

# Validation of non-invasive central blood pressure devices: ARTERY Society task force consensus statement on protocol standardization

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## Introduction

The original Riva-Rocci method to measure blood pressure (BP) using a cuff at the upper arm assumed the pressure obtained by this

technique was a good proxy for central aortic BP.<sup>1,2</sup> The clinical (prognostic) importance of brachial cuff BP is undeniable for both the assessment of cardiovascular risk associated with elevated BP and the benefits of treatment-induced BP reduction.<sup>3</sup> However, it is also

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generally appreciated that peripheral artery systolic BP (SBP; brachial or radial artery) may be an inaccurate substitute for central SBP.<sup>4</sup> This has been reported in human studies using intra-arterial catheterization of peripheral and central arteries.<sup>5–8</sup> There may also be a discrepancy between peripheral and central BP responses to vasoactive drugs.<sup>9</sup> These findings are corroborated in larger studies using non-invasive central aortic BP methods,<sup>10–13</sup> and, while yet to be fully adopted in clinical practice, an independent prognostic value of central BP has been demonstrated.<sup>14–16</sup> Altogether, there is a growing interest among clinicians towards improving risk estimates by using devices that provide more accurate measures of central aortic BP than those provided by current brachial cuff BP methods.

Many non-invasive devices have been developed that purport to estimate central BP from different peripheral artery sites (e.g. radial, brachial, carotid arteries) using different principles of recording the pressure or surrogate signals (e.g. applanation tonometry, oscillometry, ultrasound, or magnetic resonance imaging) and different calibration methods to derive central BP. Since upper arm cuff-based devices to estimate central BP are more clinically appealing, in recent years several companies have developed such devices using a variety of techniques (e.g. oscillometric sub-diastolic or supra-systolic waveform analysis with generalized transfer functions), which employ a variety of signal processing steps to estimate central BP from peripheral signals.<sup>17,18</sup> Yet, with no standardized guidelines,<sup>17</sup> the accuracy testing of these new devices (as well as the preceding devices) has not been undertaken in a uniform fashion with comparable protocols, emphasizing the need for guidance in this field.<sup>19–22</sup> An international task force was convened to address this situation.

## Task force aims

- (1) To identify issues that need to be addressed and reach consensus relating to methods for assessing and reporting the accuracy of central BP devices.
- (2) To provide recommendations regarding appropriate protocols to assess and report the evaluation of accuracy (validation) of central BP devices.

## Task force process

Initiation of the task force emanated from issues raised at an organized debate relating to central BP at the ARTERY Society Meeting, Maastricht, The Netherlands in October 2014. Task force members were invited to provide feedback on a draft document of intent prior to the first meeting at the ESH Meeting, Milan, Italy, June 2015. At this meeting, terms of reference, principal issues, and topics were refined. A second meeting to discuss outstanding issues was held at the 2015 ARTERY Society meeting, Krakow, Poland, with communication of upgraded documents to members for input, and with disagreements settled by majority consensus.

*Identified issues and recommendations* (a glossary of terms is provided in Table 1):

(1) *Disparity of non-invasive central BP devices as to what is being measured.* Most central BP devices claim to produce an estimated central BP relative to cuff brachial BP with brachial SBP usually higher than central SBP. This can be achieved by a variety of techniques including:

- (a) Brachial forearm or radial applanation tonometry and a peripheral waveform-aorta transfer function<sup>23</sup> or the radial waveform second systolic peak.<sup>24</sup>
- (b) Local derivation of carotid BP on the assumption that with appropriate waveform calibration (i.e. mean arterial pressure [MAP] and diastolic BP [DBP]) carotid BP represents central aortic BP. This can be achieved by non-invasive carotid artery tonometry or ultrasound/magnetic resonance imaging of the carotid diameter/area waveform.<sup>25–27</sup> (similar techniques are also being applied on aortic distension waveforms).<sup>28</sup> However, for practical applications, the radial or brachial artery waveform is more readily recorded where waveforms are registered with more consistent reproducibility and repeatability, and are less prone to noise introduced by incorrect vessel applanation or respiration as can occur with carotid waveforms.
- (c) Calculated central BP through transfer function and modified calibration of peripheral pressure waveforms.<sup>26,29,30</sup>

Methods (b) or (c) may produce central SBP estimates higher than brachial cuff SBP (discussed within issue 2).

