Clinical Study Reports

Studied by: Gangnam Severance Hospital

Official Title: A prospective, made in public and randomly allocated clinical study for a single-arm in a single-center to assess the preciseness of a wrist band type blood pressure gauge, H2-BP for measuring the blood pressure on radial artery

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CONFIDENTIAL

Overall information herein shall be strictly kept as confidential.

Contents

1. Title of Study

A prospective, made in public and randomly allocated clinical study for a single-arm in a single-center to assess the preciseness of a wrist band type blood pressure gauge, H2-BP for measuring the blood pressure on radial artery.

2. Summary of the protocol

Objectives of Study	Compare and assess the accuracy of wrist band type and stethoscope type blood pressure gauge by applying to the out subjects, hospitalized patients and applicants who show symptoms of hypotension, normal blood pressure, borderline hypertension and high blood pressure
Overview of Study Design	Prospective, single-arm, single-center, open-label, non-randomized study
Clinical Trial Institution	Gangnam Severance Hospital, Yonsei university
Count of targeted subjects	141subjects (Minimum 85 subjects) The subjects of this study should be recruited while taking the following into account **1. Wrist Circumference Distribution of Study Subjects [1)]** • At least 20% of the experimenters shall have the circumference within 1/4 of the entire limb circumference. (Minimum 17 subjects) • At least 10% of the experimenters shall have the circumference within top 1/8 of the entire limb circumference. (Minimum 9 subjects) • At least 10% of the experimenters shall have the circumference within lowest 1/8 of the entire limb circumference. (Minimum 9 subjects) H2-BP shall take the wrist circumference as the criterion of measuring as it is a wrist band type and measures the pressure by wearing on the wrist. The wrist circumference is marked in centimeter. The minimum subjects in each sector are as follows as H2-BP is regulated for the people with 15-19cm wrist circumference to use the unit. • 15.0–15.5625 cm: At least 10% (minimum 9 subjects) • 15.5625–16.125 cm: At least 10% (minimum 9 subjects) • 16.125–17.25 cm: At least 20% (minimum 17 subjects) • 17.25–18.375 cm: At least 20% (minimum 17 subjects) • 18.375–18.9375 cm: At least 10% (minimum 9 subjects) • 18.9375–19.5 cm: At least 10% (minimum 9 subjects) **2. Age Constitution[1) 2)]** - Over 19

	3. Gender Constitution of Study subjects [1) 2)] - Minimum respective 30% of female and male shall constitute entire subjects **4. Upper Arm Circumference Distribution of Study Subjects** [1)] - The bladder length of the comparator device should be 75–100% of the subject's upper arm circumference. - The bladder width of the comparator device should be 37–50% of the subject's upper arm circumference.
Inclusion/Exclusion Criteria	**1. Inclusion/Exclusion Criteria for Subjects of the Investigational Device** **1) Inclusion Criteria** (1) The out patients, hospitalized patients and applicants over 19 who show symptoms of hypotension, normal blood pressure, borderline hypertension and high blood pressure (2) Inclusion of patients who meet the count of the targeted patient and rationale of estimation, i.e. wrist circumference, age, gender and circumference of the upper arm (Refer to section 6) (3) Inclusion of patients who agreed in written form to decide the participation and comply the cautions after listening and understanding fully the details on this clinical study. **2) Exclusion Criteria** (1) The subjects who disagreed to participate into this study (2) The subjects likely not to maintain the constant blood pressure about 30 minutes due to hypovolemia or quasi equivalent disease and situation (3) The subjects likely not to maintain the constant blood pressure about 30 minutes due to short-termly active vasoactive agonist or quasi equivalent medication (4) Subjects with cardiac arrhythmia (5) Subjects who ate food within 30 minutes (6) The patients who took caffeine drink within 1 hour or smoked within 15 minutes (7) The subjects who made exercise immediately before measuring the blood pressure (8) Other subjects who are inappropriate to this study by the decision of the research staff

	2. Inclusion/Exclusion Criteria for Users of the Investigational Device [3)] **1) Inclusion Criteria** (1) The subjects to be tested with the stethoscope type blood pressure gauge shall acquire appropriate hearing power and eyesight. (2) The subjects to be tested with the stethoscope type blood pressure gauge shall have training and experience on measuring. (3) The subjects who voluntarily agreed to sign after listening the explanation on the objective and procedure of the clinical study **2) Exclusion Criteria** The subjects who were decided as inappropriate for participating into the clinical study by the person in charge for the clinical study and other research staff
Clinical study Period	About 23 months - Study Protocol and IRB Approval: approximately 2 months - Study Contract and Administrative Procedures Execution: approximately 1month - Subject Recruitment and Study Procedure Execution: approximately 19 months - Analyze data and report results: approximately 1 month
Investigational Device	**1. Investigational Device** 1) Model: H2-BP 2) Product name(Product category No.) and class: Automatic electronic blood pressure gauge(A23010.04)/Class II 3) Manufacturer: Charmcare Co., Ltd 4) Shape and structure: -H: 81.5mm, L: 79.5mm, W: 25.5mm 5) Storage conditions: Store at room temperature **2. Comparator**[4)] 1) Model: big ben® Sphygmomanometer 2) Product name(Product category No.) and class: Aneroid type blood pressure gauge(A23010.01) / class I 3) Manufacturer: Riester 4) Shape and structure: - H: 250mm, L: 250mm, W: 250mm 5) Storage conditions: Store at room temperature
Instructions for use	The Investigational Device will be applied to one wrist of the patient to measure blood pressure, followed by the application of the comparator to the upper arm of the same arm to measure blood pressure. The procedure for use

