NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Tool Revision History:

Version Number	Version Date	Summary of Revisions Made
1.0	21 Mar 2018	Original version
2.0	15 Mar 2019	Version 2
3.0	18 July 2019	Version 3 – Inclusion to NYU Langone Neurocritical Intensive Care Unit

ACCURACY OF NON-INVASIVE NON-OSCILLOMETRIC BLOOD PRESSURE WRISTBAND

A single-center study of the accuracy of a non-invasive, non-oscillometric blood pressure wristband when compared with an intra-arterial blood pressure catheter

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NYULMC Study Number:	*17-00884*
Funding Sponsor:	*LiveMetric*
IND/IDE Number:	*IDE Exempt*
Regulatory Sponsor:	*N/A*
Study Product:	*LiveMetric Blood Pressure Wristband*
Study Product Provider:	*LiveMetric*
ClinicalTrials.gov Number	*NCT03629535*

Initial version: 08/01/2017
Amended: 03/15/2019
Amended: 07/18/2019

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience

CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

Protocol Summary

Title	Accuracy of non-invasive, non-oscillometric blood pressure wristband
Short Title	Non-invasive blood pressure wristband accuracy
Brief Summary	In an intensive care unit patients who already have an intra-arterial blood pressure monitor in place, this wristband device will be applied and blood pressure readings compared for approximately 30 minutes. Blood pressure readings will be gathered and compared.
Phase	N/A
Objectives	The primary objective of the present investigation is to determine the accuracy of a non-invasive non-oscillometric blood pressure wristband device when compared to invasive intra-arterial blood pressure monitors.
Methodology	Open, single arm, pilot study
Endpoint	The percentage of blood pressure measurements falling within the acceptable standard deviation will be compared.
Study Duration	Total study duration is expected to be 1 month.
Participant Duration	Participant involvement duration is expected to be approximately 30 minutes.
Duration of IP administration	Total duration of investigational device use is 30 minutes.
Population	Patients admitted to the Intensive Care Unit who are already fitted with an invasive Arterial Line (A Line) are eligible for the trial, and no volunteer candidates for an A Line are requested. Sample size is expected to be approximately 15 patients.
Study Sites	NYU Langone Health Surgical Intensive Care Unit, Cardiovascular Intensive Care Unit, Neurologic Intensive Care Unitand NYU Langone Brooklyn Surgical Intensive Care Unit and Neurologic Intensive Care Unit
Number of participants	Total sample size is expected to be 15 patients.
Description of Study Agent/Procedure	The device is a band intended to be worn on the wrist for intermittent blood pressure measurements. The device applies no inflatable mechanics or moving parts. The wristband is watertight and can be worn as any type of bracelet.
Reference Therapy	The investigational wristband is being compared to an intra-arterial blood pressure monitor.
Key Procedures	Wristband application for 30 minutes.
Statistical Analysis	For each of the subjects, 10 intra-arterial blood pressure measurements will be collected and 10 wristband measurements will be collected at the same time points.

	Systolic and diastolic blood pressure measurements will be compared using an acceptable standard deviation of 10 mm Hg (+/-5 mm Hg). Mean arterial pressure measurements will be compared using an acceptable standard deviation of 5 mm Hg (+/- 2.5 mm Hg). The percentage of blood pressure measurements falling within the acceptable standard deviation will be compared. The percentage of blood pressure measurements for each patient falling within the acceptable standard deviation will also be compared.

Schematic of Study Design

1. Patients in the ICU with an intra-arterial blood pressure monitor already in place will be considered as subjects.
2. Verbal consent to participate will be obtained.
3. The blood pressure wristband will be applied to one wrist to allow for blood pressure measurements to be obtained and recorded. The blood pressure wristband will then be applied to the contralateral wrist for measurements. The total time of device application is expected to be approximately 30 minutes.
4. Demographics of the subject will be anonymous collected – height, weight, age, current medications, and general condition.
5. Blood pressure measurements from both the wristband and the intra-arterial blood pressure monitor will be compared.

1. Key Roles

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2. Introduction, Background Information and Scientific Rationale

2.1. Background Information and Relevant Literature

Hypertension is a common medical condition that increases the risk of ischemic heart disease, stroke, peripheral vascular disease, and other cardiovascular diseases. Currently the gold standard for blood pressure management is an invasive intra-arterial blood pressure monitor.

A noninvasive wristband device has been developed for measurement of intermittent blood pressure. It is intended to be work in day-to-day life by people with hypertension or other conditions where blood pressure monitoring is important.