(i) *Recommendations:* Device manufacturers should clearly state the purported measurement function of their device. While recognizing wide variety in devices, these can be broadly categorized into two types based on their function:

Type I—device purports to give an estimate of central BP relative to measured brachial BP (i.e. relatively accurate pressure difference between central and peripheral sites).

Type II—device purports to estimate the intra-arterial central BP (i.e. relatively accurate absolute central BP value despite inaccuracy at the peripheral site).

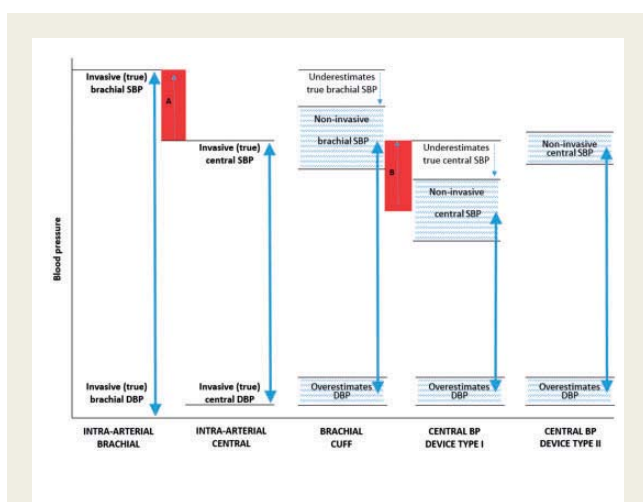
Both function types may be available within a single device. A summary of differences between device types in comparison to intra-arterial brachial and central aortic BP are presented in Figure 1.

(2) *Calibration of peripheral artery signals using brachial cuff BP.* Accuracy of non-invasive central BP methods depends on the accuracy of methods used to calibrate the peripheral artery (radial, brachial, or carotid) waveform. Central BP estimations can be acquired with reasonable accuracy if peripheral waveforms are calibrated with invasive BP.<sup>23,30,31</sup> However, brachial cuff BP is commonly used for calibration purposes and this introduces error<sup>32,33</sup> as a consequence of the recognized underestimation of intra-arterial brachial SBP together with overestimation of intra-arterial brachial DBP.<sup>34–36</sup> Therefore, calibrating the waveform to brachial cuff SBP and DBP is likely to result in underestimation of central SBP and central pulse pressure, but overestimation of central DBP relative to intra-arterial central DBP. Furthermore, amplification of SBP from brachial to radial arteries may compound the error in underestimation of central SBP and central pulse pressure when radial artery waveforms are calibrated using brachial SBP and DBP.<sup>37–40</sup> The magnitude of calibration-induced error may often exceed 10 mmHg for each of SBP, pulse pressure, and DBP, irrespective of brachial cuff BP methods (e.g. auscultation or oscillometry).<sup>41</sup>

Despite these issues, calibration of peripheral waveforms with brachial SBP and DBP still results in the estimation of a central SBP that is relative to, and usually lower than, the measured brachial cuff SBP (device Type I). This information is important to know because brachial cuff SBP is used clinically and the proportional difference with

**Table 1** Glossary of terms

Intra-arterial (invasive) blood pressure	Direct measurement of blood pressure within the artery using an in-dwelling catheter-based pressure transducer
Peripheral (non-invasive) blood pressure	Blood pressure at a site distal from the aorta. This most often refers to brachial or radial artery blood pressure, but for the purpose of this paper also includes carotid blood pressure even though local derivation is regarded as a surrogate of central blood pressure
Central (aortic) blood pressure	Blood pressure in the proximal ascending aorta
Systolic blood pressure amplification	The increase in systolic blood pressure from proximal to peripheral arterial vessels (e.g. aorta-to-brachial, or brachial-to-radial arteries)
Transfer function	Signal processing step to estimate central blood pressure waveforms from peripherally recorded waveforms
Calibration	Process of scaling a waveform using units of pressure



