Amended protocol for:

Observational Trial: Determining the accuracy of the HeartBeat Algorithm for calculating blood pressure

Contents

Funder: Centre for Aging and Brain Health Innovation (CABHI)

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1. Introduction and Rationale

The gold standard instrument for blood pressure measurement is a mercury-filled sphygmomanometer with cuff and stethoscope (Canadian Agency for Drugs and Technologies in Health; Canadian Electronic Library, 2012). However, such a device is not the most convenient for client self-monitoring or virtual (remote) care. Thus, there is a desire for an accurate, reliable alternative for the traditional mercury-containing sphygmomanometer.

HeartBeat Technologies Ltd. ("Heartbeat") has developed a novel approach to measuring blood pressure after an initial blood pressure reading using the conventional measurement method, supplemented by specific characteristics of a person (age, gender, height, weight, and heart rate), has established a "baseline measurement" for the person. The "novel approach" uses a finger pulse oximeter, the Contec CMS50EW device (Figure 1) (manufactured by Contec Medical Systems Co., Ltd., Shanghai, People's Republic of China). The finger pulse oximeter detects the changes in blood volume directly below the person's skin and indirectly measures oxygen saturation in the blood. The measurement is in the form of a photoplethysmogram (PPG) which is captured by the Contec oximeter and then, by Bluetooth technology, transmitted to a smartphone or tablet. A HeartBeat application, called MediBeat, on the smartphone or tablet then transmits the PPG to a server where a proprietary algorithm analyzes the baseline measurement for the person and the PPG to calculate the person's current blood pressure.

Figure 1. Contec CMS50EW. Source: *http://www.contecmed.com/index.php?page=shop.product_details&flypage=flypage.tpl&product_id=118&category_id=27&option=com_virtuemart&Itemid=618*

Heartbeat's intent is that the current blood pressure reading would then be made available to both the client and the health provider through separate web-based interfaces. Providers would be able to log onto the HeartBeat web-based application from anywhere to review and monitor the blood pressure of multiple clients, while clients can log onto the application to track their own measurements.

2. Study purpose

Though the Contec finger pulse oximeter has been approved for use by Health Canada (Licence No. 90629) and the FDA (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm?lid=465210&lpcd=DQA), the proprietary algorithm developed by Heartbeat Technologies Ltd. has not been approved for use. The purpose of this study is to validate the accuracy of the algorithm as compared with the standard manual sphygmomanometer with stethoscope for measuring blood pressure. If the algorithm is shown to be accurate, Heartbeat Technologies Ltd. will apply to Health Canada and the FDA for approval for its use to measure blood pressure.

3. Study Design/Methodology

Trial registration

This study will be registered with ClinicalTrials.gov as it is one of two registered bodies approved and recommended by Health Canada. This will serve as a publicly accessible platform for patients and practitioners to understand the current study's objectives and goals, and be kept informed of the results.

Protocol

The European Society of Hypertension International Protocol revision 2010 for the validation of blood pressure measuring devices in adults (ESH-IP) (**Appendix A**) (O'Brien et al., 2010) will be followed precisely, except it will be modified to follow the extra guidance in the international consensus statement for validation (**Appendix B**) (Stergiou et al., 2018). The international consensus statement (Stergiou et al., 2018) reviewed the adequacy of the number of participants in a variety of established protocols including the ESH-IP, and recommended that, to increase study power and accuracy, the number of participants in a study following the ESH-IP should be at least 85 rather than 33 as in the 2010 version of the ESH-IP.

Setting and clinicians

Study site

The study site will be a room with a comfortable temperature and with no noise or other influences that may cause disturbance, such as telephones.

Health professionals involved

A supervisor and two observers are required to take the necessary recordings for this study. Three registered nurses will be identified for the study, with training and experience in blood pressure measurement. One will act as the supervisor and two will act as the observers, as specified in ESH-IP. These roles will be outlined below in the section entitled "Interactions with participants and data collection".

Clinicians who participate in this study will be trained and experienced in blood pressure measurement. They will be instructed to follow the ESH-IP guidelines for data collection and record all blood pressure measurements to the nearest 2 mmHg.

A familiarization session with the supervisor and the observers will be held in advance of interactions with participants. This session will involve a number of test measurements. The agenda for the session with the supervisor, who will be recording the data from the observers and from the novel approach, can be seen in **Appendix C**.

Conventional equipment
Two standard mercury sphygmomanometers, the components of which will be checked carefully before the study, will be used as the reference standards by the observers. They will be within 1m of where the observers will be when interacting with a participant, so that they will be able to follow the menisci at eye level from 40mmHg to 180 mmHg. Bladders of multiple sizes will be made available so that, on each subject, there is one of sufficient length to encircle 80%–100% of the arm circumference. The observers will be supplied with good quality non-electronic stethoscopes with well-fitting earpieces.

Heartbeat equipment
The pulse oximeter, the Heartbeat application (MediBeat), and the supervisor's smartphone (Samsung Galaxy Xcover 4 with Bluetooth connectivity) will be charged, and tested each day of interactions with participants. Prior to conducting the study session, the equipment will have to be calibrated for each participant. The first step of the calibration process is to manually enter the reference data (date of birth, height, weight, baseline manual blood pressure reading and heart rate). Once data is entered, and participant has been given 10 minutes of rest, the nurse supervisor will ensure the participant is seated comfortably, with their legs uncrossed, back supported, and their arm rested on the table at heart level. The nurse supervisor will then attach the Contec finger pulse oximeter to the participant's finger (opposite to the arm with the manual blood pressure cuff) and wait for a few seconds, to make sure a stable signal is received, and the device displays both the participant's pulse and SpO_2 values. Once the values are displayed, the nurse supervisor will hit the "Add session" button, and choose the correct device to connect to via Bluetooth. The calibration process will begin, indicated by the orange background, and the MediBeat application will display the participant's heartrate and SpO_2 values. It is critical that the participant does not move during the calibration process, which will last just over 1 minute. The background of the application will turn blue once calibration has completed successfully.