The purpose of this study is to determine the accuracy of the non-invasive wristband device when compared to the invasive gold standard.

Lehman LW, Saeed M, Talmor D, Mark R, Malhotra A. Methods of blood pressure measurement in the ICU. Crit Care Med. 2013;41:34–40. doi: 10.1097/CCM.0b013e318265ea46.

2.2. Name and Description of the Investigational Agent

LiveMetric has developed a wristband device for measurement of intermittent blood pressure. It does not require any action by the user other than wearing the band on the wrist. The device uses no inflatable mechanics or moving parts. The wristband is watertight and can be worn as any type of bracelet. See attachment for device image.

The wristband device meets the criteria for IDE exemption because it is a diagnostic device that:

(i) Is noninvasive,

(ii) Does not require an invasive sampling procedure that presents significant risk,

(iii) Does not by design or intention introduce energy into a subject, and

(iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

2.3. Potential Risks & Benefits

2.3.1. Known Potential Risks

The only potential risk is the possible discomfort associated with wearing the wristband device.

2.3.2. Known Potential Benefits

There is no potential benefit to participating in this study. In the future, the device may be used to benefit patients with high blood pressure or other conditions in which blood pressure monitoring is important.

3. Objectives and Purpose

3.1. Primary Objective

The primary objective of the present investigation is to determine the accuracy of a non-invasive non-oscillometric blood pressure wristband device when compared to invasive intra-arterial blood pressure monitors within the ISO-81060-2 requirements

3.2. Secondary Objectives (if applicable)

N/A

4. Study Design and Endpoints

4.1. Description of Study Design

1. A medical professional will measure simultaneous non-invasive auscultatory readings to determine the lateral difference for later adjustment of calculation accordingly. Calculation of lateral difference is provided in section (**Error! Reference source not found.**). All data from a subject shall be excluded if: i) the lateral difference of the reference systolic BP readings is more than 15 mmHg (2,00 kPa); or ii) the lateral difference of the reference diastolic BP readings is more than 10 mmHg (1,33 kPa).
2. If subject's reading is eligible, the medical professional or research personnel will place the LiveMetric wristband on the opposite limb than the one having the A-line, providing the location of the placement has intact skin.
3. During the measurement stage, BP values are simultaneously recorded from the reference invasive A-line and the LiveMetric device. In addition, other vital signs from the monitoring equipment can be collected as available (ECG, Respiratory rate, Pleth, and HR). The invasive BP values and other vital signs are captured from the Vital Signs Monitor (available in the patient's room) and the LiveMetric device. A measurement session of 30 minutes will be conducted for each subject. During the measurements, no information from the device will be provided to the investigator or study personnel. All the data will be processed and analyzed post-measurement according to the following considerations as required by the standard: only up to 10 consecutive measurements per subject will be analyzed; measurement will be made over 30 seconds of recording; consecutive meas-

urement will be considered as the next 30 seconds following at least a 60 second interval. Measurement (data points) is defined as recording or acquisition of signal from the monitor. The medical professional will take off the wristband at the end of this process.

4. All measurements will be processed and analyzed retrospectively according to the requirements of the standard (ISO 81060-2) as detailed below in section (**Error! Reference source not found.**). A 30-minute session of measurements will be conducted for each subject. All the data will be processed and analyzed post measurement according to the following considerations as required by the standard; only up to 10 consecutive measurements per subject will be analyzed; measurement will be made over 30 seconds of recording; consecutive measurement will be considered as the next 30 seconds following at least a 60 second interval.
5. All data points recoded during the first phase will be sent for processing and calibrating the algorithm. All the data points recorded during the second stage will be post processed by algorithm and results will be analyzed by an unbiased third party (bio-statistician).
6. Demographics of the subject will be anonymous collected from the electronic medical record – height, weight, age, current medications, and general condition.
7. Blood pressure measurements from both the wristband and the intra-arterial blood pressure monitor will be compared.

4.2. Study Endpoints

4.2.1. Primary Study Endpoints

The study endpoint will be the time when 10 blood pressure measurements have been obtained from a subject wearing the wristband.

5. Study Enrollment and Withdrawal

5.1. Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Adult (>18 years old) ICU patient who already has an intra-arterial blood pressure measurement in place.

5.2. Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Body habitus that precludes patients from wearing a device on their wrist
2. Subjects without normal palpable radial artery pulse, whether congenital, due to medical intervention, or otherwise
3. Subjects with wrist circumference less than 155mm or greater than 210mm
4. Subjects implanted with VAD's or other mechanical circulatory support device whether intracorporeal or extracorporeal
5. Patients that do not have an intra-arterial blood pressure line.

