inclusion or Exclusion to the study
- Device usage and cuff placement on the subject
- Baseline heart rate
- Baseline blood pressure
- Annotations and observations used in the data analysis
- Protocol deviation reporting
- Adverse Events reporting

- Study termination

A black or blue pen will be used to record data on the data collection forms. Recorded information should be legible and completed. Erroneous entries should be crossed out, corrected with the change, initialed and dated by the individual making the correction. The Investigator(s) or designee will sign and date at indicated places on each page of the data collection form. The Protocol Deviations Reporting can be signed and dated by the designee only if there are no deviations, otherwise the Sub-Investigator or Investigator should review, sign and date. The Adverse Events Reporting should be signed and dated by the designee and a Sub-Investigator or Investigator. The Principal Investigator needs to review, sign and date all serious adverse events. The Investigator or designee will provide a final signature indicating that a thorough inspection of all subject data has been performed and will thereby certify the contents of the forms. The Investigator's Certification Statement will disclose the overall documentation, study oversight and certification of the study.

Trial Master File Documents

- Clinimark Control # B3000-000-003 - Adverse Events and Protocol Deviation Reporting System
- Clinimark Control # F2000-001-029 - Device Deficiency Form
- Clinimark Control # F2000-001-016 - Device Accountability Form
- Clinimark Control # F2000-001-015 - Delegation of Authority
- Clinimark Control # F2000-001-017 - Investigator Financial Interest Disclosure
- Clinimark Control # F2000-001-022 - Investigator's Certification Statement
- Clinimark Control # F2000-001-028 - Subject Enrollment Log
- Clinimark Control # F2000-001-027 - Site Personnel Training Log
- Clinimark Control # F2000-001-033 - Site Visit/ Monitoring Log
- Clinimark Control # F2000-001-034 - Data Clarification Form
- Clinimark Control # F2000-001-037 - Protocol Deviation Log
- Clinimark Control # F2000-001-038 - Adverse Events Log
- Clinimark Control # F2000-001-035 - Regulatory Binder Bullet Checklist

Note 1: Current revision of documents
Note 2: Documents provided by the sponsor may be used instead of the list above

Amendments to the Clinical Investigation Plan

The sponsor or site may need to make protocol changes during the study. Such amendments will be documented, reviewed and changes will be submitted to the sponsor for first approval, then to the IRB for approval. The sponsor and site will make a decision regarding the continuation of subject enrollment during this period. The site may proceed with the amendment upon receipt of IRB approval.

Deviations from the Clinical Investigation Plan

Investigators are not allowed to deviate from the Protocol or Clinical Investigation Plan (CIP) except under emergency circumstances. Deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the IRB. Such deviations shall be documented and reported to the sponsor and the IRB as soon as possible but within 5 working days of the occurrence of such deviation.

Deviations that significantly affect the safety, efficacy, integrity, or conduct of the study must be reported to the Sponsor within 5 working days from awareness of occurrence and reported to the IRB per the deviation reporting policy.

Deviations that do not affect the safety, efficacy, integrity, or conduct of the study will be documented in the data collection forms and CRF as appropriate.

Device Accountability

A Device Accountability Log will be maintained for the sponsor's equipment documenting date of receipt, description of device (including model#, lot#, serial number or unique code, and quantity) and date of return for used and unused product.

Packaging and Labeling
Research conducted for this study will utilize investigational devices and devices cleared through the 510k regulatory process. The Sponsor is responsible for packaging and labelling of the device for delivery to the study site. FDA cleared devices do not require special labelling. Investigational devices or its immediate package shall bear a label with the following information: name and place of the manufacturer, packager, or distributor, the quantity of contents, if appropriate, and the following statement:
"CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use."

The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

It is the investigator's responsibility to ensure the appropriate labelling is visible and remains intact throughout the life of the study.

The Instructions for Use (IFUs) are provided as separate documents from this protocol.

Storage and Accountability
The site will store the investigational product. The storage area should be locked/secure with access limited only to approved study staff.

The site will record/track use of the investigational device by each participant. Documentation should verify that the device use was in accordance with the approved protocol.