**Figure 1** Illustration of the differences in systolic (SBP) and diastolic (DBP) blood pressure (BP) between intra-arterial brachial and central BP, brachial cuff BP, and non-invasive central BP devices Types I and II (BP ranges of different methods represented by the double arrows). Red shaded area A, represents the true (intra-arterial) level of central-to-brachial SBP amplification, and red shaded area B represents the non-invasive estimated central-to-brachial SBP amplification (A and B may be similar in magnitude). The non-invasive central SBP estimated using central BP device Type II may be higher than non-invasive brachial cuff SBP, but this is due to underestimation of true (intra-arterial) brachial SBP with the cuff device and, therefore, does not reflect physiological amplification. The hatched areas denote that there will be a degree of variability in estimated BP between devices.

central SBP (degree of SBP amplification) may be relevant to hypertension management decisions, including monitoring the effects of drug treatment in which responses may differ between the brachial artery and the aorta.<sup>9,12</sup> Different calibration modes have been successfully employed in an attempt to derive more accurate estimations of central SBP (device Type II),<sup>8,29,30,42</sup> however, in doing so, the potentially confusing impression may be given that central SBP is substantially higher than brachial SBP (reverse amplification), which is likely to be non-physiological under normal conditions and arises

from the combination of underestimated brachial SBP by cuff, together with more accurate (higher) central SBP estimation. Nonetheless, random scatter or measurement error could also contribute to reverse amplification, particularly among older arterial ageing phenotypes where the difference between central and brachial SBP may be small. Although improved accuracy of central SBP using a Type II device is desirable in terms of better risk stratification related to BP, determination of the true degree of aorta-to-brachial SBP amplification will be lost unless a recalibrated estimation of brachial SBP is provided, along with the details of how this is derived. Notwithstanding the complex interaction of calibration and wave propagation phenomena relating central and peripheral SBP, it still needs to be determined if the recalibrated brachial SBP derived by this process is an accurate estimate of intra-arterial brachial SBP.

Data from meta-analysis indicate that using MAP and DBP could be a preferred calibration option to provide a relatively more accurate non-invasive estimation of central SBP.<sup>43</sup> Several methods may be used to derive MAP, including by calculation from potentially inaccurate brachial cuff BP [e.g.  $DBP + 1/3$  (or 40%) pulse pressure,<sup>44</sup> or from integration of the pressure waveforms calibrated to cuff BP], or estimation from the peak oscillometric signal,<sup>45</sup> but information regarding the accuracy of these approaches is limited. Central BP indices derived from oscillometric MAP and DBP calibrated peripheral waveforms show stronger associations with hypertension-related end organ disease and outcomes than either brachial BP or central BP derived by calibration using brachial oscillometric SBP and DBP.<sup>46–50</sup> These data come from independent investigators that have used the same device,<sup>46–50</sup> and it remains to be clarified if the findings may be more widely generalizable or if this is a device-specific phenomenon. The observation that much of the inaccuracy in estimated central BP lies with poor calibration from inaccurate brachial cuff BP, implies that better BP risk stratification might be achieved with more accurate brachial cuff BP *per se*. Indeed, calls have been made for more rigorous brachial BP accuracy criteria.<sup>51,52</sup>

(ii) *Recommendations.* To achieve accurate non-invasive assessment of true central BP, more accurate non-invasive estimates of intra-arterial brachial BP are needed. Establishing more rigorous accuracy criteria for brachial BP is desirable. Current evidence suggests that calibration with MAP and DBP may provide a more accurate assessment of central BP than calibration with SBP and DBP, although

further validation is required across cohorts with different characteristics (e.g. age, sex, levels of BP).