5.3. Vulnerable Subjects

No vulnerable subjects will be included in this study. Given the population at the SICU, it is possible that some patients might not have capacity to consent for themselves. Each potential subject with be assessed for their capacity to provide consent. Patients who are not alert, oriented, and able to comprehend the study will not be asked to participate in this study. Only those with capacity to consent for themselves will be enrolled.

5.4. Strategies for Recruitment and Retention

Target sample size is 15 patients. The anticipated number of patients to be screened in order to reach the target enrollment is 20 patients.
Only adult patients admitted to theNYU Langone Health Surgical ICU, Cardiovascular ICU, Neurologic ICU and NYU Langone Brooklyn Surgical ICU and Neurologic ICU will be considered. Participation is voluntary and will require verbal consent. Volunteers who do not already have an intra-arterial catheter in place will not be considered.

5.4.1. Use of DataCore/Epic Information for Recruitment Purposes

Potential subjects will be identified using the daily NYU Langone Health ICU and NYU Langone Brooklyn ICU census. The study investigators have a clinical relationship with these patients and will approach them for participation.
No DataCore/Epic information will be used for recruitment.

5.5. Duration of Study Participation

The total duration of subject participation in the study is expected to be approximately 30 minutes.

5.6. Total Number of Participants and Sites

Recruitment will end when approximately 20 participants are enrolled. It is expected that approximately 20 participants will be enrolled in order to produce 15 evaluable participants.

5.7. Participant Withdrawal or Termination

5.7.1. Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.7.2. Handling of Participant Withdrawals or Termination

A subject may withdraw from the study at any time. If a subject withdraws, his or her data will not be included in this analysis. An additional subject will be needed to allow for the goal sample size to be achieved.

5.8. Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigators. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6. Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1. Study Agent(s) and Control Description

The device is a wristband. Because the subjects also have an intra-arterial blood pressure monitor in place, the subjects will serve as their own control.

6.1.1. Acquisition

LiveMetric will provide the blood pressure wristbands for use in this study.

6.1.2. Device Specific Considerations

The device is a wristband that will be worn by the subject for approximately 30 minutes. See the attached image for further details. The BP data will be downloaded to a laptop using Medicollector software. No patient information is included only the BP signals.

6.1.4. Administration of Intervention

The wristband device will be applied by an investigator. It will be removed by an investigator at the end of the study period.

6.1.5. Assessment of Subject Compliance with Study Intervention

The subject will be directly observed by an investigator when wearing the investigational wristband to ensure compliance.

6.2. Study Procedures/Evaluations

Blood pressure measurements from the arterial line will be recorded directly from the intra-arterial blood pressure monitor screen. Blood pressure measurements from the wristband device will be downloaded to a laptop computer using Medicollector software. No patient information will be included.

6.2.1. Study Specific Procedures

The following information will be collected anonymously for each subject: Age, weight, current inpatient medications, general condition. No PHI will be saved.

6.2.2. Screening

Once a patient has been admitted to the NYU Langone Health Hospital, Surgical ICU, Cardiovascular ICU, or Neurologic ICU or NYU Langone Brooklyn Surgical ICU or Neurologic ICU, and an intra-arterial blood pressure monitor has been placed, an investigator will approach the subject to determine willingness to participate in the study and to obtain verbal consent.

7. Assessment of Safety

7.1. Specification of Safety Parameters

No specific safety parameters. The only anticipated risk is the potential discomfort associated with wearing the wristband device.

7.1.1. Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.2. Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

7.1.3. Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)

- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect, 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 (21 CFR 812.3(s)).

7.2. Classification of an Adverse Event

7.2.1. Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.2.2. Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- ***Related*** *– The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.*
- ***Not Related*** *– There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.*

7.2.3. Expectedness

The only expected potential risk is the possible discomfort associated with wearing the wristband. No other adverse events are expected.

7.3. Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

7.4. Reporting Procedures – Notifying the IRB

7.4.1. Adverse Event Reporting

Adverse events will be reported to the investigators, the involved subject, the IRB, and to LiveMetric within 24 hours of the event.

7.4.2. Serious Adverse Event Reporting

Serious adverse events will be reported to the investigators, the involved subject, the IRB, and to LiveMetric within 24 hours of the event.

7.4.3. Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within<insert timeline in accordance with policy> of the IR's receipt of the report of the problem from the investigator.