Recruitment plan

Inclusion/Exclusion Criteria
Healthy participants who are over the age of 25 and live or work in the North Simcoe Muskoka and Markham regions will be recruited to participate in this study. As outlined in the ESH-IP, only healthy subjects will be included this study; those who have heart arrhythmias, atrial fibrillations or atrial flutters, an inaudible Korotkoff sound, wounds of the upper arms/wrists, missing fingers, and/or an arm circumference of more than 55 cm will be excluded, in advance if at all possible, and at the study site if not previously excluded.

Recruitment will continue until the following quotas are met:

1. Numbers: At least 85 who fully complete the study protocol, and fall within the parameters listed in #3
2. Sex: At least 26 male and 26 female (each 30% of the total number of participants)
3. Blood pressure range: 26 to 31 subjects in each of the three SBP and three DBP recruitment ranges as shown in Form 3 – Study Results (**Appendix N**):
    - Low blood pressure (systolic: 0-129, diastolic: 0-79)
    - Medium blood pressure (systolic: 130-160, diastolic: 80-100)
    - High blood pressure (systolic: 161 or higher, diastolic: 101 or higher).

Participant Remuneration

To thank participants for their valuable time, they will be provided with a $50 VISA pre-paid gift card at the end of the study visit.

Recruitment Methods

Recruitment flyers (**Appendix E**) will also be posted in public spaces at corporate offices and medical clinics, who have agreed to participate within Central Ontario, including Markham, Toronto, and North Simcoe Muskoka.

Recruitment emails (**Appendix F**) will be sent to all relevant employees located at corporate offices and medical clinics, who have agreed to participate within Central Ontario, including Markham, Toronto, and North Simcoe Muskoka, with a link to HeartbeatStudy@sehc.com to indicate interest. Recruitment will be a two-step process.

Clinical staff, from clinics who have agreed to participate, will be provided with a short script (**Appendix G**) and Frequently Asked Questions (FAQ) document (**Appendix H**) to assist with the recruitment process. Individuals interested in participating can submit a consent to contact form (**Appendix I**) to the clinic staff, who will scan and send the forms to the research team. **Research assistant** will call individuals who had expressed their interest in participating to further explain the study (**Appendix J**) and ask if they would like to participate. The research assistant will then inform them about the consent form (**Appendix K**) that they will be asked to sign at the study site. The research assistant will provide the participant with information about a scheduled time for participating in the study and directions.

Interactions with participants and Data collection

Form 1 - Device information

Prior to the first interaction with a participant, the supervisor will fill in the information about the device in Form 1 of the ESH-IP (**Appendix D)**. As noted above, the Contec CMS50EW device is an electronic finger pulse oximeter (Contec Medical Systems Co., Ltd, Qianhuangdao, China) that generates a PPG, which is then sent to HeartBeat's proprietary algorithm to calculate blood pressure.

Confirmation of appropriate setting conditions

Before involving any participant in the study, the **nurse supervisor** and **nurse observers 1** and **2** will ensure that the following requirements for the study site and equipment outlined by ESH-IP are met (O'Brien, 2010):

1. Environment
    a. Comfortable temperature
    b. No noises or disturbances (e.g. telephone, pagers) that could influence testing
    c. Ambient noises are not at a level that could interfere with testing
2. Manual blood pressure device
    a. Stethoscopes for using the sphygmomanometer have well-fitting earpieces.

Participant consent and interaction

At the study site, the following activities will be undertaken:

1. **Nurse supervisor** will provide the patient with the consent form and obtain the patient's consent (**Appendix L**) (signed consent forms – **Appendix K**) to be enrolled into the study. The nurse supervisor will photograph and email the consent forms to the research assistant once signed and witnessed.

2. **Nurse supervisor** will explain to the participant how their blood pressure measurements will be taken using the "conventional" and the "alternative" approaches.

3. **Nurse supervisor** will also complete the recruitment details in Form 2 in the "Recruitment details" section (**Appendix M)**. **Nurse supervisor** will record the provided study participant's identification number onto the consent form.

4. The nurse supervisor will ask the participant to relax for 10–15 min.

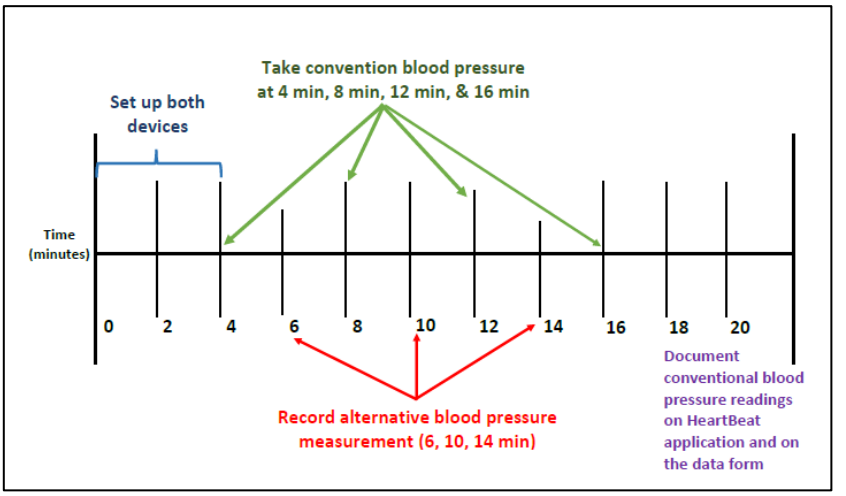
5. **Nurse supervisor** will log onto the HeartBeat application to create a new patient profile and enter all baseline data (age, gender, height, weight, and heart rate).