Statement of Compliance
The study will be conducted in accordance with the Declaration of Helsinki, ISO 14155, 21 CFR 50, and 21 CFR 812. The study will not commence until the approval has been received from the IRB.

Compliant with the following Documents
Study Procedure: Multiparameter Monitor Non-Invasive Blood Pressure Validation Study
Study ID#: PR2019-329

Reference Documents
- **ISO 81060-2:2018,** Non-invasive sphygmomanometers — Part 2: Clinical investigation of automated measurement type. Document followed with respect to same arm sequential method 5.2.4.2 as applicable to the device under test.
- International Standards Organization ISO 14155, 2011-02-01 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice
- Clinimark Adverse Events Reporting Document B3000-000-003 (current revision)
- 21 CFR 812 – NSR Medical Device Investigations
- Salus IRB Reporting forms

Informed Consent Process
- The Principal Investigator or his / her designee conducts the informed consent process
- Verify that the subject acknowledges ability to read English
- Instruct the subject to ask questions at any time during this process, especially about things they do not understand.
- Allow subject ample time to read the entire form and ask questions.
- Give a thorough description of the study and the subject's involvement – especially explain that they may withdraw from the study at any time.

- After the subject has read the form ask if they understand everything
- Ask if they would like to take part in the study and if so explain that they may sign and date the form.
- Once the subject has signed and dated the informed consent, the principal investigator or authorized designee will sign and date the form.
- Give a copy of the informed consent to the subject.
- No procedure may be performed before the informed consent is signed by the subject

If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

Safety

Subjects

Equipment is checked out for proper functionality prior to being placed on the subject.

The subject or legally authorized representative will review and sign the informed consent following a discussion of the test procedure and when all questions regarding the study have been answered. A health assessment questionnaire will be completed to disclose any pertinent issues that may affect the subject's health during the test. The study will be explained to the subject. The subject and / or representative may withdraw from the study at any time. The subject may be withdrawn by the investigator or study staff if in the best interest of the subject.

The investigator or designated study staff will be present to monitor the subject at all times. Safety monitoring includes observation of the site once the cuff is removed and direct communication with the subject for discomfort.

Investigators

All experimenters must review and understand the protocol prior to test.

All experimenters must review and understand the emergency procedures prior to the test.

Adverse Event Definitions

The definitions for adverse event, adverse device effect, serious adverse event, serious adverse device effect, unanticipated adverse device effect, and their classifications are provided below (ISO 14155, 21 CFR 812.3).

Adverse Device Effect (ADE): Adverse event related to the use of an investigational medical device resulting from insufficiencies or inadequacies in the instructions for use, the deployment, installation, the operation, or any malfunction of the investigational medical device or from error use.

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device or investigational procedure

Anticipated Serious Adverse Device Effects (ASADE): ASADE is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Mild: a mild adverse event is one in which the subject is aware of the event, but it is easily tolerated without intervention.

Moderate: a moderate adverse event is one that causes sufficient discomfort to interfere with usual activities.

Serious Adverse Device Effect (SADE): adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

Serious Adverse Event (SAE): a serious adverse event is an adverse event that results in death, inpatient hospitalization, severe or permanent disability, a life threatening illness or injury, fetal distress, fetal death, a congenital abnormality, a birth defect, or medical or surgical intervention to prevent permanent impairment to body or structure.

Severe: a severe adverse event is one that results in the inability to perform usual activities.

Unanticipated Adverse Device Effect (UADE): serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Management of Adverse Event Reporting

Should the subject experience an adverse or non-typical event, assessment of the situation is first initiated and a determination will be made of appropriate actions. The Medical Director and Principle Investigator will be contacted as appropriate. Adverse Events are reported through standard Clinimark Procedures, IRB requirements and per Vital USA's SOPs.

Records of Adverse events

The following information will be obtained will be recorded in the Case Report Form

- Type of effect (ADE, AE. ASADE, SADE, SAE, UADE)
- Date of onset and resolution
- Intensity (mild, moderate, severe)
- Serious (yes/no)
- Relationship to device (unknown, not related, possibly related, probably related, definitely related)
- Anticipated (yes/no)
- Treatment given and / or action taken (procedure stopped, withdrawn from study, no action)

Reporting of Serious Adverse Events and / or UADE

All SAE's, SADE, ASADE and UADE will be reported in writing to the Principal Investigator, Medical Director, Sponsor and IRB within 72 hrs of knowledge of the event.