	is as follows. **1. Investigational Device (H2-BP)** The device is applied to the subject's wrist, and pressure inflation begins when the button is pressed. Once the measurement is complete, the systolic and diastolic blood pressure values are displayed on the screen. For detailed instructions on usage, refer to Appendix 2_H2-BP User Manual0-42_Full Document. **2. Comparator (big ben® Sphygmomanometer)** After placing the cuff around the upper arm, the pump is manually pressed to inflate the cuff. Two operator each using a separate stethoscope connected to the same cuff, independently measure the systolic and diastolic blood pressure.
Test method	This clinical study is a prospective, single-arm, single-center, open-label, non-randomized study conducted over one day. After providing a thorough explanation of the study, informed consent is voluntarily obtained in writing from outpatients, inpatients, and subjects aged 19 years or older with hypotension, normotension, borderline hypertension, or hypertension. Each subject is assigned a screening number, and eligibility (inclusion/exclusion) criteria are assessed. Demographic information (date of birth, age, and gender) is collected, and the use of prior or concomitant medications is reviewed. The wrist and upper arm circumference of the subjects are measured, and those deemed eligible are enrolled in the clinical study. **1. test method** The wrist band-type blood pressure monitor H2-BP and the auscultatory blood pressure measurement device are used to measure blood pressure on the same arm. The wrist band-type blood pressure monitor is operated by a single operator who records the measurement values, while the auscultatory blood pressure device is used by two independent operators who measure blood pressure simultaneously. For each subject, the H2-BP is worn on one wrist, and the auscultatory blood pressure device is applied alternately to the upper arm of the same arm. Measurements are repeated until three valid pairs of measurements are obtained from a single subject, with a maximum of eight measurement attempts allowed per subject. **2. reading criteria**

	The two operators performing auscultatory blood pressure measurements must measure blood pressure independently for each subject, ensuring that they are blinded to each other's readings. Additionally, the operators must not have access to the measurement values displayed by the investigational device during the procedure. For each subject, measurements are repeated for 10 to 30 minutes until three valid blood pressure readings are obtained. All recorded values are documented accordingly.
Endpoint	-Primary Endpoint : Average on difference between blood pressures measured with test device and reference device, Standard deviation on the blood pressures measured with test device and reference device. (Based on count of measurement) -Secondary Endpoint : Standard deviation on difference between blood pressures measured with test device and reference device. (Based on the count of the patients)
Visit schedule	2 days in total : Screening(Visit 1), Medical instrument application(Visit 2) If the screening process does not take a significant amount of time, both screening and medical device application may be conducted during Visit 1.

3. Research Background and Theoretical Basis

The cardio pulmonary diseases from hypertension, arteriosclerosis and cerebral apoplexy emerge one of the factors threatening the modernists' health. According to the report from Statistics Korea in 2022, cardio pulmonary diseases ranked 2nd and 3rd in cause of death in Korea. According to the report from Statistics Korea in 2022, cardio pulmonary diseases ranked 2nd and 3rd in cause of death in Korea. [5] Over 610K people per annum in USA died for cardiac diseases.[6] The blood pressure control is one of the important factors in monitoring such cardiac pulmonary diseases.[7] The blood pressure is controlled by monitoring always with blood pressure measuring tool.

The crucial point in blood pressure measuring is the preciseness. Inaccurately measured blood pressure not only reach to its inaccuracy but also can make bad influence on the health of normal patients and hypertension patients as well by resulting in unnecessary treatment and improper control. Accordingly, the righteous understanding on how to measure and how to manage the gauge lead to measure the blood pressure exactly. Moreover, measuring the blood pressure 1-2 times can be short for exact diagnosis and treatment as it fluctuates daily and changes every time every minute depending on the activities of the patients. The electronic blood pressure gauge has a merit for heightening the reliability in blood pressure data as a few times checking are easier.

Lk++

The H2-BP from Charmcare is a blood pressure gauge to measure the blood pressure at systolic and diastolic area of the adults non-invasively. It is configured with main body, cuff, band and charging cable. Repeated pressing on the measuring button pressurizes the cuff automatically and measures the highest and lowest blood pressure and pulse by using oscillometric. H2-BP is used by wearing on the wrist like a usual wrist watch. The convenience in using by the patient is improved and it provides the environment for more frequent monitoring. Therefore, the clinical test for the accuracy of H2-BP will be made by comparing the data measured by H2-BP and stethoscope type blood pressure gauge.

4. Objectives of Study

This study is purposed to compare and assess the accuracy of wrist band type and stethoscope type blood pressure gauge by applying to the out patients, hospitalized patients and applicants who show symptoms of hypotension, normal blood pressure, borderline hypertension and high blood pressure.

5. Risk/Benefit Analysis

5.1 Risks of participating in research

In this study, subjects will have their blood pressure measured using standard methods and will additionally have their blood pressure measured using the H2-BP wrist band blood pressure monitor. Blood pressure measurement is a non-invasive test and poses little additional risk to subjects from participating in the study.[8) 9)]

5.2 Benefits of participating in research

While there is no direct benefit to you as a participant in this clinical study, you may benefit from the results of this study, which will help validate the accuracy of wearable blood pressure monitors for convenient blood pressure measurement and provide information about more convenient and useful products for people with related conditions.

5.3 Risk/Benefit Analysis

There is no additional risk of harm from this study, and the benefits to society outweigh the anticipated inconvenience of the research.

6. Planned Sample Size

Planned Sample Size: 141 Subjects (Minimum Enrollment: 85 Subjects)

Rationale for Sample Size Calculation: According to the guidelines outlined in ISO 81060-2 Third Edition 2018-11 (Non-invasive sphygmomanometers - Part 2: Clinical investigation of intermittent automated measurement type [including: Amendment 1 (2020)]) and EN 1060-4 (Non-invasive sphygmomanometers - Part 4: Test procedures to determine the overall system accuracy of automated non-invasive sphygmomanometers), a minimum of 85 subjects must be enrolled to evaluate the accuracy of electronic sphygmomanometers.
Considering potential data loss due to withdrawal of consent and other unforeseen circumstances, an anticipated dropout rate of approximately 40% has been applied. Accordingly, a total of 141 subjects will be recruited for this study.

Composition of Study Subjects: In accordance with the ISO 81060-2 Third Edition 2018-11 international standard for the clinical validation of electronic sphygmomanometers, the enrolled subjects must meet the following composition criteria.
The investigator is responsible for continuous monitoring of subject enrollment status to ensure compliance with the required composition. If the composition criteria are not met, additional subjects may be recruited as necessary to fulfill the requirements.

6.1 Wrist Circumference Distribution of Study Subjects

1) At least 20% of the experimenters shall have the circumference within 1/4 of the entire limb circumference. (Minimum 17 subjects)
2) At least 10% of the experimenters shall have the circumference within top 1/8 of the entire limb circumference. (Minimum 9 subjects)
3) At least 10% of the experimenters shall have the circumference within lowest 1/8 of the entire limb circumference. (Minimum 9 subjects)

H2-BP shall take the wrist circumference as the criterion of measuring as it is a wrist band type and measures the pressure by wearing on the wrist. The wrist circumference is marked in centimeter. The minimum subjects in each sector are as follows as H2-BP is regulated for the people with 15-19cm wrist circumference to use the unit.