6. After the period of relaxation, the nurse supervisor will make sure that the subject is seated with legs uncrossed and back supported, if the subject is not seated as described, the posture used must be recorded as a protocol adjustment.

7. **The nurse supervisor** will put the blood pressure cuff on the participant's left arm and ensure that the participant's arm is supported at heart level.

8. **The nurse supervisor** will put the Contec finger pulse oximeter on the participant's right index finger (and the participant will keep device on during duration of the study).

9. Blood pressure is measured as described in the following diagram:



10. Observer measurements will be recorded simultaneously by the observers on separate sheets. They will be checked immediately by the nurse supervisor and, if they differ by more than 4 mmHg, they will be taken again. Observers will be blinded from each other's measurements and from the device measurements.

11. Starting with the observers, the nurse supervisor will record the measurements sequentially by the supervisor, alternating between observers and the supervisors' reading of the device in the order BPA, BPB, BP1, BP2, BP3, BP4, BP5, BP6 and BP7 on Form 2.

12. **The nurse supervisor** will take a picture of the device measurements and those photographs will be emailed to the research assistant.

13. On a separate sheet, **the nurse supervisor** will keep a running total of the number of subjects recruited in the Low (LL and L), Medium (M), and High (H and HH), ranges for SBP (Box 219) and DBP (Box 220) on Form 2.

14. If any of the following occur during the study, **the nurse supervisor** will circle the appropriate item in Box 287 on Form 2 and exclude the subject:
    - Circle *Arrhythmias* if the subject is not in sinus rhythm throughout the study.
    - Circle *Device failure* if the device fails to record a measurement after three successive attempts.
    - Circle *Poor quality sounds* if the Korotkoff sounds are difficult to auscultate, regardless of the reason.
    - Circle *Observers disagreement* if the observers differ by more than 4 mmHg twice in the same subject.
    - Circle *Other* if the subject does not complete the study for any reason other than those listed and record the reason in Box 288.

15. In the event that an abnormal blood pressure reading is detected (e.g. if the blood pressure is outside clinically normal range for a specific client), one of the observers will

re-take the blood pressure to determine if the abnormal reading is accurate. If the abnormal blood pressure measurement is accurate, the **nurse supervisor** will take appropriate action as directed by professional standards. The abnormal blood pressure data will be recorded on Form 2.

Data Checking

During the data collection process, researchers will check the data daily to ensure the following as per the ESH-IP (O'Brien et al., 2010):

1. Ensure that the difference between the range with the highest count and lowest count does not exceed 19.
2. Ensure the overall systolic blood pressure is within the range of ≤100 to ≥170mmHg and the overall diastolic blood pressure is within the range of ≤50 to ≥120mmHg.
3. If the participants have a blood pressure outside the range of 90–180mmHg for systolic blood pressure and 40–130mmHg for diastolic blood pressure, only a maximum of 4 blood pressures readings outside of this range can be included in the analysis.
4. Ensure there are approximately 26-31 participants in each of the 3 blood pressure ranges (low blood pressure (systolic: 0-129, diastolic: 0-79), medium blood pressure (systolic: 130-160, diastolic: 80-100) and high blood pressure (systolic: 161 or higher, diastolic: 101 or higher)).

Data Analysis

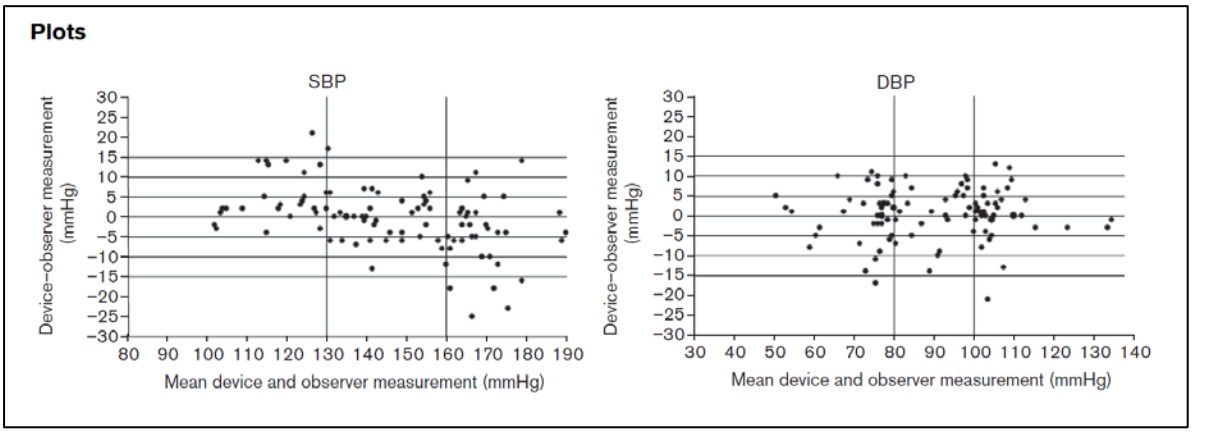
The profile of the study participants will be described based on a demographic analysis conducted on data collected from the subject data form from the ESH-IP (**Appendix M**).

All collected data on Forms 1 and 2 will be sent to the researchers at the SE Research Centre, who will consolidate the data from the Forms 1 and 2 and analyze the data as specified in Form 3, the Study Results form from the ESH-IP (**Appendix N**) (O'Brien et al., 2010).