(3) *Disparity in validation standards.* Multiple reference standards and calibration methods have been used among previous 'validation' studies, often including:

- a. Comparison of estimated central BP (by non-invasive device) with invasive central BP (by fluid filled or micromanometer-tipped intra-arterial catheter), and calibration of the non-invasive waveforms with invasive MAP and DBP on the assumption of minimal difference in MAP and DBP between central to peripheral large arteries (i.e. 1–3 mmHg). This assesses accuracy of the mathematical process of transforming peripheral into central pressure *per se* and not the accuracy of the device as used in clinical practice.
- b. Comparison of estimated central BP with invasive central BP, and calibration of the non-invasive waveforms with non-invasive BP (typically brachial SBP and DBP or MAP and DBP). This assesses accuracy of the central BP estimation as may be used in clinical practice.
- c. Comparison of estimated central BP from one non-invasive device with another non-invasive device as the reference standard (usually the SphygmoCor device),<sup>17</sup> and calibration of both devices with the same non-invasive brachial BP, to assess inter-device concordance.

(3) *Recommendations.* The reference standard against which device accuracy of central BP estimation is gauged should be intra-arterial catheter in the ascending aorta [expanded details within section entitled '*Invasive (intra-arterial) central BP reference standard*']. The calibration mode may vary depending on the operating principles of the device, but in all cases, details of the calibration method developed by the manufacturer should be provided (see Issues 1 and 2). If the brachial BP waveform undergoes recalibration to produce a 'new' brachial BP (as per two Type II devices already using this method),<sup>29,42</sup> then the recalibrated brachial BP values (and the method to derive them) should also be provided so that the level of estimated aorta-to-brachial SBP amplification can be gauged.

(4) *Limitations in performing invasive validation studies.* The accepted central BP reference standard is intra-arterial measurement by catheter,<sup>4,53</sup> but this method still requires careful handling by experienced operators to avoid measurement error. The technique is only routinely and necessarily performed in selected clinical populations (i.e. patients with suspected coronary artery disease or children with congenital heart disease), thus rendering data potentially non-generalizable to other patient populations or healthy people in whom non-invasive central BP devices may be clinically applied. Validation against the invasive standard among people for whom central artery catheterization is not clinically indicated is a matter for review by ethical boards.

(4) *Recommendations.* Whilst acknowledging that an intra-arterial validation standard is less practical, currently there are no non-invasive alternatives. In any case, with appropriate sample size it should still be possible to recruit participants from the catheterization laboratory of different age, sex, BP range, heart rate range, body habitus (e.g. body mass index, arm size), and disease status (e.g. +/- coronary artery disease, +/- diabetes). In future, it may be reasonable to use non-invasive central BP devices as reference standards for comparison among different subject populations. The acceptance criteria for such devices are yet to be determined, but may include appropriate validation by comparison with the intra-arterial standard, as well as proved clinical prognostic value. Currently such a device is

not available. A summary of issues and recommendations is provided in *Table 2*.

## Validation protocol requirements

Several scientific bodies have developed validation protocols for non-invasive peripheral BP monitors,<sup>54–59</sup> yet they differ on procedural features such as sample size and selection criteria, number of assessment phases, acceptable margin of error, BP range and pass/fail criteria.<sup>52</sup> A 'universal' brachial BP validation protocol is under development through collaboration of the American Association for the Advancement of Medical Instrumentation (AAMI), the International Organization for Standardisation (ISO), and the ESH Working Group on Blood Pressure Monitoring and Cardiovascular Variability, and projected to be in effect in 2018. This harmonized protocol is expected to inform many aspects of central BP validation protocols that equally apply to brachial BP (e.g. age, gender, BP range), but an internationally accepted central BP protocol directed by regulatory authorities is still required, as distinct from the forthcoming brachial BP protocol.

Recommendations below focus on central BP specific protocol requirements, with some relevant features drawn from existing validation guidelines.<sup>54–56</sup> For unambiguous interpretation of requirements, facets of the protocol have been listed as proposed in the revised Australian Code for the Responsible Conduct of Research, in terms of 'must', 'should' and 'may'. 'Must' indicates a necessary component for highest quality, 'should' indicates a strong recommendation, but may not be the only way that the component can be achieved, and 'may' is used to provide further guidance.<sup>60</sup> Protocol requirements are summarised in *Table 3* as a pro-forma guide for investigators. Less attention is given to protocol features equally relevant to brachial BP (i.e. sample characteristics, results reporting and pass criteria) but some proposed direction is also provided based on existing guidelines<sup>54–56</sup> for interim guidance (and to highlight outstanding issues) prior to development of an accepted international central BP validation protocol. A list of issues in need of resolution in the future development of such a protocol is provided in *Table 4*.