- 15.0–15.5625 cm: At least 10% (minimum 9 subjects)
- 15.5625–16.125 cm: At least 10% (minimum 9 subjects)
- 16.125–17.25 cm: At least 20% (minimum 17 subjects)
- 17.25–18.375 cm: At least 20% (minimum 17 subjects)
- 18.375–18.9375 cm: At least 10% (minimum 9 subjects)
- 18.9375–19.5 cm: At least 10% (minimum 9 subjects)

6.2 Age Constitution

Over 19

6.3 Gender Constitution of Study Subjects

Minimum respective 30% of female and male shall constitute entire subjects

6.4 Upper Arm Circumference Distribution of Study Subjects

- The bladder length of the comparator device should be 75–100% of the subject's upper arm circumference.
- The bladder width of the comparator device should be 37–50% of the subject's upper arm circumference.

7. Inclusion/Exclusion Criteria on Patients

7.1 Inclusion/Exclusion Criteria for Subjects of the Investigational Device

1) Inclusion Criteria

(1) The out patients, hospitalized patients and applicants over 19 who show symptoms of hypotension, normal blood pressure, borderline hypertension and high blood pressure

(2) Inclusion of subjects who meet the count of the targeted patient and rationale of estimation, i.e. wrist circumference, age, gender and circumference of the upper arm (Refer to section 6)

(3) Inclusion of subjects who agreed in written form to decide the participation and comply the cautions after listening and understanding fully the details on this clinical study.

2) Exclusion Criteria

(1) The subjects who disagreed to participate into this study

(2) The subjects likely not to maintain the constant blood pressure about 30 minutes due to hypovolemia or quasi equivalent disease and situation

(3) The subjects likely not to maintain the constant blood pressure about 30 minutes due to short-termly active vasoactive agonist or quasi equivalent medication

(4) Subjects with cardiac arrhythmia

(5) Subjects who ate food within 30 minutes

(6) The subjects who took caffeine drink within 1 hour or smoked within 15 minutes

(7) The subjects who made exercise immediately before measuring the blood pressure

(8) Other subjects who are inappropriate to this study by the decision of the research staff

7.2 Inclusion/Exclusion Criteria for Users of the Investigational Medical Device

1) Inclusion Criteria

(1) The subjects to be tested with the stethoscope type blood pressure gauge shall acquire appropriate hearing power and eyesight.

(2) The subjects to be tested with the stethoscope type blood pressure gauge shall have training and experience on measuring.

(3) The subjects who voluntarily agreed to sign after listening the explanation on the objective and procedure of the clinical study

2) Exclusion Criteria

(1) The subjects who were decided as inappropriate for participating into the clinical study by the person in charge for the clinical study and other research staff

8. Information and Management of a Medical Instrument for Clinical Study

1) Investigational Device

(1) Model: H2-BP

(2) Product name(Product category No.) and class: Automatic electronic blood pressure gauge(A23010.04) / class II

(3) Manufacturer: Charmcare Co., Ltd

(4) Shape and structure

-H: 81.5mm, L: 79.5mm, W: 25.5mm

(5) Storage conditions: Store at room temperature

2) Comparator

(1) Model: big ben® Sphygmomanometer

(2) Product name(Product category No.) and class: Aneroid type blood pressure gauge(A23010.01) / class I

(3) Manufacturer: Riester

(4) Shape and structure

-H: 250mm, L: 250mm, W: 250mm

(5) Storage conditions: Store at room temperature

The investigational device used in this clinical trial is provided by Charmcare Co., Ltd. The Investigational Device Manager (hereinafter referred to as the "Manager") is responsible for the receipt, inventory management, application and use, and return of the investigational device. The Manager shall document all relevant activities and periodically report them to the Principal Investigator (PI).

In accordance with Good Clinical Practice for medical device clinical study, the Manager shall record the application period, lot number or serial number, expiration date (if applicable), Unique Device Identification, and Subject Identification Code for each subject using the investigational device.

The Manager and relevant personnel shall maintain and document medical records verifying the device is used in accordance with the clinical study protocol for each subject The investigational site is responsible for ensuring that records related to medical device management are retained in compliance with applicable regulations and guidelines. The Principal Investigator is ultimately responsible for managing the investigational devices used in this study.

9. Study Design and Methodology

This clinical study is a single-arm, single-center, open-label, non-randomized, prospective, single-day study. The investigational device will be applied for blood pressure measurement in outpatients, inpatients, and volunteers aged 19 years or older who present with hypotension, normotension, borderline hypertension, or hypertension.

9.1 Implementation of Monitoring for Subjects Using the Investigational Device

For subjects undergoing monitoring (or their legally authorized representatives, if applicable), screening shall be conducted after obtaining written informed consent for participation in the clinical study. Based on the screening assessment, subjects who meet the inclusion criteria and do not meet the exclusion criteria will be enrolled in the study.

Blood pressure measurements will be performed in a seated position, alternating between the investigational device and the comparator device. The measurement procedure follows the steps below:

1. Using the comparator device, one valid pair of systolic and diastolic blood pressure (BP) values will be obtained from the upper arm as shown in Figure 1.
2. The investigational device will then be applied to the same arm's wrist, and one valid pair of systolic and diastolic BP values will be obtained.
3. Steps 1 and 2 will be repeated until three valid pairs of BP values are collected for each subject. A minimum interval of 60 seconds will be maintained between each measurement.
4. The same procedure will be followed for all other enrolled subjects.