In order to pass the validation process, the device must pass both parts 1 and 2 based on the accuracy criteria table (**Appendix O**).

Plots

These are mean-difference plots, and the plots modelled from the data collected should be exactly as shown in the example plots below.



The x-axis of these plots represents blood pressures in the systolic range 80mmHg–190mmHg and the diastolic range 30 mmHg–140 mmHg. The y-axes represent errors from – 30mmHg to +30mmHg. Horizontal reference lines will be drawn at 5mmHg intervals from +15mmHg to – 15 mmHg. The mean of each device pressure and its corresponding observer pressure will be plotted against their difference with a point. Differences greater than 30mmHg will be plotted at 30 mmHg. Differences less than – 30mmHg will be plotted at – 30 mmHg. The same scales will be used for both SBP and DBP plots. Where points are superimposed, these will be indicated either by proportionately larger points or by different symbols.

5. Confidentiality and security of data

Electronic data

The data obtained from the pulse oximeter is captured by the Nurse supervisor's smartphone via Bluetooth connection. The smartphones and tablets used by SE Health nurses meet the requirements for all custodians of personal health information in Ontario. The HeartBeat application on the clinicians' smartphones or tablets encrypts the data for transmission to secure Google Servers within Canada, and the algorithm is also housed on those servers. The data outputs from the algorithm are then made available on a secure web-based password-protected portal to which only the researchers have access. The data will be downloaded by the researchers from the portal to password-protected computers which meet all the requirements for custodians of personal health information in Ontario.

Paper data

Paper data from the study will be photographed/scanned and emailed to the researchers at the SE Research Centre. Once received, the photographs, scans and emails will be deleted by the senders. The digital copies received in the SE Research Centre will be stored on a password protected computer that is accessible only by researchers from the SE Research Centre. All paper forms will be destroyed in keeping with SE Health's standards for destroying paper materials in accord with Ontario's *Personal Health Information Protection Act*.

Storage and data destruction

All electronic files will be kept secure on password protected computers and only research team members will have access to them. All paper-based data records will be photographed and stored electronically in password protected computers.

Written records (lists of participants and their email addresses if they wish to receive information from the study) will be secured in a locked file cabinet in the SE Research Centre, and then scanned to create digital copies of the written records will be stored on computers secured by passwords known only to the members of the research team for analysis. After scanning, the written records will be destroyed securely in accord with SE Health Care's procedure to comply with the standards of the *Personal Health Information Protection Act* of Ontario.

When analysis has been completed, the data will be transferred to secure servers owned by SE Health, which comply with the standards of the *Personal Health Information Protection Act*. Digital records will be destroyed securely within 72 months of the research project's end (i.e. in 2025) except those excerpts of the data used in final reports, publications, presentations and training materials. In the final reports, publications, presentation materials, and training materials that emerge from this research project, the data will be presented in such a way that the identity of the participant is not knowable by a reader or viewer.

6. Withdrawal from the study

Participants will be free to withdraw from the study at any time without penalty or affects to their care. Any data (e.g. blood pressure measurements) collected prior to the participant's withdrawal from the study but before its use in the study will be deleted and not used.

List of Appendices

References

Heart and Stroke Foundation of Ontario and Registered Nurses' Association of Ontario (2005). Nursing Management of Hypertension. Toronto, Canada: Heart and Stroke Foundation of Ontario and Registered Nurses' Association of Ontario.

O'Brien, E., Atkins, N., Stergiou, G., Karpettas, N., Parati, G., Asmar, R., …, Shennan, A. (2010). European Society of Hypertension International Protocol revision 2010 for the validation of blood pressure measuring devices in adults. *Blood Pressure Monitoring, 15*(1), 23-38. doi:10.1097/MBP.0b013e3283360e98

Roland, M. & Torgerson, D.J. (1998). Understanding controlled trials: What are pragmatic trials? *BMJ, 316*(7127), 285.

Stergiou, G. S., Alpert, B., Mieke, S., Asmar, R., Atkins, N., Eckert, S., ... & Ioannidis, J. P. (2018). 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. *Hypertension*, *71*(3), 368-374.

APPENDIX M

Form 2 – Subject data

This form is to be filled by the validation supervisor for each subject. Items in clear boxes are assessed directly. Items in shaded boxes are calculated. All blood pressure measurements are recorded in mmHg and are carried out sequentially on one arm, whichever is more comfortable for the subject. Including any time required to change cuffs, At least 30 seconds should be allowed between each measurement to avoid venous congestion, but not more than 60 seconds or variability may be increased.

Prerequisites

- ☞ On a separate sheet, keep a running total of the number of subjects recruited in the Low (LL and L), Medium (M), and High (H and HH) ranges for SBP (Box 219) and DBP (Box 220).
- ☞ If any of the following occur during the study, circle the appropriate item in Box 287 and exclude the subject.
  - Circle *Arrhythmias* if the subject is not in sinus rhythm throughout the study.
  - Circle *Device failure* if the device fails to record a measurement after three successive attempts.
  - Circle *Poor quality sounds* if the Korotkov sounds are difficult to auscultate, regardless of the reason.
  - Circle *Observers disagreement* if the observers differ by more than 4 mmHg twice in the same subject.
  - Circle *Other* if the subject does not complete the study for any reason other than those listed and record the reason in Box 288.
- ☞ Starting with the observers, measurements are recorded sequentially alternating between observers and the device in the order BPA, BPB, BP1, BP2, BP3, BP4, BP5, BP6 and BP7.
- ☞ Observer measurements should be recorded simultaneously by the observers on separate sheets. They must be checked immediately and, if they differ by more than 4 mmHg, they should be taken again. Only enter final measurements on this sheet. Observers must be blinded from each other's measurements and from the device measurements throughout the study.
- ☞ If possible, a permanent record of device measurements should be kept. If software is provided, device measurements should be downloaded daily.