If the event resulted in death of a subject, the event shall be reported to the Principal Investigator, Medical Director, Sponsor and IRB within 24hrs of knowledge of the event.

Note: For Non-Significant Risk studies, the Reviewing IRB serves as a surrogate to the FDA. The term IRB was substituted in the following for applicability to this study.

Sponsor Records and Reports

Records 21 CFR 812.140 (b) 4,5

The following records shall be consolidated in one location and available for FDA inspection and copying:

- The name and intended use of the device and the objectives of the investigation;
- A brief explanation of why the device is not a significant risk device:
- The name and address of each investigator:
- The name and address of each IRB that has reviewed the investigation:
- A statement of the extent to which the good manufacturing practice regulation in part 820 will be followed in manufacturing the device; and
- Any other information required by FDA.
- Records concerning adverse device effects (whether anticipated or unanticipated) and complaints

Reporting 21 CFR 812.150 (b) 1,2,3,5,6,7,8,9,10:
The sponsor shall prepare and submit the following complete, accurate, and timely reports:

Unanticipated Adverse Device Effect
A sponsor shall immediately conduct an evaluation of an unanticipated adverse device effect. The results of such evaluation shall be reported to the IRB and participating investigators as soon as possible, but in no event later than 10 working days after the sponsor first receives notice of the effect.

Withdrawal of IRB approval
The sponsor shall report to all participating investigators and reviewing IRBs within 5 working days after receipt of the withdrawal approval by the reviewing IRB.

Current Investigator list
A current list of names and addresses of participating investigators will be submitted to the IRB

Progress Reports
The sponsor or designee shall submit progress reports to the IRB at least yearly.

Recall and device
The sponsor or designee shall notify the reviewing IRB of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.

Final Report
The sponsor or designee shall submit a final report to the IRB with 6 months after termination or completion of the investigation.

Informed consent
The sponsor or designee shall submit to the IRB a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

Significant risk device determinations – (does not apply to NSR studies)
If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.

Other
A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Investigators Records and Reporting
Records 21 CFR 812.140 (a)(3)(i)
The investigator maintains records of each subject's case history and exposure to the device and supporting data including signed and dated consent forms, health assessment form, and progress notes during the study. Records should show evidence that informed consent was signed and dated prior to the subject participating in the study.

Reports 21 CFR 812.150 (a) 1,2,5,7
The investigator shall prepare and submit the following complete, accurate, and timely reports:

Unanticipated adverse device effects.

The investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

Withdrawal of IRB approval.
The investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

Progress Reports
The investigator shall submit progress reports to the sponsor, monitor, and reviewing IRB at least yearly.

Informed consent.
If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

Final Report
An Investigator shall submit a final report within 6 months after the termination or completion of the investigation to the reviewing IRB and sponsor.

Other.
The investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Withdrawal, Early Termination or Suspension of the Investigation

Consideration for early termination or suspension of the investigation is tied to unanticipated equipment failure or a decision by Vital USA or Clinimark based on business reasons.

Participation in the study is voluntary. Subjects may choose to withdraw from the study at any point. If a subject officially withdraws from the study, the laboratory staff will document the reason for withdrawal in the CRF.

Participation in the study may also be stopped at any time by the principal investigator or by the Sub-investigators or sponsor.

- The subject's failure to cooperate fully (as determined by the investigator in his or her sole discretion) with the required conduct of this study.
- The subject's development of an illness as determined by the investigator in his or her sole discretion.
- A determination by a Clinimark representative (in his or her sole discretion), for whatever cause, that the study should be discontinued.
- A determination by the sponsor (in his or her sole discretion), for whatever cause, that the study should be discontinued

The collection of data for study subjects will cease in the following cases:

- Subject completes all study requirements
- Subject withdraws consent
- Investigator's decision that it is in subject's best interest to be discontinued from the study
- Subject death
- Adverse event other than death requiring withdrawal of the subject from the study
- Determination that the subject was ineligible for the study.

There will not be any follow-up procedures for withdrawn or discontinued subjects required, unless a follow-up is required at the Investigator's discretion.