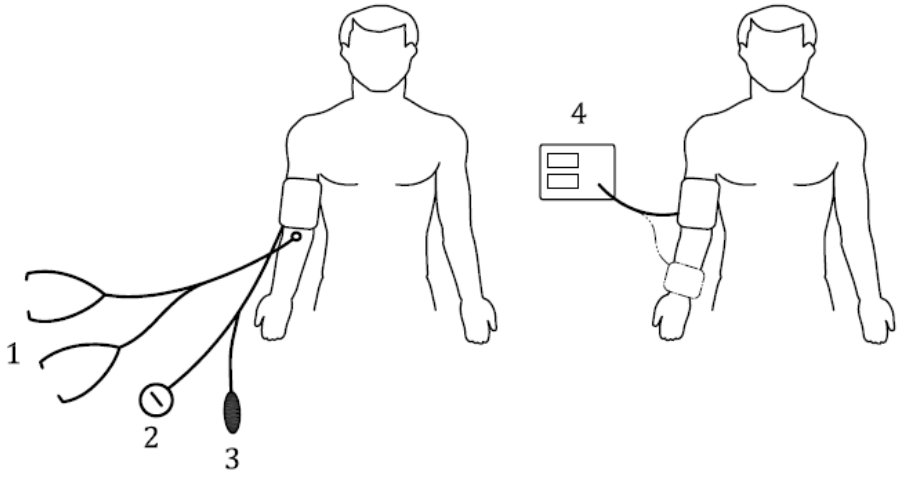


Figure 1. ①Stethoscope ②Comparator Device Manometer ③Pump ④Investigational Device

The investigational device measurement is recorded by a single operator. In contrast, the comparator device measurement is recorded by two independent operators, each using a separate stethoscope to simultaneously assess and document the blood pressure readings.

When measuring diastolic blood pressure (DBP) using auscultation, Korotkoff Phase V should be recorded. If Korotkoff Phase V is not audible, the subject shall be excluded from the study.

The two operators using the auscultatory blood pressure measurement method must conduct their measurements independently, ensuring that they cannot communicate or be aware of each other's recorded values for each subject. Additionally, during the measurement process, the operators must not have access to the investigational device's readings.

* If the difference between the two simultaneous measurements exceeds the following thresholds, the corresponding blood pressure value pair shall be excluded:

- If the systolic blood pressure (SBP) difference between the two operators is greater than 4 mmHg, the value pair is excluded.
- If the diastolic blood pressure (DBP) difference between the two operators is greater than 4 mmHg, the value pair is excluded.

To ensure validity and representativeness of the blood pressure measurements, the final collected values from the comparator device must meet the following distribution criteria:

1) At least 5% of SBP values should be ≤100 mmHg.
2) At least 5% of SBP values should be ≥160 mmHg.
3) At least 20% of SBP values should be ≥140 mmHg.
4) At least 5% of DBP values should be ≤60 mmHg.
5) At least 5% of DBP values should be ≥100 mmHg.
6) At least 20% of DBP values should be ≥85 mmHg.

10. Study Procedures and Assessments

10.1 Clinical Study Schedule

	Screening	Medical instrument application	Assessment
Study Visit	**Visit1** [6]	**Visit2** [6]	
Day	**-2W-Day1**	**Day1**	
Obtain agreement letter[1]	O		
Screening numbering	O		
Check selection/exclusion criteria[2]	O		
Obtain demographic information[3]	O		
Check medication taken or under taking [4]	O		
Measure wrist circumference	O		
Check circumference of upper arm	O		
Measure blood pressure		O (H2-BP, stethoscope type blood pressure gauge)	O
Check taking medication		O	
Check abnormal examples[5]		O	

1) Any procedure in this observatory study shall not start before having patient's agreement letter (Letter of consent on using information). Voluntary agreement shall be made preferentially by the patient, but for impossibility of making the agreement letter due to emergencies (Endotracheal intubation and cardio pulmonary resuscitation), the agreement letter may be obtained from the legal proxy person. In this case, additional agreement letter shall be taken from the patient after stabilization or finalization of the emergent situation to the patient.
2) Check the selection/exclusion criteria, obtain demographic information, check the medication taken in advance or under taking and measure the wrist circumference and circumference of upper arm after screening numbering.
3) Demographic survey: Survey the demographic information (Date of birth, age and gender).
4) Check the medication taken in advance or under taking: Collect overall information on advanced medication and taken medication before applying the clinical study medical instrument from 2 weeks before screening till applying clinical study medical instrument.
5) Survey the abnormal reactions from the first test related procedure (Namely, signing date of the patient on the agreement letter) till the last assessment date.
6) Screening the visit and the medical instrument applying visit can be processed concurrently.

10.2 Observational Examination Method for Subjects Using the Investigational Device

1) Assignment of Screening and Enrollment Numbers

A Screening Number shall be assigned only to subjects who have provided written informed consent for participation in this clinical trial. Screening numbers will be assigned in the order of consent acquisition. If multiple subjects provide consent on the same day, the screening numbers will be assigned based on the order of arrival.

The Screening Number shall consist of a single-digit site identifier, the letter 'S' (indicating Screening), and a three-digit sequential subject number, assigned according to the following method

Site Number	S	-	Three-digit number assigned sequentially based on Screening order
Gangnam Severance Hospital: **1**	S	-	001,002,003, …
Example: The Screening Number for the first subject screened at Gangnam Severance Hospital is 1S-001.			

For subjects enrolled after Screening, an Enrollment Number will be assigned, consisting of a single-digit site identifier, the letter 'R' (indicating Registration), and a three-digit sequential subject number, according to the method described below. The target sample size will be counted based on the number of enrolled subjects, regardless of the total number of screened subjects.

Site Number	R	-	Three-digit number assigned sequentially based on Screening order
Gangnam Severance Hospital: **1**	R	-	001,002,003, …
Example: The Screening Number for the first subject screened at Gangnam Severance Hospital is 1R-001.			

2) Demographic Data Collection

At the time of Screening (Visit 1), detailed demographic information of the subject will be collected and recorded. The demographic data will include the subject's date of birth, age, and gender.

3) Adverse Event Monitoring

The investigator will observe for the occurrence of adverse events (AEs) throughout the clinical study period, starting from Visit 2 (application of the investigational medical device). Any adverse events identified will be documented in the Case Report Form (CRF), including the onset date, resolution date, severity, causal relationship, and actions taken.

4) Concomitant Medication Monitoring

Information on all prior medications administered within 2 weeks prior to Screening (Visit 1) and before the application of the investigational device, as well as on concomitant medications administered after the application of the investigational device, will be collected. For both prior and concomitant medications, the following details will be recorded: drug name (active ingredient), purpose of administration, daily dosage, route of administration, and duration of administration.