Recruitment details

Date and time [201]

Study number and Subject number [202] [203]

Date of birth [204]

Age [205]

Sex *Male* *Female* [206]

On antihypertensive medication *Yes* *No* [207]

Arm circumference *cm* [208]

Cuff for test device *Small* *Standard* *Large* *Other* [209]

Wrist circumference *cm* [210]

Height *ft, in*

Weight *lbs*

Box 209: This is only required for arm devices. If the arm circumference is such that no suitable cuff is available, circle *Cuff size unavailable* in Box 287 and exclude the subject.

Box 210: This is only required for wrist devices.

Entry measurements

Ask the subject to relax for 10–15 min. Then make sure that the subject is seated with legs uncrossed and back supported. Ensure that the arm is supported at heart level. If a wrist device is being tested, the wrist must be supported according to the manufacturer's instructions. If the subject is not seated as described, the posture used must be recorded as a protocol adjustment.

	Observer 1 SBP	Observer 1 DBP	Observer 2 SBP	Observer 2 DBP	Device SBP	Device DBP	Heart Rate *bpm*
BPA	[211]	[212]	[213]	[214]			
BPB					[215]	[216]	
	Observer Mean		Category		Count		

	SBP	DBP	SBP	DBP	SBP	DBP
BPA	[217]	[218]	*LL L M H HH* [219]	*LL L M H HH* [220]	[221]	[222]

Boxes 217, 218: Enter the rounded up averages of Boxes 211 and 213 and of Boxes 212 and 214 respectively.

Box 219: Circle the range according to the BP in Box 217. LL: < 90, L: 90–129, M: 130–160, H: 161–180, HH: >180.

Box 220: Circle the range according to the BP in Box 218. LL: < 40, L: 40–79, M: 80–100, H: 101–130, HH: >130.

Boxes 221, 222: Update the running totals, for the ranges (counting LL and L together and counting HH and H together) in Boxes 219 and 220, and enter them respectively.

- ☞ If both Box 221 and Box 222 are greater than 12 or if an *LL* or *HH* is circled and there are already 4 such items circled, circle *Ranges complete* in Box 287 and exclude the subject.
- ☞ If one of Box 221 or Box 222 is greater than 12 but the other is not, it may be necessary to include this subject, and remove another, in order to achieve the correct range distribution; in the removed subject, circle *Range adjustment* in Box 287.

Validation measurements

	BP1		BP3		BP5		BP7	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Observer 1	223	224	225	226	227	228	229	230
Observer 2	231	232	233	234	235	236	237	238
Observer mean	239	240	241	242	243	244	245	246
Observer difference	247	248	249	250	251	252	253	254

	BP2		BP4		BP6	
	SBP	DBP	SBP	DBP	SBP	DBP
Device	255	256	257	258	259	260
Device–Previous observer	261	262	263	264	265	266
Device–Next observer	267	268	269	270	271	272
Error group	*A B C D* 273	*A B C D* 274	*A B C D* 275	*A B C D* 276	*A B C D* 277	*A B C D* 278
Observer value	281	282	283	284	285	286

Difference
A 0–5 mmHg
B 6–10 mmHg
C 11–15 mmHg
D > 15 mmHg

Within 5 mmHg

SBP	DBP
279	280

Boxes 239–246: Enter the rounded up averages of Boxes 223 and 231, of Boxes 224 and 232, of Boxes 225 and 233, of Boxes 226 and 234, of Boxes 227 and 235, of Boxes 228 and 236, of Boxes 229 and 237 and of Boxes 230 and 238 respectively.

Boxes 247–254: Enter the differences Box 223–Box 231, Box 224–Box 232, Box 225–Box 233, Box 226–Box 234, Box 227–Box 235, Box 228–Box 236, Box 229–Box 237, and Box 230–Box 238 respectively.

Boxes 261–266: Enter the 'Device–Previous Observer Mean' differences. These are Box 255–Box 239, Box 256–Box 240, Box 257–Box 241, Box 258–Box 242, Box 259–Box 243, and Box 260–Box 244 respectively.

Boxes 267–272: Enter the 'Device–Next Observer Mean' differences. These are Box 255–Box 241, Box 256–Box 242, Box 257–Box 243, Box 258–Box 244, Box 259–Box 245, and Box 260–Box 246 respectively.

☞ Each device measurement is compared to the nearer of the previous and next observer measurement. As described below, the smaller error is circled and the corresponding observer measurement is copied to aid the analysis.

Box 273: First, circle the smaller value, in absolute terms, of Boxes 261 and 267 (Box 261 if both are the same). Then circle A if this is less than or equal to 5, B if this is 6–10, C if this is 11–15 or D if this is greater than 15.

Boxes 274–278: Circle A, B, C or D, as described for Box 273, based on the smallest absolute values (also circled) of Boxes 262 and 268, Boxes 263 and 269, Boxes 264 and 270, Boxes 265 and 271and Boxes 266 and 272 respectively.

Box 279: Enter the number of 'A's circled in Boxes 273, 275 and 277.

Box 280: Enter the number of 'A's circled in Boxes 274, 276 and 278.

☞ The numbers of 'A's, 'B's and 'C's will be used in the analysis to calculate the number of device-observer differences within 5 mmHg, 10 mmHg and 15 mmHg.

