Cardiac Safety Research Consortium (CSRC) BP Thinktank

Measurement Techniques & Methodology – Early Development

Session IV

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Agenda

- Technology and methodology considerations
- Overview of technology options – early development
- Reference studies

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Blood Pressure Monitoring – technology and methodology: Points to Consider

- **Blood pressure endpoint**
  - **Dose response/concentration effect**
  - **Standard vital sign monitoring**
  - ***General question for study integration: How will this measure help define/identify if a BP signal exists?***

- **Patient population versus healthy volunteer**
  - **Is the selected BP technology appropriate for the study population**
  - **Validation of the device within specific population**
  - **Participant compliance**

- **Differentiation between devices developed for clinic environment versus personal/individual use**
  - **Device calibration**

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Blood Pressure Monitoring – technology and methodology: Points to Consider

- BP device validation & industry standards
  - Regulatory validation
    - FDA 510(k)
    - CE Mark
  - Industry standards – “protocols”
    - AAMI – Association of Advancement of Medical Instrumentation
    - BHS – British Hypertension Society
    - ESH – International protocol
  - Population specific studies
    - Pediatric
    - Obese

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Blood Pressure Monitoring – technology and methodology

- **Should we be focused on ascultatory vs. algorithm based BP assessment?**
  - **Clinical culture and behavior change**
  - **Existing industry and clinical BP data – “manual" can we use this data as standard industry data set?**

- **Variability based on methodology/technology**
    - **Human factor – ascultatory & manometer**
    - **Algorithm and device validation**

- **Validation vs. Training/Certification**
  - **Are devices validated based on sufficient rigor and protocol?**
  - **Are study sites trained appropriately either for ascultatory or automated device procedures?**

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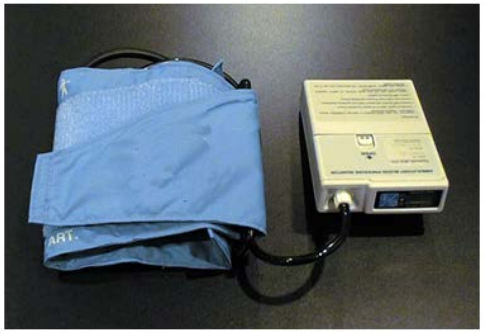
Technology



ABPM

Home/Office BP

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BP Device – Strengths/Limtations and Implementation

BP methodology - technology	Strength	Limitation	Clinical phase Application	White Coat Effect	Night Time Data	orthostatic evaluation	AASI, CASP - other
Auscultatory Clinic BP measurement using mercury, aneroid devices	Traditional standard used in epidemiological and large trials. Use to calibrate automated oscillometric devices	Mercury environmental concerns Unable to provide sleep reading, associated with white coat effect	Phase I-IV	Y	N	Y	N
Auscultatory Clinic BP measurement using digital manometer	Removes mercury issue, enhanced validation and easier to read BP values, Use to calibrate automated oscillometric devices	Still based on well trained observer to obtain BP readings	Phase I - IV	Y	N	Y	N
Automated Clinic Oscillometric BP Measurement	Not subject to observer bias, select inflation sequence, may remove white coat effect, a number of devices allow to 'toggle" to a manual mode	accuracy should be checked on each patient	Phase I-IV	N	N	Y	N

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BP methodology - technology	Strength	Limitation	Clinical phase Application	White Coat Effect	Night Time Data	orthostatic evaluation	AASI, CASP - other
Automated Clinic Oscillometric BP Measurement - centralized monitoring (C-OBPM)	Provides early visibility into Clinic based BP trends. Removes white coat as well.	Learning curve for sites to implement process	Phase I - III	N	N	Y	N
Ambulatory Blood Pressure Monitoring (ABPM)	Provides large number of readings over a 24 hr period. Only method providing sleep BP High short and long term reproducibility	Tolerability by patients may limit number of days patient will wear device	Phase I-IV	N	Y	Y	Y?
Automated self measured home oscillometric BP measurement	Provides out of office readings, recognized correlation to ABPM data	Requires patient to transcribe BP values into diary, device validation for population	Phase II-IV	N	Y/N	N	N
Automated self measured home oscillometric BP measurement - telemonitoring (T-SMBP)	Ability to transfer and process large amount of data easily, trend analysis and alert criteria	Working with telecommunication providers to move to a data transmission focus	Phase II-IV	N	Y/N	N	N
Hemodynamic BP evaluation - pulse wave form evaluation	provides non-invasive BP associated endpoints such as CASP, arterial compliance	Open debate on best endpoint	Phase I- IV	NA	NA	NA	Y

