WHITE PAPER

Within-session blood pressure variability in clinical trials

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Contents

Background

As described in the most recent update to the FDA pressor effect guidance, 24-hour ambulatory blood pressure monitoring (ABPM) is the recommended methodology to assess potentially relevant blood pressure (BP) effects of a drug intended for long term use (>12 weeks).[1] The guidance additionally describes the importance of proper technique for intermittent clinic BP measurement in clinical trials. This is relevant to characterize the dose or exposure response relationship of any BP effect and to serve as part of the overall safety monitoring program, particularly for drugs with a potential hypertensive effect. Best practice BP collection bolsters the accuracy of results and reduces variability, also critically important when assessing efficacy rather than safety, as is the case for drugs intended to treat hypertension.[2]

Blood pressure variability (BPV) is classified depending on the time interval across which the variability is observed (Table 1[3,4]). Short-term variability often refers to BPV seen within a 24-hour period, typically collected using ABPM. Very short-term variability refers to the differences in BP measurements across heart beats using non-invasive tonometry, intra-arterial lines or photoplethysmography. The time interval between BP measurements collected with replicate inflations during office visits in clinical trials is usually 1 minute to 5 minutes and falls between very short-term and short-term BPV. Clario prefers to use the term 'within session' BPV to describe the variability of systolic BP (SBP) and diastolic BP (DBP) recorded just minutes apart using standard brachial cuff oscillometric methods.

Table 1. Classifications of BPV

	Very short-term BPV	Short-term BPV	Mid-term BPV	Long-term BPV
Measurement frequency	Continuous beat-to-beat or across several beats	Every 15-30 minutes within 24 hours (day vs night)	Between days	Weeks, months, years
Measurement method	Intra-arterial lines, hotoplethysmography, tonometry	ABPM, office BP	Office BP, home BP, ABPM	Office BP, home BP, cuffless BP (not generally accepted in the clinical community)
Use case	Assessment of autonomic cardiovascular modulation	Evaluation of the 24-hour BP profile and circadian rhythm pattern	Long-term BP monitoring	Long-term BP monitoring

Historically, office BP measurements collected in clinical trials have been reported as single measurements per time point or as the mean of a set of serial measurements without capturing the individual inflation readings. Several large clinical trials (NHANES[5], KNHANES[6] and BP-CARE[7]) used auscultatory methods to capture replicate measurements using different recording methods (mercury or aneroid sphygmomanometers), while others have used oscillometric devices (Sprint trial[8] and Maastricht study[9]).

Within the scientific community and clinical trial arena, no universally accepted guidelines have been established on how to best measure BP within the clinic. While there has been ongoing discussion on the topic, there is, for example, no consensus on the exact number of BP replicates to use or which measurements from the replicate set should be included in the time point mean calculation.[10,11]

At Clario, we have seen the following BP measurement sequences across different studies:

- Capture four consecutive readings, excluding the first, and take the average of the last three.
- Capture three consecutive readings, and generate the average of all three.
- Capture three consecutive readings, and generate the average of readings two and three, excluding reading one.
- Capture five consecutive readings, and generate the average of readings four and five, excluding readings one to three.

BPV is impacted when data collection and analysis are not standardized within the clinical trial BP assessment.

Within-session blood pressure variability seen across clinical studies at Clario

Clario offers an office BP solution that includes devices validated according to the ANSI/AAMI/ISO 2013, ESH-IP 2002 and BHS 1993 protocols. Additional studies have been performed with these devices in relevant patient populations such as those with chronic kidney disease, pre-eclampsia or atrial fibrillation. These specific population studies, as is typical for most validation studies, are relatively small studies compared with the large clinical trials Clario supports through our centralized clinic BP services. Our solution allows configuration of a rest period prior to the start of the first inflation, the number or inflations per time point and the time elapsed between inflations. All data are stored in the system, and rules can be implemented on which data should be used to calculate the mean BP for the time point.

We have reviewed the data from studies enrolling both hypertensive and normotensive patients using our office BP solution (Table 2). All measurements were collected with the study participant in a sitting position. The data from the first three measurements in a session were used in the analysis with a 1- to 3-minute interval between measurements. On average, the SBP recorded during the first inflation was higher than the last two inflations in both populations, justifying why, in some clinical trials, the decision is made to exclude the first measurement and use the average of the last two measurements as the time point estimate.

Table 2. Mean SBP measurements across consecutive inflations

Parameter	Population	Inflation 1, mean±SD	Inflation 2, mean±SD	Inflation 3, mean±SD
SBP (mmHg)	Hypertensive patients	145.7±18.90 (N=14,988)	144.9±18.44 (N=15,204)	144.7±18.30 (N=15,212)
	Normotensive non-healthy patients	124.74±14.79 (N=7,397)	123.01± 13.96 (N=7,366)	121.68±13.40 (N=7,322)

In studies of hypertensive patients, the absolute differences in SBP (|ΔSBP|) between inflations 1 and 2 were within 10, 20 and 30 mmHg for 76.7%, 94.2% and 98.3% of the sessions, respectively (Table 3). In normotensive patients, higher stability between consecutive measurements was observed. The |ΔSBP| between inflations 1 and 2 were within 10, 20 and 30 mmHg for 83.2%, 95.4% and 98.2% of the sessions, respectively (Table 4). A similar trend was seen in differences between inflations 2 and 3, indicating that the changes seen across inflations are not solely due to an acclimatization to the procedure.