10.3 Clinical Study Schedule

1) Visit 1 (Screening, Day 0)

Complete the following Screening procedures before the application of the investigational device:

1. Obtain written informed consent from the subject or their legal representative (proxy) prior to conducting any study procedures.
2. Assign a Screening number after obtaining the subject's consent.
3. Review the inclusion and exclusion criteria following the assignment of the Screening number.
4. Collect demographic information.
5. Verify prior/concomitant medications.

6. Measure the wrist circumference.
7. Measure the upper arm circumference.

2) Visit 2 (Day 1)

Subjects assigned a Screening number and enrolled in the clinical trial will undergo the application of the investigational device on Day 1. Note that the Screening date and Day 1 may occur on the same day.

1. Measure blood pressure using the H2-BP device and an auscultatory blood pressure monitor.
2. Verify concomitant medications.
3. Monitor for adverse events (AEs).

11. Effectiveness Evaluation Parameter

Evaluate the accuracy by adopting the following evaluation parameters by measuring the blood pressure in three times at systolic and diastolic area from total 141 subjects. The qualification decision shall be pursuant to the following criteria. (The minimum subjects shall be over 85 and measured data shall be over 255 cases.)

11.1 Primary Endpoint

(1) Average on difference between blood pressures measured with investigational device and comparator

n=Count of measurement Ex) For 85 subjects-> n=255
i is a separate index for count of measurement.

$$p_{\text{comparator}_{-sq_i}} = \frac{1}{4} \times (p_{\text{comparator}_{i,1}} + p_{\text{comparator}_{i,2}} + p_{\text{comparator}_{i+1,1}} + p_{\text{comparator}_{i+1,2}})$$

$p_{\text{comparator}_{i,1}}$ is the blood pressure data measured at i − th time by the operator 1

$p_{\text{comparator}_{i,2}}$ is the blood pressure data measured at i − th time by the operator 2

[Formula for calculating the primary endpoint]

$$Average\ of\ difference(\overline{x}_n) = \frac{1}{n} \times \sum_{i=1}^{n} (p_{Investigational\ device_i} - p_{\text{comparator}_{-sq_i}})$$

Corresponding endpoint shall have error range less than ±0.67 kPa.

(2) Standard deviation on the blood pressures measured with investigational device and comparator. (Based on count of measurement)

n= Count of measurement Ex) For 85 subjects -> n=255
i is a separate index for count of measurement.

[Formula for calculating the primary endpoint]

$$Standard\ deviation\ of\ difference\ based\ on\ count\ of\ the\ measurements(s_n) = \sqrt{\frac{1}{n-1} \times \sum_{i=1}^{n} (x_i - \overline{x}_n)^2}$$

Corresponding endpoint shall have error range less than 1.07 kPa.

11.2 Secondary Endpoint

(1) Standard deviation on difference between blood pressures measured with investigational device and comparator. (Based on the count of the subjects)

m= Count of measurement Ex) For 85 subjects -> n=255
j is a separate index for count of measurement.
d is the count of measurement per experimentee.
k is an index for the individual factor.

$$x_j = \frac{1}{\mathrm{d}} \times \sum_{k=1}^{\mathrm{d}} (p_{investigational\ device_{j,k}} - p_{comparator_{-sq_{j,k}}})$$

$$p_{comparator_{-sq_{j,k}}} = \frac{1}{4} \times (p_{comparator_{j,k,1}} + p_{comparator_{j,k,2}} + p_{comparator_{j,k+1,1}} + p_{comparator_{j,k+1,2}})$$

[Formula for calculating the secondary endpoint]

$$Standard\ deviation\ of\ difference\ based\ on\ count\ of\ the\ subjects(s_m) = \sqrt{\frac{1}{m-1} \times \sum_{j=1}^{m} (x_j - \overline{x}_n)^2}$$

The secondary endpoint shall meet the Table 1 or 2 based on ISO 81060-2 standard depending on the blood pressure data.

Table 1 – Average subject data acceptance (criterion 2) in mmHg

$\bar{x}_n$	Maximum permissible standard deviation, s_m, 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	6,90	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 of ±4,2mmHg the maximum permissible standard deviation is 5,49 mmHg.										

Table 2 – Average subject data acceptance (criterion 2) in kPa

$\bar{x}_n$	Maximum permissible standard deviation, s_m, as function of, $\bar{x}_n$ kPa									
	0,000	0,010	0,020	0,030	0,040	0,050	0,060	0,070	0,080	0,090
±0,0	0,9266	0,9266	0,9266	0,9266	0,9226	0,9246	0,9233	0,9223	0,9213	0,9203
±0,1	0,9193	0,9183	0,9173	0,9163	0,9152	0,9138	0,9119	0,9099	0,9079	0,9059
±0,2	0,9039	0,9007	0,8989	0,8970	0,8946	0,8906	0,8878	0,8855	0,8826	0,8785
±0,3	0,8756	0,8723	0,8679	0,8641	0,8601	0,8562	0,8519	0,8471	0,8414	0,8374
±0,4	0,8333	0,8283	0,8226	0,8169	0,8119	0,8059	0,7999	0,7933	0,7853	0,7793
±0,5	0,7739	0,7669	0,7599	0,7531	0,7463	0,7388	0,7319	0,7237	0,7157	0,7077
±0,6	0,6999	0,6891	0,6802	0,6723	0,6670	0,6595	0,6488	0,6386	-	-
Example For mean of ±0,520kPa the maximum permissible standard deviation is 0,7599 kPa.										

12. Anticipated Adverse Effects and Precautions for Use

12.1 Precautions for Use in Operating Environment

Do not use in locations exposed to moisture.

- Do not use the device with wet hands.
- Do not store the device in direct sunlight.
- Do not store near heating appliances.
- Avoid storing in areas with sudden humidity changes or poor ventilation.
- Do not store in locations where the device may be subjected to excessive impact or vibration.
- Use the device within an ambient temperature of 5–40℃ and relative humidity of 5–95%.
- Consider ambient temperature and humidity during use, and keep the device away from dust, chemicals, and flammable substances.
- Do not disassemble or dismantle the device.

12.2 Precautions During Use

- Do not drop or subject the device to strong impacts.
- Do not measure blood pressure after smoking, drinking alcohol, exercising, bathing, eating, or consuming caffeine.
- Do not activate the device when it is not worn on the wrist.
- Dispose of the device, components, and accessories in accordance with local regulations to prevent environmental pollution.
- Check for any visible abnormalities on the blood pressure monitor.
- Inspect the charging cable for visible damage or abnormalities.

