Study protocol and Statistical Analysis Plan

Clinical evaluation of sphygmomanometer BN1(Bionet BNiBP module) according to ISO 81060-2:2018 protocol

Clinical Research Ethics Review Committee :

Hanyang University Seoul Hospital IRB(Institutional Review Board)

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1. Name and address of the clinical trial institution

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222-1, Wangsimni-ro Seongdong-gu, Seoul, Korea (04763)

2. Purpose and background of clinical trials

A blood pressure monitor is a basic medical device that is essential for diagnosing cardiovascular diseases, and its importance is very high. Most of the electronic sphygmomanometer equipment or modules (components) used in Korea are foreign products. Recently, a new electronic sphygmomanometer module was developed by Bionet, a domestic company, and has been approved by the Ministry of Food and Drug Safety and is being applied to clinical practice. In order for a blood pressure monitor to be used as a medical device for diagnosis of various diseases, it is important to test the accuracy of blood pressure to know the exact degree of blood pressure measurement. In this study, a clinical study was conducted to investigate the performance of the equipment using the auscultation method used as a reference (gold standard) for non-invasive blood pressure measurement (NIBP) at the Department of Family Medicine at Hanyang University Hospital and the newly developed equipment at the same time. We want to help the industry.

3. Medical device information for clinical trials

3-1. Medical device in test

- Name/code name of drug/device/procedure method: BM5 with BN1 (BNiBP) (Bionet Co., Ltd., Korea)
- Item name: Patient monitoring device
- Purpose and efficacy: Displays biometric information such as electrocardiogram (ECG), non-invasive blood pressure (NIBP), invasive blood pressure (IBP), body temperature (TEMP), blood oxygen saturation (SPO2), and respiration (RESP) on the screen. It is a monitoring device that analyzes blood pressure values during vital sign measurement and displays Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP).

- Other functions of BM5 are disabled and only the performance of NIBP function is evaluated.

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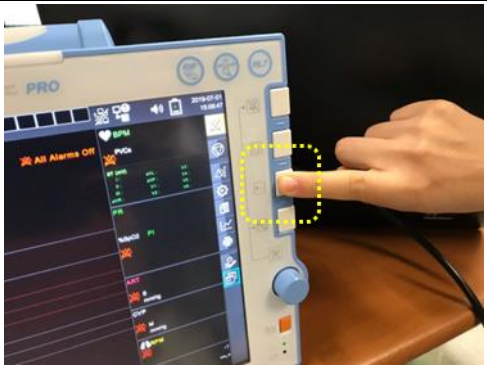
- Cuff Specification and Method

Cuff Type	A Cuff (V0014C)	B Cuff (V0013C)	C Cuff (V0012C)
Pictures			
Available arm circumference range	27.5 ~ 36.5 cm	20.5 ~ 28.5 cm	13.8 ~ 21.5 cm

Pictures	Explanation
	- The cuff is wrapped around the arm of the subject to be measured.

	- When you press the NIBP operation button of the BM5, blood pressure measurement starts automatically. -(If necessary) If you press the NIBP operation button while measuring blood pressure, blood pressure measurement is stopped.
	- When blood pressure measurement is finished, the result value is displayed at the bottom of the BM5 screen.

3-2. Auscultational measuring tool to be used as a reference

- 2 stethoscopes (connected to Y-piece or T-piece):

Pictures	Explanation
	- Product Name: Littmann Classic 2 - Manufacturer : 3M | Littmann - Connect two stethoscopes with a T-piece so that two nurses required by the protocol can measure simultaneously.

- Aneroid sphygmomanometer :

Pictures	Explanation
	- Product Name: Greenlight 300 - Manufacturer: ACCOSON - Measurement method: non-mercury auscultation method
- Shown to be compliant with the US standard for non-automated sphygmomanometers, ANSI/AAMI SP9:1994, and has been approved by the FDA (K040410). - It has also been shown to be compliant with the European standards EN1060-1, EN1060-2 and EN1060-3. - Approved by British Hypertension Society (www.dableducational.org)	

- Hose

Pictures	Explanation
	- A hose from one cuff to both the electronic sphygmomanometer and auscultation sphygmomanometer - Length: 2M

- Cuff Specification

Cuff Type	A Cuff (V0014C)	B Cuff (V0013C)	C Cuff (V0012C)
Pictures			
Available arm circumference range	27.5 ~ 36.5 cm	20.5 ~ 28.5 cm	13.8 ~ 21.5 cm

4. Indication

Normal blood pressure/Attention blood pressure/Pre-hypertension/Hypertension

5. Research period

From IRB approval to October 31st, 2021

6. Method of clinical trial

6-1. Study subjects

[Selection Criteria]

- - Subjects who have consented to participate in the clinical trial and voluntarily consented in writing
- - Subjects who meet the criteria presented in ISO 81060-2:2018 Protocol 5.1 Subject requirements
  - ■ Number
    : In order to evaluate the accuracy of the electronic blood pressure monitor, the number of study subjects should be at least 85.