Table 3. Categorical analysis of absolute SBP changes between consecutive inflations seen in hypertensive patients

Parameter	Category	Inflation 1 vs 2	Inflation 2 vs 3
|ΔSBP|	Total observations	14,945	15,151
	Within 10 mmHg across all replicates, N (%)	11,444 (76.57)	11,738 (77.47)
	Within 20 mmHg across all replicates, N (%)	14,077 (94.19)	14,287 (94.30)
	Within 30 mmHg across all replicates, N (%)	14,687 (98.27)	14,907 (98.39)

|ΔSBP|: absolute differences in SBP

Table 4. Categorical analysis of absolute SBP changes between consecutive inflations seen in normotensive patients

Parameter	Category	Inflation 1 vs 2	Inflation 2 vs 3
|ΔSBP|	Total observations	7,365	7,316
	Within 10 mmHg across all replicates, N (%)	6,125 (83.16)	6,281 (85.85)
	Within 20 mmHg across all replicates, N (%)	7,025 (95.38)	7,060 (96.50)
	Within 30 mmHg across all replicates, N (%)	7,232 (98.19)	7,230 (98.82)

|ΔSBP|: absolute differences in SBP

We also performed an analysis to determine how many BP sessions would have needed to be repeated in case at least one of the consecutive measurement pairs was above a pre-set threshold (i.e., either inflation 1 vs 2 or inflation 2 vs 3 was above the threshold; Table 5). These data show that 9.7% of the sessions conducted in hypertensive patients would have to be repeated if a threshold of 20 mmHg was used. In normotensive patients, 6.8% of the sessions would have to be repeated using this threshold. These results indicate that within-session BPV may be higher in hypertensive patients than in normotensive patients.

Table 5. Frequency of exceeding pre-defined systolic BP thresholds of 10, 20 and 30 mmHg in hypertensive and normotensive patient populations

	Hypertensive patients	Normotensive patients
Total observations	15,197	7,366
|ΔSBP| >10 mmHg inflation 1 vs 2 or inflation 2 vs 3, N (%)	5,491 (36.1)	1,838 (25.0)
|ΔSBP| >20 mmHg inflation 1 vs 2 or inflation 2 vs 3, N (%)	1,472 (9.7)	498 (6.8)
|ΔSBP| >30 mmHg inflation 1 vs 2 or inflation 2 vs 3, N (%)	442 (2.9)	192 (2.6)

|ΔSBP|: absolute differences in SBP

Within-session blood pressure variability in published trials

We performed a literature search to investigate if the within-session BPV reported in the literature differs significantly from the variability we have observed in studies supported by Clario. A search was performed using **pubmed.ncbi.nlm.nih.gov** specifically focusing on articles in which the BP measurements were performed in close succession. We only selected articles published within the past 12 years since BP methodology and thoughts on BPV have changed extensively in the recent decade. The most relevant hits were found when combining “blood pressure” and “within visit” as keywords.

The main conclusions from the literature review are described in the following sections.

Large differences between consecutive measurements using both oscillometric and auscultatory methods

- Papaioannou TG et al, using auscultatory methods, showed a maximum absolute difference >10 mmHg within triplicate SBP and DBP readings in 12.9% and 13% of the triplicates, respectively.[12]
- Lacruz et al, using oscillometric methods, showed that ~20% of the study participants had SBP differences >10 mmHg and DBP differences >5 mmHg between inflations 1 and 2.[13] SBP changes >40 mmHg were seen.
- Okada R et al showed that 75.4% of the consecutive measurements had ΔSBP ≤10 mmHg and 93.8% had ΔSBP ≤20 mmHg. The BP collection method was not described.[14]
- Li Y et al, using oscillometric methods, showed that 14.2% of the replicate inflations had a maximum difference >19 mmHg between the lowest and highest SBP measurements in a triplicate. Absolute values ranged between 0 and 52 mmHg for SBP and 0 and 34 mmHg for DBP.[15]

Causes for within-session variability

Both intrinsic and extrinsic factors contribute to BPV.[16,17] Intrinsic factors include autonomic tone, neurological and humoral state, vascular, rheological as well as renal and genetic diseases. Extrinsic factors include environmental, emotional and therapeutic treatment effects, along with behavioral elements. Finally, inappropriate BP monitoring techniques can also have an impact on the accuracy of the measurement.[4]

There are no published studies nor consensus statements on the factors that contribute to within-session BPV, but some factors that influence short-term BPV individually or in combination include the following[6,14]:

- Older age
- Comorbid diseases (e.g., diabetes, chronic kidney disease, atherosclerosis)
- Increased sympathetic nerve activation (influenced by the participant's neurological and emotional state)
- Respiratory status
- Increased arterial stiffness
- Decreased baroreflex function (related to an exaggerated pressor response in reaction to mental and physical stimuli)

Relationship between blood pressure variability and cardiovascular risk

The potential association between within-session BPV and increased cardiovascular risk and mortality remains unclear. Muntner et al suggested that the variability in BP assessed over a short period (within a clinical visit) may reflect conditions surrounding the measurement of BP or measurement errors rather than reflecting a true biologic factor with prognostic importance.[18] Their findings suggest that short-term within-visit BPV is not associated with an increased risk for all-cause or CVD mortality. A similar conclusion was made by Shutte et al regarding the association of within-visit BPV with total mortality and fatal and nonfatal cardiovascular events.[19] More recent publications, however, have shown an association between BPV and cardiovascular risk.[20] Papaioannou et al concluded, based on the same dataset as Muntner et al, that within-visit variability of 3 sequential DBP measurements is a significant predictor of all-cause mortality, independent of demographic and clinical characteristics.[21] The European Society of Hypertension (ESH) position paper by Parati et al states: "Elevated short-term BP variability and nocturnal BP non-dipping are associated with higher cardiovascular risk." No thresholds were defined.[16]

Best practices to reduce within-session blood pressure variability

Although some BPV is physiologically inherent to patient characteristics, all efforts should be made to reduce variability introduced artifactually by the assessment methodology. This can be done by assuring that well-validated and appropriate clinic BP equipment is used, site personnel are properly trained in best practice methods and the patients receive instruction on best practices to ensure successful clinic BP assessments (Table 6).[4,22,23,24]

Table 6. Best practices for seated office blood pressure measurement collection

Blood pressure device requirements

- Use a blood pressure device that has been properly validated according to industry standards and preferably clinically tested in the intended study population.
- Use the same device for all visits for a given participant and preferably across all sites in a clinical trial.
- Ensure cuffs and devices are validated together. Using cuffs from a different manufacturer can result in erroneous measurements.

Site staff training

- **All** site personnel involved in the collection of blood pressure measurements need to complete proper training prior to performing the first measurements. This includes training on how to operate the supplied equipment and how to prepare and instruct a participant prior to starting the measurements. Site personnel should not talk during the rest and measurement periods.

Participant instructions

- The participant should be instructed not to smoke, drink caffeinated or alcoholic beverages or exercise within 0.5 hour prior to the blood pressure measurement.
- The participant should empty a full bladder prior to the blood pressure measurement.
- The participant should be placed in a room with a comfortable temperature in the seated position for at least five minutes prior to blood pressure readings.
- The participant should sit with their legs uncrossed, feet flat on the ground and back supported.
- Use the appropriate cuff size. Cuffs that are too tight can result in falsely high measurements, while cuffs that are too loose can generate lower measurements.
- Place the cuff on the bare arm, not over clothing as this may significantly increase systolic blood pressure. Do not roll up sleeves as this may produce a tourniquet effect.
- At the first visit, record blood pressure for both arms, and use the arm with the highest reading for all following measurements.
- The arm should be supported, and the mid-arm should be at heart level.
- The participant should remain sitting quietly in the appropriate position and avoid conversations, TV, phones or other distractions.
- Take a minimum of three measurements per session (1-3 minutes between replicate inflations). Pre-specify the method for calculating the time point mean (e.g., average of all three inflations, average of inflations 2 and 3 only).
- Consider inclusion of a threshold for the difference between replicate inflation results that will trigger a repeat session.

Summary

Within-session BPV is a well-described phenomenon that should be anticipated during clinical trial conduct. It is unclear whether this represents true physiologic changes in BP, is partly artefactual due to failure to follow best practice techniques during BP collection or is due to poor performance of a device's algorithm to determine BP accurately from the oscillometric waveform. There is currently no consensus as to what magnitude of difference between BP readings is too large to accept. The within-session BPV we have observed in clinical trials is consistent with the variability described in the published literature.

BPV can be minimized using standardized devices and procedures across all study sites, with a particular focus on site staff training to ensure best practices are followed. Clario's experience with BPV provides not just a benchmark for comparison to other trials but also an opportunity to better understand the sources of BPV. This experience also allows the opportunity to implement mitigation strategies proactively or during a study if higher than expected variability is observed. An understanding of this expected variability can also influence study design, sample size and data analysis strategies. The experts and scientists at Clario are using this knowledge and experience to implement measures to mitigate and reduce BPV within our supported trials. Our data suggest that acceptability criteria for within-session variability with automated oscillometric BP devices should be established, including a threshold for repeating the session if excess variability is observed. The learnings produced from these efforts will benefit sponsors, sites and study participants while maximizing data quality and reliability of study results.

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Clario's global team of science, technology, and operational experts have helped deliver over 26,000 trials and contributed to over 800 regulatory approvals in more than 100 countries. For more than 50 years, we have delivered deep scientific expertise and the most comprehensive endpoint technologies to help transform lives around the world.