12.3 Anticipated Adverse Effects

- Using the device during an MRI scan may result in severe burns. Do not wear the device during MRI procedures. If this occurs during proper use, immediately remove the device from the patient.
- Avoid placing the blood pressure cuff over sites with arterial catheters or intravenous lines.
- Individuals with severe hematological disorders or blood conditions should use the device under a doctor's supervision. Temporary bruising or bleeding may occur due to cuff compression.

12.4 General Precautions

- Do not adjust medication dosage based on the measurement results.
- Take medications only as prescribed by a doctor. The diagnosis and treatment of hypertension can only be performed by a physician.
- Consult a doctor before using this device if you experience any of the following conditions:
- Arrhythmias such as atrial or ventricular extrasystoles or atrial fibrillation, arteriosclerosis, reduced arterial elasticity, diabetes, advanced age, pregnancy, preeclampsia (eclampsia or pre-eclampsia), or kidney disease.
- Movement, tremors, or chills during measurement may affect blood pressure readings.
- Do not use the device simultaneously with other electronic medical devices.
- Do not measure blood pressure on wrists that are injured or under treatment.
- If you experience pain or other unusual skin sensations while using the device, stop using it immediately and consult a doctor.

For more details, refer to Appendix 2_H2-BP User Manual0-42_Full Document.

13. Criteria on Termination and Early Suspension (Criteria on drop out in the middle and etc.)

The test may be terminated or stopped in the middle for the patients falling on the following cases.

- When the subject withdrew the agreement for participation
- When the study is discontinued due to severe abnormal reaction or contingent accident
- When the subject does not visit and follow the procedures specified in the plan or at impossibility of those matters
- Difficulties on continuing the study due to the severe complication occurrence
- When the subject inappropriate to the selection criteria participated into the study
- When the subject falling on the exclusion criteria participated into the study
- When the blood pressure difference measure with the reference device is over the following error range
  - Entire data from the experimenters is excluded when any pair of the blood pressure data at the systolic area measured with the reference device is differed over 1.60kPa.
  - Entire data from the experimenters is excluded when any pair of the blood pressure data at the diastolic area measured with the reference device is differed over 1.07kPa.
- Other cases decided as disturbing the consistent study by the researcher-in-charge.

The experimenter is entitled to stopping the study freely when the experimenter withdraws the agreement for participating. The reasons and the data related to the clinical study shall be recorded and kept when the study is suspended.

14. Criteria, Methods, and Reporting for the Assessment of Safety, Including Adverse Events

14.1 Safety Evaluation Variables

1) **Adverse Events (AEs)**

Any clinically significant medical condition or abnormality observed after the application of the blood pressure monitor will be recorded as an Adverse Event (AE). Clinically significant abnormalities identified during safety assessments, such as vital sign monitoring or physical examinations, will also be classified as AEs. If a clinically significant medical condition or abnormality confirmed before the application of the investigational device worsens after its application, it will be considered a new AE.

14.2 Definitions of Adverse Events

1) Adverse Event (AE)

An AE refers to any unintended sign (e.g., abnormal laboratory finding), symptom, or disease that occurs in a subject during the clinical trial, whether or not it is causally related to the investigational device.

2) Adverse Device Effect (ADE)

An ADE refers to any harmful and unintended reaction caused by the investigational device, for which a causal relationship with the device cannot be excluded.

3) Unexpected Adverse Device Effect

A Unexpected Adverse Device Effect is an ADE that differs in nature or severity from the information provided in the investigator's brochure, device labeling, or other available medical device documentation.

4) Serious Adverse Event/Serious Adverse Device Effect (Serious AE/ADE)

An SAE/SADE refers to an AE or ADE that meets any of the following criteria:

(1) Results in death or poses a life-threatening risk

(2) Requires hospitalization or prolongation of existing hospitalization

(3) Results in permanent or significant disability or functional impairment

(4) Causes a congenital anomaly or birth defect

(5) Involves other medically significant conditions

For medically significant situations that are not explicitly listed but are deemed to have a serious impact on the subject's health and well-being, the determination of SAE will depend on the medical judgment of the investigator and relevant experts. Pre-planned hospitalizations or treatments, as well as hospitalizations for unchanged pre-existing conditions during the trial, will not be classified as SAEs.

14.3 Safety Assessment Criteria and Methods

Consider the frequency and severity of adverse events described in the supporting documentation, together with any abnormal findings if other clinical tests are performed. Adverse events should be recorded and categorized according to the medical glossary for regulated adverse events and documented in the case record, including whether the event occurred, the name of the event, the date of occurrence, the outcome, the date of disappearance, whether it was a serious adverse event (SAE), the severity of the event, the causal relationship to the investigational device, the treatment involved, and whether it was treated.

1) Severity of Adverse Events

The severity of AEs will be assessed using the following criteria:

(1) Mild: Causes minimal discomfort that does not interfere with normal daily activities and is easily tolerated by the subject.

(2) Moderate: Causes noticeable discomfort that significantly interferes with daily activities.

(3) Severe: Causes discomfort that makes normal daily activities impossible.

Expected adverse reactions will also be classified as AEs, and their severity will be categorized as mild, moderate, or severe. Other adverse effects due to surgical interventions will be managed through medication or surgical treatment, and the investigator may decide to terminate the trial if necessary.

2) Causal Relationship Between Adverse Events and the Investigational Device

(1) Definitely related: The temporal relationship between the event and device use is plausible, and no other cause better explains the event. The AE resolves upon discontinuation of device use and reoccurs upon reapplication (if reapplication is feasible). Additionally, the AE is consistent with previously known information about the device.

(2) Probably related: There is evidence of device use, the temporal relationship between device use and AE occurrence is plausible, reapplication is unnecessary, and the AE resolves upon discontinuation of the device.

(3) Possibly related: There is evidence of device use, and the temporal relationship is plausible, but other potential causes cannot be ruled out. The AE resolves upon discontinuation of the device.

(4) Possibly not related: There is evidence of device use, but a more probable alternative cause exists. The AE resolves upon discontinuation of the device, or the causality remains unclear. Additionally, if reapplication is performed (where feasible) and the AE does not recur, or the causality remains unclear, the event is considered possibly not related.