: Unless otherwise specified, at least three valid blood pressure data pairs should be obtained from each study subject, and therefore the number of valid data pairs should be at least 255.

- Gender distribution
  : Male – more than 30%, Female – more than
- Age distribution
  : Bionet's NIBP module includes adults and children (Children: 3 to 12 years).
  : Therefore, at least 35 children are included.
- Limb size distribution
  : Each cuff should be evaluated for at least $\frac{1}{2\times c}$ of all subjects. (where c is the number of cuffs)

  : At least 40% of personnel with arm circumferences greater than half of the measurable range specified on the cuff.
  : At least 40% of personnel with arm circumferences less than half of the measurable range specified on the cuff.
- Blood pressure distribution
  : At least 5% of the reference SBP data must be less than or equal to 100 mmHg.
  : At least 5% of the reference SBP data must be 160 mmHg or higher.
  : At least 20% of the reference SBP data must be 140 mmHg or higher.
  : At least 5% of the reference DBP data must be less than or equal to 60 mmHg.
  : At least 5% of the reference DBP data must be 100 mmHg or higher.
  : At least 20% of the reference DBP data must be 85 mmHg or higher.

[Exclusion criteria]

- Emergency surgery patient
- Subjects with psychiatric disorders such as mental retardation or autism
- Subjects whose blood pressure measurement is difficult or expected to be difficult
- Subjects who did not consent to the study

[Number of target subjects and basis for calculation]

- Number of target subjects

  : According to ISO 81060-2:2018 5.1 Subject requirements, the number of NIBP subjects for adults and children should be 85 or more, including 35 or more children.

  : Considering the dropout rate of 20%, 102 subjects (including more than 35 children) were recruited.

- Method of recruiting research subjects and obtaining consent

  : Recruitment is made through the recruitment notice for patients and their guardians who visit Hanyang University Hospital. After giving a sufficient explanation in a language that the subject can understand and waiting for 15 to 30 minutes to understand the contents of the study, the principal investigator obtains written consent from the subject or his/her representative. In addition, we accept withdrawal from research participation at any time during the study participation period without loss of the research subject's refusal.

- Random assignment method and blinding method

  : This clinical trial does not use randomization or blinding methods.

6-2. Research method overview

[Prepares]

- The auscultation-type blood pressure monitor used as a comparison target in accuracy evaluation must satisfy international standards.
- Prior to evaluating the accuracy of the electronic blood pressure monitor, two measurers should be trained to detect the same auscultation sound for each study subject.
  e.g. British and Irish Hypertension Society: BP Measurement auscultatory tutorials
- Two measurers must undergo an audiogram hearing test.

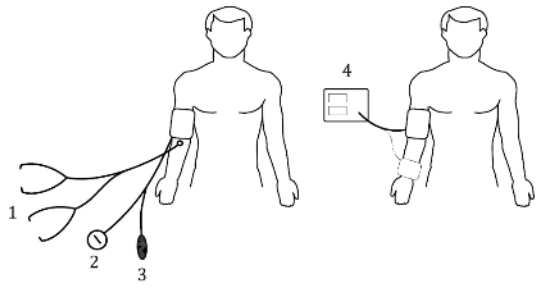
[Measurement considerations]

- The auscultation method has the following sources of error and should be considered when measuring.
  - Improper combination of cuff size and arm width
  - The stethoscope or transducer is not positioned over the brachial artery
  - Measurer's hearing loss or incorrect technique
  - Fast cuff deflation

[Measurement method]

- Use the sequential measurement method.
- The test configuration comparing the accuracy of the electronic blood pressure monitor and the auscultation method blood pressure measurement is prepared to measure one arm of a subject at the same time using a Y-piece or a T-piece as shown in the figure. Since the exhaust speed of the automatic sphygmomanometer is fast and it is impossible to measure with the electronic sphygmomanometer and auscultate at the same time, a method of sequentially measuring the electronic sphygmomanometer and the auscultation method is taken.

EXAMPLES *Switching the power off and on, removing the* BLOOD PRESSURE *module and reinstalling it or issuing a reset command are methods to clear the memory of the previous* DETERMINATION.



Key
1 double stethoscope
2 REFERENCE SPHYGMOMANOMETER display
3 REFERENCE SPHYGMOMANOMETER hand pump
4 SPHYGMOMANOMETER-UNDER-TEST

NOTE Only one CUFF is connected to the SPHYGMOMANOMETER-UNDER-TEST.