*Study setting.* The isolated room should be without disturbing influences of excessive ambient noise from monitoring devices.

*Non-invasive central BP device measurement standards.* The manufacturer, model, software version, and description of operating principles, including the signal processing step/s (averaging, filtering) and complete calibration processes (including methods to derive calibration points such as SBP, DBP, and MAP) must be provided. The time taken to complete the measurement of BP, including the time points at which brachial BP and central BP are estimated and the cuff deflation speed should be reported. This is relevant to the timing of non-invasive BP measurements with respect to intra-arterial monitoring because there may be substantial beat-to-beat variation in intra-arterial BP that may not be captured using a non-invasive BP device.<sup>56</sup> The appropriate cuff size must be defined and used. The dimensions of the inflatable bladder for all cuff sizes available with the device should be reported, as well as the process to determine appropriate cuff size (e.g. measurement of upper arm and/or fitting within prescribed range indicated on the cuff). A process of familiarization with

**Table 2** Summary of issues in the assessment and reporting of central blood pressure (BP) monitors and recommendations

Issue	Recommendation
1. Disparity of non-invasive central BP devices as to what is being measured	Device manufacturers should clearly state the purported measurement function of their device. These can be broadly categorized into two types based on function: Type I—estimates central BP relative to measured brachial BP; Type II—estimates intra-arterial central BP Both function types may be available within a single device
2. Calibration of peripheral artery signals using brachial cuff BP	To achieve accurate non-invasive assessment of true central BP, more accurate non-invasive estimates of intra-arterial brachial BP are needed. Establishing more rigorous accuracy criteria for brachial BP is desirable. Current evidence suggests that calibration with MAP and DBP may provide a more accurate assessment of central BP than calibration with SBP and DBP
3. Disparity in validation standards	The reference standard against which device accuracy of central BP estimation is gauged should be intra-arterial catheter in the ascending aorta. Details of the calibration method should be provided. If the brachial BP waveform undergoes recalibration to produce a 'new' brachial BP, then the recalibrated brachial BP values (and the method to derive them) should also be provided so that the level of estimated aorta-to-brachial systolic BP amplification can be gauged
4. Limitations in performing invasive validation studies	In future, it may be reasonable to use non-invasive central BP devices as reference standards, but the acceptance criteria for this are yet to be determined

the equipment, involving test measurements before starting the validation study should be performed and reported. If there are additional or optional features or functions, separate validation studies must be performed. Any process used to gauge quality control of waveform or BP measures, and the process used to delineate acceptable quality for analysis must be reported. For example if runs of bigeminy, trigeminy, atrial fibrillation, or isolated premature beats and the following compensatory beats have been removed from analysis.<sup>54</sup> The number of readings deemed unacceptable must be reported, together with the reason/s for exclusion.

*Invasive (intra-arterial) central BP reference standard.* Micromanometer-tipped catheters are the preferred instruments to use, but meticulously handled fluid-filled catheters may also be acceptable for accurately measuring intra-arterial BP.<sup>61–63</sup> For measurement of waveform features, in which minor inflection points need to be identified (i.e. augmented pressure), high frequency, micromanometer-tipped catheters with high-frequency acquisition systems should be used as signal-dampening will alter waveform features. A full description of the type, make and model of catheter, the frequency response and handling procedures must be provided. This should include: the process to determine frequency response; catheter French size; tubes length and number of taps and connectors, flushing protocol, sensor/s position on the catheter; how the manifold position was maintained at heart level (for fluid-filled devices where hydrostatic pressure may influence BP data); calibration/zeroing steps performed together with details of additional equipment used for this process where relevant (note: zero drift may still be a cause of imprecision when using micromanometer-tipped catheters); details of how positioning in the central aorta was confirmed in each case (e.g. fluoroscopy); sampling rate at which waveforms were recorded and all waveform data processing steps together with details of equipment/software used for this purpose; process by which waveform period for comparison with non-invasive central BP device was confirmed (e.g. marking relevant time points). As the recording