7.5. Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the DCC/study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in Section 1, Key Roles.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the

effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

7.6. Study Halting Rules

If any SAE occurs, during the study, the study will be stopped.

7.7. Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8. Clinical Monitoring

PI will be conducting monitoring to ensure safety of subjects.

9. Statistical Considerations

Data from the A-line monitor and from the LiveMetric device shall be collected and processed using a validated Software. Categorical parameters shall be presented in percentages and will be compared using X2 testing. Continuous variables shall be reported as mean □ standard deviation and will be compared using the Student's t-test. Correlation shall be determined via linear regression analysis. Agreement shall be determined via the Bland and Altman technique. The analysis shall be conducted for intermittent values by applying the reference ISO 81060-2:2013.

The LiveMetric device shall provide values for each intermittent session and shall be compared to a range measured by the A-Line (data point). The data point is defined as the interval between the lower and higher value read by the A-Line, providing: the interval is no less than 30 seconds; the difference range from the reference device is less than the permissible highest range of 20 mmHg for SYS and 12 mmHg for DIA. Should the LiveMetric device read within the same range as the A-line, then the reading is considered accurate. However, if the reading is not within the defined range, then the error rate is defined as the range in mmHg between the closest edges of the reference reading to the values obtained by the LiveMetric device

9.1. Statistical and Analytical Plans (SAP)

Baseline demographics including age, weight, current medications, and general medical condition will be collected anonymously.

For each of the subjects, 10 intra-arterial blood pressure measurements will be collected and 10 wristband measurements will be collected at the same time points.
Systolic blood pressure measurements will be compared using an acceptable standard deviation of 10 mm Hg (+/-5 mm Hg).
Diastolic blood pressure measurements will be compared using an acceptable standard deviation of 10 mm Hg (+/-5 mm Hg).

Mean arterial pressure measurements will be compared using an acceptable standard deviation of 5 mm Hg (+/- 2.5 mm Hg).

The percentage of blood pressure measurements falling within the acceptable standard deviation will be compared.
The percentage of blood pressure measurements for each patient falling within the acceptable standard deviation will also be compared.

9.2. Statistical Hypothesis

The hypothesis is that >90% of wristband blood pressure measurements will be within the accepted standard deviation when compared to the intra-arterial blood pressure measurements.

9.2.1. General Approach

All statistal analysis for this study will be performed by Dr. Patricia Ayoung-Chee, MD, MPH using Stat 15 software when needed.

9.2.2. Analysis of the Primary Efficacy Endpoint(s)

N/A

9.2.3. Baseline Descriptive Statistics

N/A

9.2.4. Planned Interim Analysis

N/A

9.3.1. Determining the reference BP
The invasive SYS and DIA BP values shall be determined from the recordings. (The BP reading will be recorded beat to beat, without any averaging, from the A-line and from the LiveMetric device). The mean and experimental standard deviation of the SYS and DIA BP from the recordings will be determined.

Since there is no cuff inflation interruption by the LiveMetric device, the A-line ranges shall be determined from the recording for a duration of 30 seconds, while simultaneously recording the same period of the data point from the LiveMetric device.

The reference SYS is defined as the range of a ± 1 experimental standard deviation around the mean value of the invasive systolic BP values obtained during the data point range performed by the LiveMetric device. The reference DIA BP is defined as the range of ±1 experimental standard deviation around the mean value of the invasive diastolic BP values obtained during the same period.

Isolated VPB’s shall be addressed by removing the pressure pulse associated with the VPB and the following compensatory beat.

9.3.2.
If the value obtained from the LiveMetric determination lies within the range of the reference BP as determined in (**Error! Reference source not found.**), assign an error of 0 mmHg (0 kPa) to this determination.

If the value obtained from the LiveMetric determination lies outside the range of the reference BP as determined in (**Error! Reference source not found.**) subtract the value of the determination from the adjacent limit of the range of the variation of BP. That difference represents the error for this determination.

The arithmetic mean of the error is calculated and its experimental standard deviation from the errors of each recording for each BP value (SYS & DIA) and determination for each patient.

9.3.3. Data Analysis

The data set will be collected for clinical investigation purposes andwill be processed and analyzed according to the formulas provided in the ISO 81060-2: 2013.

The lateral difference will be calculated initially as the average difference between the readings or determination made on each limb according to Formula:

$$LD = \frac{1}{3} \times \left(\sum_{i=1}^{3} Pi - \sum_{j=1}^{3} Pj \right);$$

i is the index for the determination on the limb used for the sphygmomanometer-under-test determination;

j is the index for the reading on the limb used for the reference reading.