Consideration for early termination or suspension of the investigation is tied to unanticipated equipment failure or a decision by the sponsor or the site. Both Sponsor and Clinimark reserve the right to discontinue the study at any time for administrative or other reasons. Written notice of study termination will be submitted to the investigator in advance of such termination. Termination of a specific site can occur because of, but not limited to, inadequate data collection, low subject enrollment, or non-compliance with the protocol or other research requirements.

Early termination results when the study is closed prior to the end of the study. A study suspension is a temporary postponement of the study activities related to enrollment. Both are possible for the study. If the study is terminated or suspended, no additional enrollment will be allowed unless otherwise informed by the sponsor. The current subjects will be followed according to the protocol.

If the study is terminated prematurely or suspended by the sponsor/investigator, the sponsor /investigator will promptly inform the regulatory authorities (if required) of the termination and the reason(s). IRB/IECs will also be promptly informed and provided with the reason(s) for termination or suspension by the sponsor/ investigator. The investigator will promptly inform the subjects and assure appropriate follow-up for the subject.

If the investigator (or IRB/IEC) terminates or suspends the investigation the investigator will promptly inform the institution (if required) and the IRB/IEC, and provide a detailed written explanation of the termination or suspension. The investigator will promptly inform the subjects and assure appropriate therapy and follow-up for the subjects. The sponsor will inform the regulatory authorities (if required).

Withdrawal of IRB approval shall be reported to the sponsor by the investigator within 5 working days. In case of early termination of the study, all study subjects should be followed until the resolution of any pending adverse event(s).

Publication Policy

The results of this investigation will not be submitted for publication.

References

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3. Bickler, P.E., Schapera, A., & Bainton, C.E., (1990). Acute radial nerve injury from use of an automated blood pressure monitor. *Anesthesiology, 73*, 186-188.

4. Tollner, U., Bechinger, D., & Pohlandt, F. (1980). Radial nerve palsy in a premature infant following long-term measurement of blood pressure. *Journal of Pediatrics, 96*, 921-922.

5. Bause, G.S., Weintraub, A.C., & Tanner, G.E. (1986). Skin avulsion during oscillometry. *Journal of Clinical Monitoring, 2,* 262-263.

6. Celoria, G., Dawson, J.A., & Teres, D. (1987). Compartment syndrome in a patient monitored with an automated blood pressure cuff. *Journal of Clinical Monitoring, 3,* 139-141.

Principal Investigator Signature Page

Protocol No PR2019-329

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in accordance with the Declaration of Helsinki, 14155, 21 CFR 50, and 21 CFR 812:

- Ensuring that the required EC approval is in place prior to the start of the Clinical Investigation.
- Ensuring informed consent of each subject is obtained,
- Ensuring the investigation is conducted according to the Clinical Investigation Plan,
- Personally conducting or supervising the investigation,
- Protecting the rights, safety, and welfare of participants,
- Preparing and maintaining adequate, current, and complete case histories or records,
- Retaining records for two years following the date the marketing application is approved or withdrawn,
- Furnishing the required reports to the sponsor, including reports of adverse events and study completion,
- Providing timely reports to the IRB, including reports of changes in the research activity needed to avoid immediate hazards to participants, unanticipated problems involving risks to participants or others, including adverse events to the extent required by the IRB,
- Ensuring that changes are not implemented without prospective IRB approval, unless required to eliminate immediate hazard to participants,
- Complying with all FDA test article requirements,
- Adequately maintaining control of test articles, including appropriate tracking documentation for test articles to the extent that such control and documentation are not centrally administered,
- Supervising the use and disposition of the test article,
- Disclosing relevant financial information, and
- Ensuring that all associates, colleagues, and employees assisting in the conduct of the investigation(s) are informed about their obligations in meeting the above commitments.
- An investigator shall, upon request by reviewing IRB or FDA, provide accurate, complete and currant information about any aspect of the investigation.

17 APR 2019

Signature of Investigator Date

Arthur Cabrera, MD

Investigator Name (print or type)

Principal Investigator

Investigator Title

Clinimark, LLC

Name of Facility

Louisville, CO USA

Location of Facility (City, State, Country)