Box 281: Enter the value in Box 239 if Box 261 is circled or Box 241 if Box 267 is circled.

Box 282: Enter the value in Box 240 if Box 262 is circled or Box 242 if Box 268 is circled.

Box 283: Enter the value in Box 241 if Box 263 is circled or Box 243 if Box 269 is circled.

Box 284: Enter the value in Box 242 if Box 264 is circled or Box 244 if Box 270 is circled.

Box 285: Enter the value in Box 243 if Box 265 is circled or Box 245 if Box 271 is circled.

Box 286: Enter the value in Box 244 if Box 266 is circled or Box 246 if Box 272 is circled.

Signoff

Please use the comments to explain unlisted subject exclusion or any problems during the procedure

Excluded

Ranges complete *Range adjustment* *Arrhythmias* *Device failure*
Poor quality sounds *Cuff size unavailable* *Observer disagreement* *Distribution* *Other* 287

Comments 288

Supervisor signature 289

☞ Note: Subjects initially included may be excluded due to changes in pressure. See *observer measurements in each recruitment range* in *Form 3 – Study Results.*

If a printout of test device data is possible, print the device data for this subject and attach it to this form.

APPENDIX N

Form 3 – Study results

The data from *Form 2 – Subject Data* for each subject should be appropriately analysed so that the results on this form can be completed. All references to boxes 201–289 refer to values obtained from all of the Forms 2 from the relevant subjects. All blood pressure measurements are in mmHg.

Table 1 Screening and recruitment details

Screening and recruitment

Total screened	301
Total excluded	302
Ranges complete	303
Range adjustment	304
Arrhythmias	305
Device failure	306
Poor quality sounds	307
Cuff size unavailable	308
Observer disagreement	309
Distribution	310
Other reasons*	311
Total recruited	312

Recruitment ranges

		mmHg	All	On Rx
SBP	Low	< 90	314	324
		90–129	315	
	Medium	130–160	316	325
	High	161–180	317	326
		> 180	318	
DBP	Low	< 40	319	327
		40–79	320	
	Medium	80–100	321	328
	High	101–130	322	329
		> 130	323	

*Explanation summary

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Box 301: The total number of subjects screened, regardless of whether or not they were included in the study.

Box 302: The total number excluded. This equals the sum of Boxes 303–311.

Box 303: The number of subjects excluded with *Ranges complete* circled in *Box 287* (*Form 2 for each excluded subject*).

Box 304: The number of subjects excluded with *Range adjustment* circled in *Box 287*.

Box 305: The number of subjects excluded with *Arrhythmias* circled in *Box 287*.

Box 306: The number of subjects excluded with *Device failure* circled in *Box 287*.

Box 307: The number of subjects excluded with *Poor quality sounds* circled in *Box 287*.

Box 308: The number of subjects excluded with *Cuff size availability* circled in *Box 287*.

Box 309: The number of subjects excluded with *Observer disagreement* circled in *Box 287*.

Box 310: The number of subjects excluded with *Distribution* circled in *Box 287*.

Box 311: The number of subjects excluded with *Other reasons* circled in *Box 287*. A summary of those reasons must be provided in Box 313.

Box 312: The total recruited equals the number screened (Box 301) less the number excluded (Box 302). This should equal 33 except in validations in some specific populations.

Box 313: A summary of why those counted in Box 311 were excluded (*Box 288*).

Boxes 314–323: In a completed study in a general adult population, the sum of Boxes 314 and 315, Box 316, the sum of Boxes 317 and 318, the sum of Boxes 319 and 320, Box 321 and the sum of Boxes 322 and 323 must each be between 10 and 12. The sum of Boxes 314, 318, 319 and 323 must be at most 4. The sum of Boxes 314–318 and the sum of Boxes 319–323 must each be exactly 33. Studies in specific populations may have different restrictions and totals (*Boxes 219* and *220 – Form 2 for each included subject*).

Boxes 324–329: The number of subjects in each range on antihypertensive medication (*Boxes 207, 219* and *220*).

Table 2 Subject details

Sex	Male : Female	330	
Age (years)	Range (Low : High)	331	
	Mean (SD)	332	
Arm circumference (cm)	Range (Low : High)	333	
	Mean (SD)	334	
Cuff for test device (Upper arm devices only)	Small	335	____ –____ cm
	Standard	336	____ –____ cm
	Large	337	____ –____ cm
	Other	338	____ –____ cm
Wrist circumference (cm) (Wrist devices only)	Range (Low : High)	339	
	Mean (SD)	340	
		SBP	DBP
Recruitment BP (mmHg)	Range (Low : High)	341	342
	Mean (SD)	343	344

Note: The values in Boxes 314–380 refer only to the final recruited subjects, each of whom contributes SBP and DBP measurements for analysis. Excluded subjects are not included in any of this analysis.

Box 330: Enter the number of males, a colon and the number of females. They should total 33 except in validations in some specific populations. If the minimum requirements (10 for a general population) are not met, subjects must be replaced as necessary (*Box 206*).

Box 331: Enter the age of the youngest subject, a colon and the age of the oldest subject e.g. *31:74*. Subjects outside the required range (25 and over for a general population) are not permitted (*Box 205*).

Box 332: Enter the mean and, in parentheses, the SD of the subject ages. Values should be rounded up to one decimal place e.g. *52.3* (*11.9*) (*Box 205*).

Box 333: Enter the smallest arm circumference, a colon and the largest arm circumference e.g. *24:34* (*Box 208*).

Box 334: Enter the mean and, in parentheses, the SD of the subject arm circumferences. Values should be rounded up to one decimal place e.g. *29.0* (*3.1*) (*Box 208*).