unit and A/D converter also have their frequency characteristics, the frequency response of the overall acquisition system from fluid-filled catheter or micromanometer-tip to the end-recording unit (graph-plotter or digital data recorded) should be provided. Procedures such as the 'pop test' may be used to evaluate the overall acquisition system natural frequency and damping coefficient.<sup>62</sup> Alternatively, the performance of the fluid filled catheter systems may be assessed by comparison with micromanometer-tipped catheter (including challenging the fluid filled system across different heart rates).

*Data acquisition at rest.* By necessity, subjects will be supine during catheterization. Before recording resting values, the subject should be allowed a period of undisturbed rest (e.g. without talking or movement for at least 5 min<sup>54,64</sup>) and must be free from the acute effects of interventions causing hemodynamic changes (e.g. vasoactive drugs,<sup>65</sup> contrast dye<sup>66</sup>). There must be no talking whilst BP measures are being recorded. Medications used during the procedure should be reported. The non-invasive central BP values must be compared with the intra-arterial central BP (reference) values averaged over a time-period matching the deflation cycle of the non-invasive device and recorded under stable conditions, ideally simultaneously, or as contemporaneous as possible. If simultaneous measurement is not possible, a complete description of the protocol and the interval between intra-arterial and non-invasive BP measures must be provided, and ideally with the order between measures randomised. The time difference between measures should be in the immediate vicinity and without possibility of disturbing influences such as subject positional changes, drugs, or other interventions. The average intra-arterial monitoring period will vary between devices being tested due to different operating characteristics (e.g. range 10s to 1 min) and should be reported. Comparison of single beat intra-arterial BP with non-invasive central BP is not acceptable due to potential for selective bias, but also because of the aforementioned issues of beat-to-beat variation of intra-arterial BP, which can be influenced by respiration (2–4 mmHg lower BP with inspiration) under normal circumstances,

**Table 3** Summary of central blood pressure (BP) device validation protocol components and requirements

Protocol section	Protocol item	Protocol requirement	Protocol undertaken (circle yes/no. ...comment)
Study setting	Isolated room without disturbing influences	Should	YES NO. ....
Non-invasive central BP device measurement standards	List manufacturer, model, software version, operating principles, signal processing step/s, calibration processes	Must	YES NO. ....
	Time for BP measures; time points of brachial BP and central BP; cuff deflation speed	Should	YES NO. ....
	Define and use appropriate cuff size	Must	YES NO. ....
	Dimensions of inflatable bladder for all cuff sizes available; process to determine cuff size	Should	YES NO. ....
	Process of familiarization with equipment	Should	YES NO. ....
	Separate validation studies for additional or optional features or functions	Must	YES NO. ....
	Process/s of quality control; process used to delineate acceptable quality; number of unacceptable readings; reason/s for exclusion	Must	YES NO. ....
Invasive (intra-arterial) central BP reference standard	Micromanometer-tipped catheter used if minor inflection points to be identified	Should	YES NO. ....
	Full description of catheter; frequency response and handling procedures	Must	YES NO. ....
	Performance comparison of fluid filled catheter with micromanometer-tipped catheter	May	YES NO. ....
Data acquisition at rest	Period of undisturbed rest; medications used	Should	YES NO. ....
	No talking. Free from acute hemodynamic interventions	Must	YES NO. ....
	Test device compared with reference over time-period matching the test device deflation cycle; recorded under stable conditions	Must	YES NO. ....
	Complete description of protocol; time interval between test device and reference measures	Must	YES NO. ....
Data acquisition at BP intervention	Hemodynamic change from resting state	May	YES NO. ....
	Description of the intervention procedure	Must	YES NO. ....