Only data within the inclusion criteria as defined in section (**Error! Reference source not found.**) will be processed for the purpose of clinical investigations.

The mean value of the errors for SYS and DIA BP, x_n of the n individual paired determination of the LiveMetric device as determined above for all subjects, will be calculated according to Formula:

$$\bar{X}_n = \frac{1}{n} \times \sum_{j=1}^{n} X_1$$

and Formula:

$$S_n = \sqrt{\frac{1}{n-1} \times \sum_{j=1}^{n} (X_i - \bar{X}_n)}$$

Where;

X_1 is the error of the i^{th} individual determination as determined in (**Error! Reference source not found.**);

n is the total number of determinations;

i is the index for the individual determination.

Mean or standard deviation outside the specified ranges above, mandate further algorithm modification until subsequent testing with new data sets done in accordance with this protocol meets the above criteria.

9.3.4. Analysis of the Primary Efficacy Endpoint
Primary Endpoint is determined by meeting the success criterion for SYS and DIA BP as defined by ISO 81060-2: 2013

9.5. Sample Size

As determined in ISO 81060-2 / 2013; a reference invasive BP monitoring equipment clinical investigation shall consist of a minimum of 15 patients. For each patient shall be a minimum of 150 valid BP measurements in the clinical investigation.
The goal sample size is 15 patients. It is expected that 25 patients will need to be screened to obtain the desired sample size.

9.6. Measures to Minimize Bias

Blinding is not an option in this investigation. All subjects will utilize both the intra-arterial blood pressure monitor which is already in place and the wristband that is applied during the study.

10. Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11. Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12. Ethics/Protection of Human Subjects

12.1. Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2. Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3. Informed Consent Process

12.3.1. Consent/Assent and Other Informational Documents Provided to Participants

An IRB-approved consent script will be provided to the patient and verbal consent will be obtained from the subject or LAR.

12.3.2. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved

and the participant or the Legal Authorized Representative will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the consent script and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will provide verbal informed consent prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the consent script will be given to the participants for their records. However, a signed informed consent will not be requested as this would only create additional PHI documents that would need to be protected. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Only verbal consent will be obtained. A signed informed consent document will not be stored in the subject's research record. We are requesting a waiver of written documentation of consent and a waiver of HIPAA authorization because the only record linking the subject and the research would be the consent document, and the principal risk of the research would be potential harm resulting from a breach of confidentiality.

12.4. Participant and Data Confidentiality

No PHI will be collected. All data will be stored anonymously.
No signed consent documents will exist. Only verbal consent will be obtained.
Data collection will end at the time the wristband is removed.

13. Data Handling and Record Keeping

13.1 Data Collection and Management Responsibilities

Only anonymous data will be collected. No PHI will be retained.
Anonymous data will be recorded and saved electronically.
Intra-arterial blood pressure monitor data will be recorded automatically as per ICU standards.
Data collection will be the responsibility of the investigators and will be stored on REDCap.

13.1. Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.2. Protocol Deviations

Any deviation in protocol will be reviewed by the investigators to determine if data from the involved subjects can be included. If not, additional subjects will be required to obtain the goal sample size.

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or

the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4. Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

14. Study Finances

14.1. Funding Source

LiveMetric will provide the investigational wristband device. No other funding is being received.

14.2. Costs to the Participant

There is no cost to the subject for participation in this study.

14.3. Participant Reimbursements or Payments

No compensation will be provided for participation in this study.

15. Study Administration

This study includes only the investigators listed in prior sections.

16. Conflict of Interest Policy

All investigators will follow the applicable *Conflict of Interest policies related to research. See: https://nyumc.ellucid.com/documents/view/1119*

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

17. References

Chung E, Chen G, Alexander B, Cannesson M. Non-invasive continuous blood pressure monitoring: a review of current applications. Front Med. 2013;7(1):91-101.

Lehman LW, Saeed M, Talmor D, Mark R, Malhotra A. Methods of blood pressure measurement in the ICU. Crit Care Med. 2013;41:34–40. doi: 10.1097/CCM.0b013e318265ea46.

McGhee BH and Bridges EJ. Monitoring arterial blood pressure: What you may not know. Crit Care Nurse. 2002;22:60-79.

Henneman E and Henneman P. Intricacies of blood pressure measurement. Heart Lung. 1989;19:263-273.

[redacted]

18. Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

1. Consent Script
2. Waiver for written consent