- In the sequential measurement method, the procedure for measuring the reference value and the blood pressure of the test equipment is as follows.

First blood pressure measurement		
1.	Reference blood pressure measurement by two observers	R0
2.	test medical device blood pressure measurement	T0
Blood pressure measurement to evaluate accuracy		
3.	First reference blood pressure measurement by two observers	R1
4.	First test medical device blood pressure measurement	T1

5.	Second reference blood pressure measurement by two observers	R2
6.	Second test medical device blood pressure measurement	T2
7.	Third reference blood pressure measurement by two observers	R3
8.	Third test medical device blood pressure measurement	T3
9.	Fourth reference blood pressure measurement by two observers	R4

: Reference (R0 ~ R4) is the average value of the blood pressure measurement values by auscultation method of two measurers.

: Measure R0 and T0 to check the function of the test medical device.

: Blood pressure measurement for accuracy evaluation. Measure in order of R1, T1, R2, T2, R3, T3, R4.

: Measure at least 1 minute apart.

: Each study subject has the following three data pairs.

T1 vs (R1, R2 mean), T2 vs (R2, R3 mean), T3 vs (R3, R4 mean)

- Other

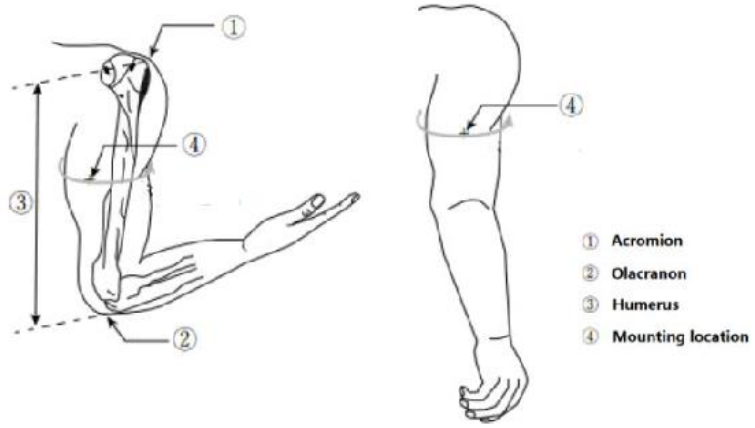
: If the reference SBP value of any two pairs is greater than 12 mmHg or the reference DBP value is greater than 8 mmHg, all data of the subject should be excluded.

: Despite these requirements, if the reference blood pressure of the subject does not meet the above criteria during the trial period, two consecutive pairs of reference blood pressure that meet the above criteria may be used.

: The number of study subjects using 2 pairs of reference blood pressure should be less than 10% of the number of study subjects using 3 pairs of reference blood pressure.

: If there are data to be excluded by both measurers (observers), additional measures are made, and up to 8 times per study subject is possible.

: To measure the circumference of the upper arm, with the forearm facing upward, and keeping the elbow angle at 90 degrees, measure the circumference at ④, the midpoint between ① and ②, as shown in the figure below.



: During the test, follow the American Heart Association (AHA) measurement guidelines below.

American Heart Association (AHA) measurement guidelines	
Recommend	Explanation
The patient sits comfortably on his back. Don't cross your legs. Arms are supported. The patient sits and rests for at least 5 minutes before measurement.	DBP is high in a sitting position, and SBP is high in a standing position.
	A non-recumbent position can increase DBP, and a cross-legged position can increase SBP.
	In the case of elderly patients, blood pressure in the sitting and standing state is periodically measured to differentiate orthostatic hypotension.
Arms should be supported at heart level. The meter is placed in the center of the sternum.	If the arm is lower than the right atrium, the blood pressure is measured too high, and if the arm is higher than the heart, the blood pressure is measured too low.
	If your arm is not supported, your blood pressure will be high.
The cuff wraps more than 80% of the patient's arm circumference.	A blood pressure cuff that is small relative to the patient leads to measurement errors, and a cuff that is too small leads to a deviation of 2 to 10 mmHg or more.
The mercury meter deflates at a rate of 2 to 3 mmHg per second.	When subtracting more than 2 mmHg per second, the SBP is lower than the actual value and the DBP is higher than the actual value.
Measure SBP and DBP at the first and last beating sounds, respectively.	Measures with an accuracy of up to 2 mmHg.
Neither the patient nor the measuring person should speak.	Deviations may occur in measurements. Just by listening, it rises above 10 mmHg.

	Factors causing deviations in measurement include exercise, smoking, drinking, muscle tension, bladder distension, room temperature, and ambient noise.