Box 335: If a small cuff was supplied, enter the number of subjects on whom it was used. If it was not supplied, enter an 'X'. Enter the arm sizes for which it is recommended beside it. (Applicable only for arm devices) (*Box 209*).

Box 336: Enter the number of subjects on whom a standard (or medium) cuff was used. Enter the arm sizes for which it is recommended beside it. (Applicable only for arm devices) (*Box 209*).

Box 337: If a large cuff was supplied, enter the number of subjects on whom it was used. If it was not supplied, enter an 'X'. Enter the arm sizes for which it is recommended beside it. (Applicable only for arm devices) (*Box 209*).

Box 338: If a different size cuff was supplied, enter the number of subjects in whom it was used. If no such cuff was supplied, enter an 'X'. Enter the arm sizes for which it is recommended beside it. (Applicable only for arm devices) (*Box 209*).

Box 339: Enter the smallest wrist circumference, a colon and the largest wrist circumference e.g. *15:22* (Applicable only for wrist devices) (*Box 210*).

Box 340: Enter the mean and, in parentheses, the SD of the subject wrist circumferences. Values should be rounded up to one decimal place e.g.*18.1*(*2.3*) (Applicable only for wrist devices) (*Box 210*).

Boxes 341–342: Enter the lowest pressure, a colon and the highest pressure from BPA measurements only e.g.*104:180.* (*Boxes 217* and *218*).

Boxes 343–344: Enter the mean and, in parentheses, the SD of the subject pressures from BPA measurements only. Values should be rounded up to one decimal place e.g. *140.4* (*20.3*). (*Boxes 217* and *218*).

Table 3 Distribution

SBP		DBP	
Overall range (Low : High)	345	Overall range (Low : High)	350
Low (<130)	346	Low (<80)	351
Medium (130–160)	347	Medium (80–100)	352
High (>160)	348	High (>100)	353
Maximum difference	349	Maximum difference	354

This section analyses the distribution of comparative measurements.

Box 345: Enter the lowest pressure, a colon and the highest SBP from the observer measurements (Boxes 281, 283 and 285).

Boxes 346–348: The observer measurements (three per subject) for SBP are categorised similarly to the recruitment ranges. Enter the counts of measurements falling into each range. These must total 99 (Boxes 281, 283 and 285).

Box 349: Subtract the smallest value from Boxes 346 to 348 from the largest one and enter the result.

Box 350: Enter the lowest pressure, a colon and the highest DBP from the observer measurements (Boxes 282, 284 and 286).

Boxes 351–353: The observer measurements (three per subject) for DBP are categorised similarly to the recruitment ranges. Enter the counts of measurements falling into each range. These must total 99 (Boxes 282, 284 and 286).

Box 354: Subtract the smallest value from Boxes 351 to 353 from the largest one and enter the result.

- In order to ensure a uniform distribution, there must be at least 22 measurements and at most 44 measurements (Boxes 346 to 348 and 351 to 353) in each of the low, medium and high ranges and the maximum differences (Boxes 349 and 354) must be at most 19. If not, further recruitment will be necessary. Subjects to be excluded will be those whose pressures drifted from recruitment pressures.
- The overall SBP range must be from ≤ 100 mmHg to ≥ 170 mmHg and the overall DBP range must be from ≤ 50 mmHg to ≥ 120 mmHg. If not, further recruitment will be necessary. Subjects to be excluded will be the last recruited within the relevant ranges.
- The minimum number of replacements should take place. If a subject is replaced for either of these reasons, circle *Distribution* in *Box 287 of Form 2* for that subject.
- In validations carried out in specific populations requiring more than 33 subjects but with similar blood pressure distributions, similar proportions should be used. If the blood pressure distribution in the specific population differs from the standard distribution, ignore this table but comment on the distribution in the discussion.

Table 4 Observer differences

This section is for the differences in pressures between the two observers

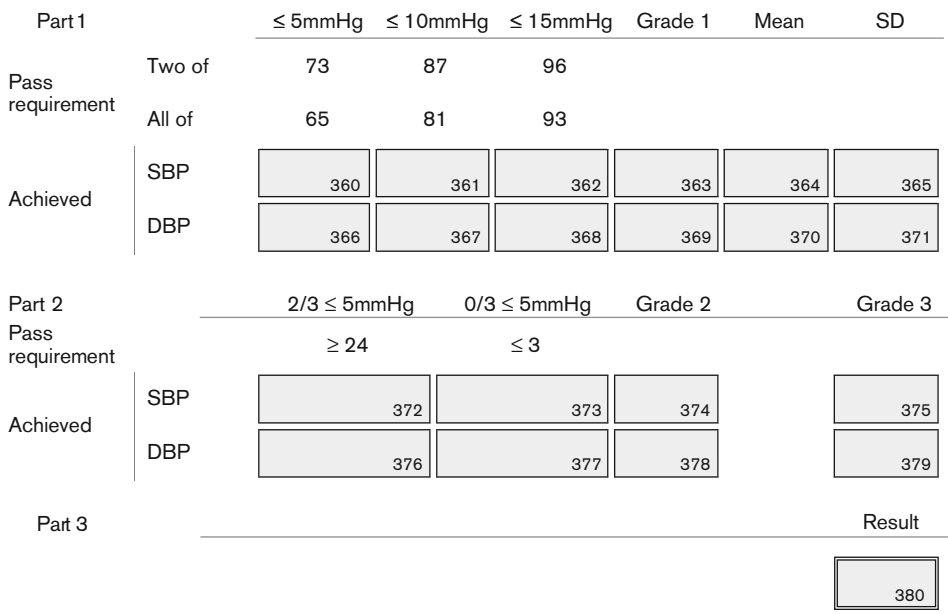
		SBP	DBP	
Observer 2–Observer 1	Range (Low : High)	355	356	Repeated measurements
	Mean (SD)	357	358	359

Boxes 355–356: Enter the lowest difference, a colon and the highest difference between the observers. Include the signs e.g. −3:+4. *(Boxes 247*, *249*, 251 and *253* and *Boxes 248, 250, 252* and *254).* If the range is outside −4:+4, then this is a violation. Relevant subjects should be excluded, by reason of Observer Disagreement, and replaced.