SBP, systolic BP; DBP, diastolic BP. Complete details of protocol components and requirements are contained within the body text. Must, necessary component for highest quality; Should, strong recommendation, but probably not the only way that the component can be achieved; May, further guidance required.<sup>60</sup>

but with greater differences (>10 mmHg lower BP with inspiration) in the presence of cardiac or respiratory abnormalities such as constrictive pericarditis or severe pulmonary disease.<sup>53</sup> Due to limits around the amount of time that can be dedicated to validation studies within the clinical laboratory, it may not be feasible to undertake repeat measures for comparison, but whenever possible this is preferred, with three measures being optimal.<sup>54</sup>

*Data acquisition at BP intervention.* Validation testing under hemodynamic conditions involving a change from the resting state may be undertaken. 24 hour ambulatory BP monitoring is used as an adjunct to clinical BP to determine underlying BP control and devices with ambulatory central BP capacity are available.<sup>47,67,68</sup> Testing the performance of non-invasive central BP monitors under ambulatory conditions is not feasible using intra-aortic monitoring, but in any case this may not necessarily be required since subjects undertaking 24 hour ambulatory BP are instructed to avoid exercise and temporarily stop moving or talking, to relax the arm and breathe normally

during device operation.<sup>69</sup> Thus, the main objective for validation testing of ambulatory BP monitors is to determine device performance under conditions of a change in BP and heart rate from the stable resting state. To this end, a variety of standardized interventions causing a statistically significant ( $P < 0.05$ ) hemodynamic change for BP and heart rate, may be acceptable, for example administering a standard dose of glyceryl trinitrate,<sup>9</sup> table tilting, isometric hand grip exercise, or supine cycling.<sup>31</sup> Once the hemodynamic change has been initiated, performance of the non-invasive BP test device can be tested against the intra-arterial standard, as described for the resting state. Description of the intervention procedure must be reported. Care should be taken to avoid testing during phases of large and acutely variable hemodynamic shifts such as may occur with bolus administration of vasoactive drugs, contrast dye or in the early phase of table tilting.

*Sample characteristics.* A sample size of at least  $n = 85$  adults is proposed based on brachial BP validation protocols and the requirement

**Table 4** Summary list of issues for consideration in development of an internationally accepted central blood pressure (BP) validation protocol

Validation protocol features	Comments
Reference method	
Non-invasive reference standard	What criteria needed to satisfy for an acceptable non-invasive alternative to the invasive method which restricts study sample characteristics?
Error	
Minimum standard	What is the magnitude of the minimum acceptable error and its frequency based on the invasive reference standard?
Study sample	
Definition of general population sample	Which populations should be considered as special as there may be different device measurement accuracy from the general population, and therefore require separate validation?
Minimum sample size for a general population study	Based on the reference method for an acceptable statistical risk of false positive and negative results
Sample size for validations in special groups	To be defined after a successful study in the general population has been completed
Sex and age distribution	Representation of males and females, adolescents, young and middle aged adults and elderly
BP and heart rate range criteria	Based on reference central BP measurements and heart rate during the procedure?
Cuff size	Minimum number of subjects investigated per different cuff size, or number of different cuffs to be studied in a single study?
Exclusion criteria	On the basis of increased reference BP variation within individual validation procedures or clinical conditions
Procedural	
Number of measurements	Procedure for the number of reference and test BP measurements in a validation session
Comparison with reference	How to compare when operating characteristics differ between reference (i.e. beat-to-beat) and non-invasive test devices (i.e. averaging over seconds to minutes) and influence of respiratory variation and arrhythmias?
Reporting	
Data and pass criteria	What data, statistics and study features to be reported? What pass/fail criteria?