(5) Definitely not related: The device was not used, or the temporal relationship between device use and AE occurrence is implausible, or a clear alternative cause is identified.

(6) Unknown: Information is insufficient or conflicting, and further investigation is not feasible or cannot confirm causality.

3) Treatment and progress

During this clinical study, the principal investigator and personnel in charge shall ensure the safety of the subjects, and in the event of a serious adverse medical device event (SADE), prompt and appropriate measures shall be taken to minimize the adverse event, and the principal investigator may stop the trial in consultation with the sponsor. All adverse events occurring during the clinical study period, even if not related to the medical device, shall be recorded in detail in the case record, including symptoms and signs, onset/end date, severity, treatment and outcome, and relationship to the test device. In addition, the adverse event shall be observed, as far as possible, until the adverse event returns to the condition or baseline value prior to the application of the medical device, or until the principal investigator or responsible person can determine that the adverse event has normalized, or until further observation is deemed unnecessary.

14.4 Safety Reporting Method

The Principal Investigator (PI) shall educate the study personnel, subjects, and legally authorized representatives on all potential adverse events (AEs) that may occur following the use of the investigational device. Subjects shall also be instructed to report any events that occur post-use.

During the clinical study, the investigator must report all Serious Adverse Events (SAEs) and Serious Adverse Device Effects (SADEs) to the designated monitor within 24 hours of becoming aware of the event, regardless of their causal relationship with the investigational device. The investigator must also report the event to the Institutional Review Board (IRB) according to the safety reporting procedures of the clinical trial site. To protect subject confidentiality, the subject identification code shall be used instead of personal identifiers such as name, social security number, or address.

The designated monitor shall submit a written report to the sponsor within 24 hours of receiving the SAE/SADE report. The sponsor and IRB shall review the initial report, and if necessary, contact the investigator for further details. The sponsor will assess the causal relationship between the adverse event and the investigational device.

If the investigator considers the event to be serious, unexpected, and potentially related to the use of the investigational device, the event shall be documented as an Unexpected Serious Adverse Device Effect (USADE) and reported to the Ministry of Food and Drug Safety (MFDS) within the following timeframes:

(1) Death or life-threatening events: Must be reported within 7 days of awareness, with a follow-up detailed report submitted within 8 days of the initial report.

(2) All other serious or unexpected adverse device effects: Must be reported within 15 days of awareness.

Events that do not immediately threaten life, result in death, or require hospitalization but are deemed medically significant and necessitate immediate intervention based on medical judgment shall also be classified as SAEs.

For emergency room visits exceeding 24 hours, hospitalization criteria shall be met. However, the following situations shall not be classified as SAEs:

(1) Emergency room visits lasting less than 24 hours

(2) Pre-planned hospitalizations prior to investigational device application

(3) Hospitalization for cosmetic surgery

(4) Scheduled surgeries or procedures without adverse events

(5) Planned hospitalizations or extended stays for pre-scheduled surgeries or examinations

15. Points to be Considered in Data Analysis and Statistics

15.1 Statistical Analysis Methods

(a) Efficacy Analysis Population

A. Intention-To-Treat (ITT) Population

All subjects who were randomly assigned for the clinical study must be included in the primary analysis. Complete follow-up of all randomized subjects is required.

B. Full Analysis Set (FAS) Population

This population adheres most closely and completely to the ITT principle. It includes subjects who provided informed consent, participated in the study, received the investigational device, and were assessed for the efficacy evaluation variables.

C. Per Protocol (PP) Population

This population consists of subjects from the FAS group who completed the trial without major protocol deviations. Major protocol deviations include violations of inclusion/exclusion criteria, missing efficacy evaluation variables, and other critical deviations. Subjects with significant protocol violations will be reviewed and determined in the analysis population adjudication meeting prior to analysis.

(b) General Principles of Outcome Analysis

The primary efficacy analysis is performed based on the PP population. For statistical hypothesis testing, a two-sided test is conducted with a significance level of 5%, and a two-sided 95% confidence interval is presented.

(c) Handling of Missing Data

If missing data occur due to dropout or other reasons, no imputation is performed. Analyses will be conducted only on the collected data.

(d) Handling of Outliers

Outliers are defined as cases where the subject's blood pressure remains inconsistent. Such cases will not be reflected in the efficacy evaluation. For criteria regarding inconsistent blood pressure, reference should be made to the exclusion criteria and dropout criteria.

15.2 Primary Endpoint

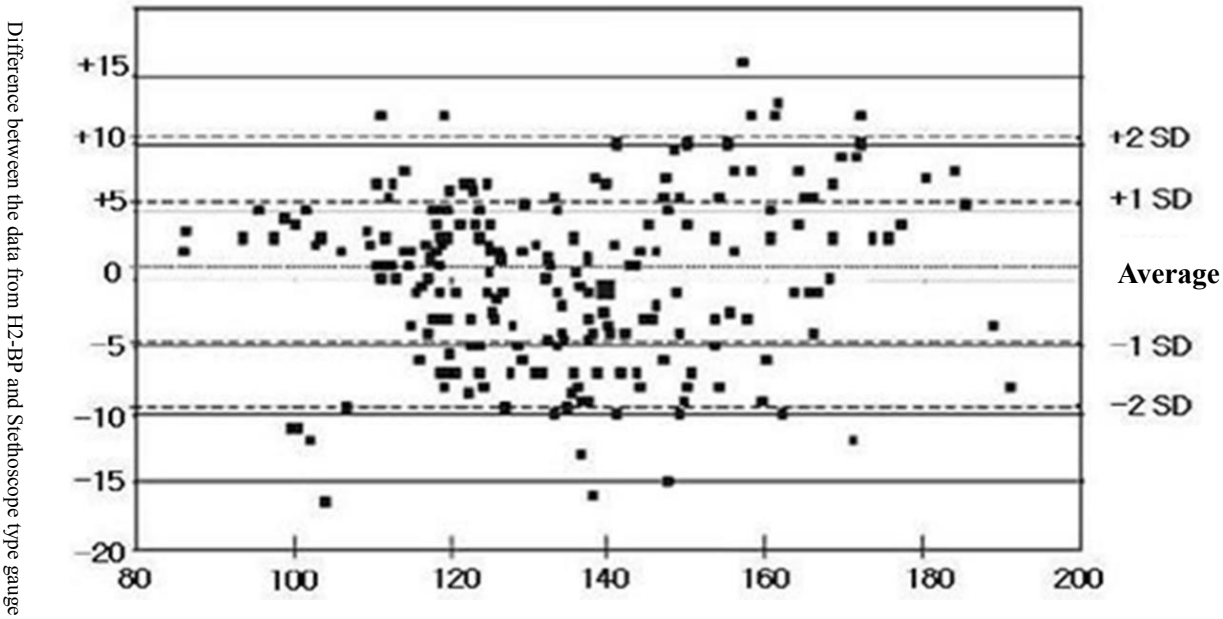
(1) Average on difference between blood pressures measured with investigational device and comparator
(2) Standard deviation on the blood pressures measured with investigational device and comparator. (Based on count of measurement)