Boxes 357–358: Enter the mean and, in parentheses, the SD of the observer differences. Values should be rounded up to one decimal place e.g. *0.3 (1.2) (Boxes 247, 249, 251* and *253* and *Boxes 248, 250, 252* and *254).*

Boxes 359: Enter the number of measurements that were repeated in the included subjects because observers were more than 4 mmHg apart.

Table 5 Validation results



☞ In order for the device to pass, all protocol requirements must be fulfilled. A fail in any part will result in an overall fail

Box 360: Enter the number of SBP differences (at most 99) between observer and device measurements falling within 5 mmHg. (The total number of *Boxes 273*, *275* and *277* circled A in the 33 subjects)

Box 361: Enter the number of SBP differences (at most 99) between observer and device measurements falling within 10 mmHg. (The total number of *Boxes 273*, *275* and *277* circled A or B in the 33 subjects)

Box 362: Enter the number of SBP differences (at most 99) between observer and device measurements falling within 15 mmHg. (The total number of *Boxes 273*, *275* and *277* circled A, B or C in the 33 subjects)

Box 363: If Boxes 360, 361 and 362 fulfil the Pass requirements, then this is 'Pass'; otherwise, it is 'Fail'.

Boxes 364–365: Enter the mean and standard deviation respectively of the 99 SBP differences between observer and device measurements. (Use data from circled *Boxes 261* or *267*, *263* or *269* and *265* or *271*)

Box 366: Enter the number of DBP differences (at most 99) between observer and device measurements falling within 5 mmHg. (The total number of *Boxes 274*, *276* and *278* circled A in the 33 subjects)

Box 367: Enter the number of DBP differences (at most 99) between observer and device measurements falling within 10 mmHg. (The total number of *Boxes 274*, *276* and *278* circled A or B in the 33 subjects)

Box 368: Enter the number of DBP differences (at most 99) between observer and device measurements falling within 15 mmHg. (The total number of *Boxes 274*, *276* and *278* circled A, B or C in the 33 subjects)

Box 369: If Boxes 366, 367 and 368 fulfil the Pass requirements, then this is 'Pass'; otherwise, it is 'Fail'.

Boxes 370–371: Enter the mean and standard deviation respectively of the 99 DBP differences between observer and device measurements. (Use data from circled *Boxes 262* or *268*, *264* or *270* and *266* or *272*)

Box 372: Enter the number of subjects (at most 33) with two or three of the absolute differences between observer and device SBP measurements within 5 mmHg. (*Box 279* is 2 or 3)

Box 373: Enter the number of subjects (at most 33) with none of the absolute differences between observer and device SBP measurements within 5 mmHg. (*Box 279* is 0)

Box 374: If Boxes 372 and 373 fulfil the Pass requirements, then this is 'Pass'; otherwise, it is 'Fail'.

Box 375: If Boxes 363 and 374 are both 'Pass', then this is 'Pass'; otherwise, it is 'Fail'.

Box 376: Enter the number of subjects (at most 33) with two or three of the absolute differences between observer and device DBP measurements within 5 mmHg. (*Box 280* is 2 or 3)

Box 377: Enter the number of subjects (at most 33) with none of the absolute differences between observer and device DBP measurements within 5 mmHg. (*Box 280* is 0)

Box 378: If Boxes 376 and 377 fulfil the Pass requirements, then this is 'Pass'; otherwise, it is 'Fail'.

Box 379: If Boxes 369 and 378 are both 'Pass', then this is 'Pass'; otherwise, it is 'Fail'.

Box 380: If Boxes 375 and 379 are both 'Pass', then this is 'Pass'; otherwise, it is 'Fail'.

☞ In validations carried out in specific populations requiring more than 33 subjects, proportionally equivalent passing criteria should be used.

Appendix O – International Protocol Accuracy Criteria

ESH International Protocol 2010			
Sequential Measurements			
IP Grading Part 1 - Minimum Requirements (at least 255 pairs of individual measurements)			
N	≤ 5 mmHg	≤ 10 mmHg	≤ 15 mmHg
Two of	188	224	247
All of	167	209	240
IP Grading Part 2 (85 subject mean pressures)			
N	2/3 ≤ 5 mmHg		0/3 ≤ 5 mmHg
At least	62		
At most			8
Recruitment Ranges (n = 85)			
SBP		DBP	
mmHg	Subjects	mmHg	Subjects
90*...129	26 – 31	40*...79	26 – 31
130...160	26 – 31	80…100	26 – 31
161…180*	26 – 31	101…130*	26 – 31
*	Altogether, up to 4 recruitment pressures are permitted to be outside these limits.		
Test Measurement Distribution			
SBP		DBP	
mmHg	Measurements	mmHg	Measurements
≤ 100	≥ 3	≤ 50	≥ 3
< 130	57 – 113*	< 80	57 – 113*
130...160	57 – 113*	80…100	57 – 113*
> 160	57 – 113*	> 100	57 – 113*
≥ 170	≥ 3	≥ 120	≥ 3
*	The difference between the maximum and minimum of these 3 counts for SBP and, separately, for DBP, must be less than or equal to 19.		