7. Observation items, clinical examination items, and observational examination methods

[Basic items]

- Date and time
- Clinical trial number & subject number
- date of birth
- age
- gender
- On antihypertensive medication
- arm circumference
- Pulse
- Cuff Size (A Cuff, B Cuff, C Cuff)

[Items excluded from clinical trials]

- Complete blood pressure range recruitment (Range complete)
- Arrhythmia
- Device failure
- Cuff size unavailable
- Poor quality of Korotkoff sounds
- Observers disagreement
- Other factors

[Record blood pressure readings]

- All blood pressure units are recorded in mmHg, and the measurement interval, including the time required for cuff replacement, should be at least 60 seconds. A separate sheet is used to record the study subject's running total according to the blood pressure range.

[Compare]

- It is evaluated by statistically comparing the blood pressure measured by the test medical device with the blood pressure measured by the auscultation method.

[Statistical analysis]

- For 85 or more study subjects, the following two criteria must be satisfied for more than 255 valid data pairs by measuring 3 times per subject with a test medical device and auscultation method.

- Criterions 1

  - It is calculated separately for SBP and DBP, and the difference between the data pairs for n test medical devices and auscultation-type blood pressure measurement values of all subjects must satisfy the following conditions.

    : The average value $\bar{x}_n$ for the difference between the test medical device and the auscultation method blood pressure calculated according to Equation (1) should be within ±5.0 mmHg.

    : The standard deviation $s_n$of the data pair calculated according to Equation (2) should be within 8.0 mmHg.

    : $\bar{x}_n$ and s_n must be expressed in units of at least 0.1 mmHg.

$$\bar{x}_n = \frac{1}{n} \times \sum_{i=1}^{n} \left(p_{SUT_i} - p_{REF-sq_i} \right) \quad (1)$$

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

$p_{SUT_i} - p_{REF-sq_i}$: Difference between the i-th blood pressure data pair
i : Index to individual element
n : number of measurements
p_{REF-sq_i} : The i-th reference blood pressure measurement calculated according to equation (3)

$$p_{REF-sq_i} = \frac{1}{4} \times (p_{REF_{i,1}} + p_{REF_{i,2}} + p_{REF_{i+1,1}} + p_{REF_{i+1,2}} \quad (3)$$

$p_{REF_{i,1}}$: i-th blood pressure reading by measurer 1

$p_{REF_{i,2}}$: i-th blood pressure reading by measurer 2

- Criterions 2

  ■ For m study subjects, the standard deviation s_m of the average value of the difference between data pairs of each study subject calculated according to Equation (4) must satisfy Table 1 below.

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

$p_{SUT_i} - p_{REF-sq_i}$: Difference between the i-th blood pressure data pair

j : Index to individual element

m : Number of study subjects

x_j : Test medical device blood pressure measurement calculated according to Equation (5)

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

d : Number of measurements per subject

k : Index to individual element

$p_{REF-sq_{j,k}}$: Reference blood pressure calculated according to equation (6)

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

Table 1. Averaged subject data acceptance (Criterions 2) in $mmHg$

$\bar{x}_n$	Maximum permissible standard deviation, sm, as function of, $\bar{x}_n$ $mmHg$									
	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
± 0	6.95	6.95	6.95	6.95	6.93	6.92	6.91	6.9	6.89	6.88
± 1	6.87	6.86	6.84	6.82	6.8	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	6.3
± 3	6.25	6.2	6.14	6.09	6.03	5.97	5.89	5.83	5.77	5.7
± 4	5.64	5.56	5.49	5.41	5.33	5.25	5.16	5.08	5.01	4.9
± 5	4.79	-	-	-	-	-	-	-	-	-

8. References

[1] BS Alpert, Validation of the Welch Allyn Spot Vital Signs blood pressure device according to the ANSI/AAMI SP10:2002. Accuracy and cost-efficiency successfully combined. Blood Press Monit. 2007. 12(5): p.345-7.

[2] Andrew C., et al, Validation of the Omron 705IT(HEM-759-E) oscillometric blood presusre monitoring device according to the British Hypertension Society protocol. Blood Press Monit. 2006 11(1): p.27-32

[3] Guidelines for Accuracy Evaluation of Electronic Sphygmomanometers – KFDA Food and Drug Administration

[4] O'Brien et al., European Society of hypertension international protocol revision 2010 for the validation of blood pressure measuring devices in adult, BPM, 2010, pp.23-38

[5] Stergiou et al., A universal standard for the validation of blood pressure measuring devices: Association for the advancement of medical instrumentation/European Society of Hypertension/International Organization for Standardization (AAMI/ESH/ISO) Collaboration statement, Journal of Hypertension, 2018, 36(3), pp.472-478.