15.3 Secondary Endpoint

(1) Standard deviation on the blood pressures measured with investigational device and comparator. (Based on count of subjects)

15.4 Bland-Altman Analysis

For the data measured with H2-BP and stethoscope type blood pressure gauge, it is desirable to follow the analysis procedures suggested Bland and Altman(1986).[10) 11)] Make the respective scatter plot on averages of blood pressure data at the systolic and diastolic area to compare by matching with the data from H2-BP and stethoscope type blood pressure gauge. (See the example of the scatter plot). Make respective plot for the systolic and diastolic area.



Average of data measured with H2-BP and stethoscope type blood pressure gauge

Example of scatter plot. N = 255, SD = Standard Deviation to check matching level between the data measured at systolic area with H2-BP and stethoscope type blood pressure gauge

"Average" on the above plot means the average of the data measured with H2-BP and stethoscope type blood pressure gauge at each point, and the "difference" is the one between data measured with H2-BP and stethoscope type blood pressure gauge at each point. The average should be known from each scatter plot and the horizontal line should be drawn to find ±SD and ±2SD.

16. Measures for Data Confidentiality and Protection of Personal Information

If the subject consents to the collection of personal information, their data will be coded using a unique identification number, excluding any personally identifiable information, to ensure privacy protection. All research data will be kept confidential and stored in a secure, access-controlled environment, such as a restricted-access computer system or a secure physical location, to prevent unauthorized access by individuals other than authorized study personnel.

A data safety monitoring assessment will be conducted every three months to evaluate the status of the study records. The collected data may be shared with co-investigators, and once data usage and analysis are complete, the related documents will be securely stored in a locked facility at Gangnam Severance Hospital. The data will be retained for three years following the completion of the clinical study and will be disposed of thereafter.

17. Collection, Management, Storage, and Disposal of Human-Derived Materials and Genetic Information

Not applicable

18. Subject Recruitment Methods and Informed Consent Process

18.1 Subjects for Investigational Device Application

: Subjects for the investigational device application shall include outpatients, inpatients, and volunteers aged 19 years or older who present with hypotension, normotension, borderline hypertension, or hypertension.

Voluntary informed consent from the subject is prioritized; however, if the subject is unable to express their consent due to endotracheal intubation, cardiopulmonary resuscitation (CPR), or other critical medical conditions, informed consent may be obtained from the legally authorized representative (LAR). In such cases, additional consent shall be obtained directly from the subject once their condition stabilizes or the emergency situation has resolved before discharge.

If informed consent is obtained from a legally authorized representative, the rationale for obtaining LAR consent must be documented in the electronic medical record (EMR) with supporting documentation.

Informed consent shall be obtained by the Principal Investigator (PI) or designated research personnel in an

independent setting where subjects are provided with adequate and clear verbal and/or written information about the nature, purpose, potential risks, and benefits of the study.

Subjects shall be informed that, even after providing written consent, they may withdraw from the study at any time without any penalty or consequences

19. Protection Measures for the Recruitment of Vulnerable Subjects

: This study involves the collection of blood pressure data and does not impose any additional risk or discomfort on the subjects. There are no interventions or invasive procedures added due to participation in the study, and participation does not pose any harm to the subjects.

Regardless of the study's progress, any abnormal situations that may arise during the subject's biometric monitoring will be managed with emergency medical care, independent of the study's continuation.

Even after obtaining informed consent from the subject or proxy consent from a legally authorized representative (LAR), the subject retains the right to withdraw consent at any time. Withdrawal from the study will not affect the subject's standard medical care or treatment in any way.

20. Plan for quality control and reliability assurance (Material Safety Monitoring Plan)

All study data will be securely stored in restricted-access locations under the responsibility of the Principal Investigator (PI).

1. Subject data will be coded using a unique identification number different from the enrollment number, ensuring that personally identifiable information remains protected.
2. Medical records and test results will be documented in the Case Report Form, with only the necessary study variables recorded to prevent exposure of confidential subject information.
3. Under the supervision of the Principal Investigator, data safety monitoring will be conducted every three months to ensure the integrity of all subject-related data. The study documentation, including source documents, CRFs, and the study protocol, will be cross-verified to ensure data completeness, and subject safety data will be reviewed accordingly.

21. Clinical Study plan(Schedule)

Development details	Detailed milestones (19 months)																								
	2022	2023												2024											
	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Study Protocol and IRB Approval	■	■																							
Study Contract and Administrative Procedures Execution			■																						
Subject Recruitment and Study Procedure Execution				■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Analyze data and report results																									■

22. Informed Consent Form

The clinical study investigator shall provide a comprehensive explanation to the subjects regarding the purpose and methodology of the study, the effects of the investigational device, and any potential adverse events. Informed consent shall be obtained from the subjects after they have received sufficient information.

Appendix 1: Subject Information Sheet and Informed Consent Form

23. Management of Investigational Medical Devices

The Principal Investigator (PI) shall be designated as the person responsible for managing the investigational device (H2-BP, manufactured by Charmcare). Records shall be maintained regarding the receipt, use, and transfer of the investigational device, including the date of receipt, product serial number, name of the recipient or user, quantity used, and reason for use. Upon completion of the clinical study, the investigational device and control device shall be returned to Charmcare in accordance with the procedures established by the manufacturer. The device manager shall ensure that the power status and operational condition of the device are checked regularly. When not in use, the device shall be stored with the power turned off, following the instructions in the user manual. The investigational device (H2-BP by Charmcare) shall be stored in an environment with a temperature range of 10°C to 40°C and a humidity range of 15% to 90%.

24. References

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