to detect a mean difference of 5 mmHg [standard deviation (SD) of the difference 8 mmHg] with an estimated power of >99% (two-sided alpha of 5%), as currently proposed by the AAMI standard. Nevertheless, invasive BP measures during clinical procedures face additional constraints that can increase BP variability, such as selective patient characteristics and limited time for repeat measurements. Thus, a definitive sample size based on robust statistical methods is still needed. If devices are to be used in paediatric age groups, then wherever possible, accuracy should be tested separately in those groups and not extrapolated from adults. Participants should have a sex distribution of at least 30% male and female and in sinus rhythm unless the device is being tested for accuracy during arrhythmias.<sup>55</sup> In keeping with all other brachial cuff BP validation guidelines, devices should be tested over a range of BP. An indicative range for invasive central SBP may be  $\leq 100$  mmHg ( $\geq 5\%$  of readings),  $\geq 140$  mmHg ( $\geq 20\%$  of readings), and  $\geq 160$  mmHg ( $\geq 5\%$  of readings), and the indicative range for invasive central DBP may be  $\leq 60$  mmHg ( $\geq 5\%$  of readings),  $\geq 85$  mmHg ( $\geq 20\%$  of readings), and  $\geq 100$  mmHg ( $\geq 5\%$  of readings).<sup>54</sup> Device accuracy should also be tested across a range of heart rates (i.e. 60–100 b.p.m.), because heart rate influences aortic stiffness and SBP amplification.<sup>70,71</sup> Exact criteria for BP and heart rate ranges needs to be resolved. Unless testing device performance in specific cardiac or respiratory diseases, it should be noted that subjects with the following conditions have a higher likelihood of

measurement error due to abnormal haemodynamics: severe valvular stenosis or regurgitation, severely impaired left ventricular systolic function, atrial fibrillation, constrictive pericarditis, pericardial tamponade, restrictive cardiomyopathy or severe pulmonary disease.

*Statistical requirements.* Beyond the reporting of details already mentioned, description of subjects must be presented and should include basic demographics (age, sex, ethnicity, body mass index), medications and clinical conditions including outcome of coronary catheterization procedure. Comparison between non-invasive and reference BP's must report mean difference, SD of the mean difference, and limits of agreement (LOA), illustrated by modified Bland–Altman plots<sup>72</sup> in which the mean of measurements is replaced by the reference catheter measurement. Scatter plots of the measures obtained with the non-invasive device (on Y axis) vs. the reference method (on X axis), with the line of equality, may also be provided for descriptive purposes. Non-uniformity of SD across the range of measurement or evidence of non-constant bias (e.g. increasing difference between measures with increasing values) must be visually checked on the Bland–Altman plots. An increase in variability of the differences as the magnitude of the measurement increases can be dealt with by log transformation of both measurements before analysis and the LOA derived from log transformed data should be reported after back-transformation (and thus expressed as ratios of the actual measurements). When log transformations do not solve the

problem of a relationship between the difference and the mean, regression approaches or non-parametric approaches can be used instead, but with preference for the latter (for details see<sup>72</sup>). Absolute BP differences from the reference should be presented as a clinically meaningful illustration of the results but without a pass/fail criteria.<sup>54</sup> The proposed pass criteria is if the device has a mean difference of  $\leq 5$  mmHg with  $SD \leq 8$  mmHg compared with the reference, based on the magnitude of minimum tolerable error and frequency,<sup>54</sup> but also recognizing this is a feature requiring resolution in future guidelines.

## Conclusions and future directions

A major reason for producing this document to improve device validity has been the ongoing controversy over whether central BP adds prognostic value to that from routine brachial cuff BP. A recent Framingham paper found no additional value,<sup>73</sup> while two systematic reviews not including those data came to opposite conclusions.<sup>14,74</sup> For unfamiliar readers, an accompanying editorial addresses the issues.<sup>75</sup> A number of perceived deficits relating to both brachial and central BP measurement have been brought to attention in this current paper, and accordingly some points of intent require additional explanation. Firstly, despite the premise of clinical brachial BP measurement being based on essentially inaccurate cuff measures, brachial BP is still important and regarded as the clinical standard. This document should not be interpreted as challenging the clinical utility of brachial BP measurement, nor its value in hypertension management. Similarly, this document does not seek to undermine the potential clinical use of currently available non-invasive central BP devices that have not undergone the validation procedures recommended in this document, but have already proved to provide measurement of physiological (e.g. vascular ageing)<sup>76</sup> or prognostic significance. Nevertheless, with the advent of 'precision medicine', clinical decisions are expected to be refined and improved by using more accurate BP monitors into the future, whether brachial or central BP, and this is a key research need. Additional guidance on central BP validation protocols is keenly awaited from regulatory authorities.

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