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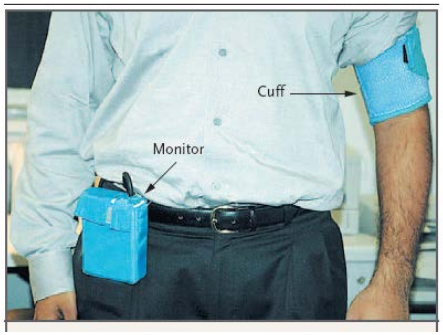
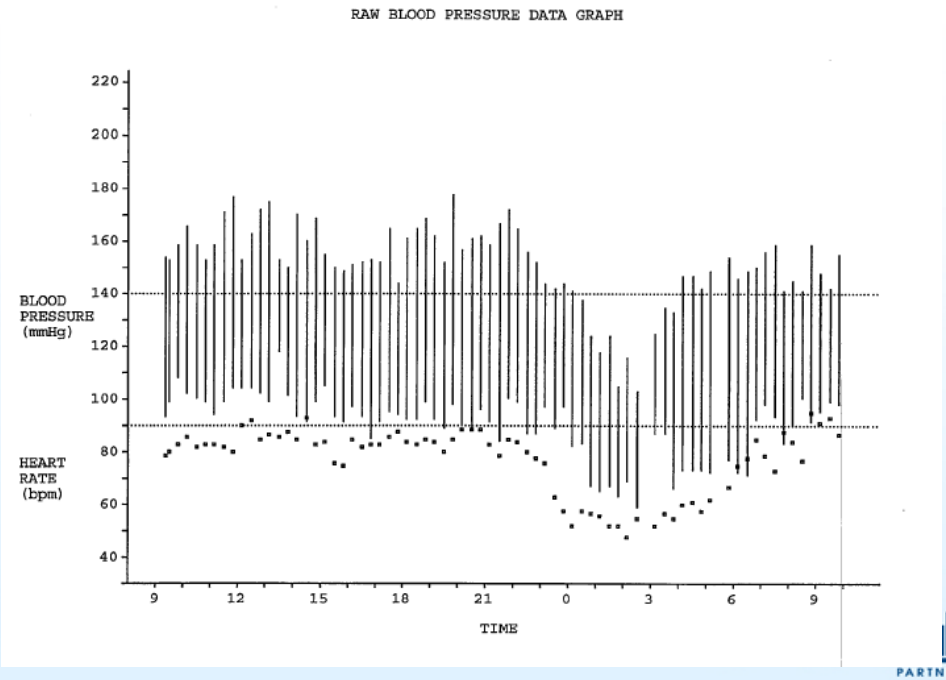
ABPM – Ambulatory Blood Pressure Monitoring

- Oscillometric devices
- Configurable inflation sequence
- 24 hour BP monitoring
- High number of BP readings over 24 hour period
- Time matched BP readings
- Dose response
  - Comparison to baseline
- Screening tool – mean values
  - 24 hr. mean
  - Daytime
  - Nightime





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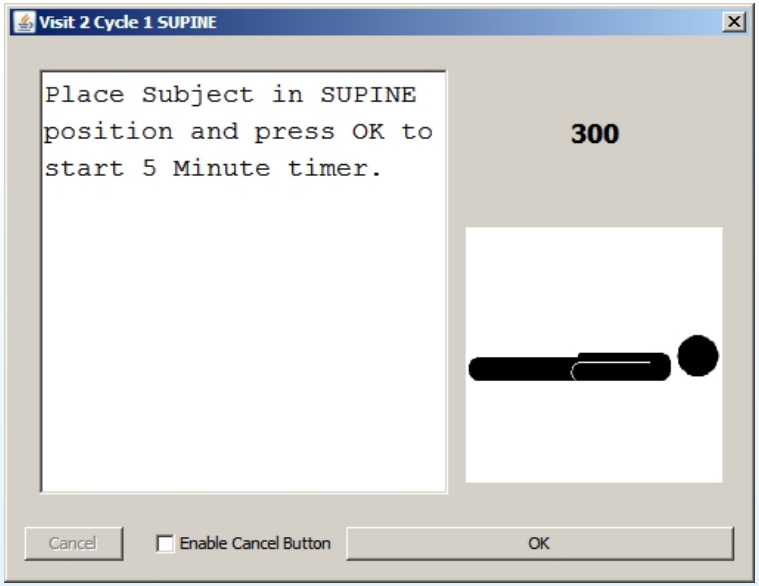
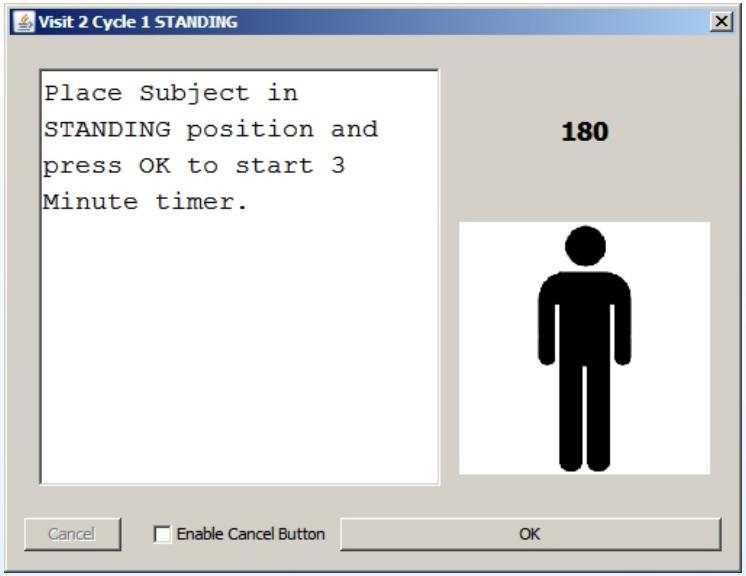
Automated Clinic Blood Pressure

- Oscillometric devices
- Configurable inflation sequence
- Time matched BP readings
- Electronic data capture
- Automated averaging





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ABPM – cardiac safety endpoint –early development

Protocol	Indication	Objective
A randomized, parallel, double-blind, placebo-controlled, time-lagged, ascending, multiple-dose, pharmacokinetic, pharmacodynamic, safety and tolerability study of XXX in healthy volunteers	Clinical Pharmacology - CNS	Evaluate the safety and tolerability of once daily dose, oral of XXX in healthy volunteers
A randomized, double-blind, placebo-controlled, cross-over study to investigate the effect of YYY on ambulatory blood pressure	Clinical Pharmacology - CNS	Primary endpoint - change in 24 hr. average SBP and DBP from Baseline
A Randomized, Observer-Blind, Placebo-Controlled, Four Treatment Latin Square Study to Evaluate the Safety and Tolerability of Concomitant Administration of XXX and YYY	Clinical Pharmacology - Urology	Evaluate the effects on BP and HR when single doses of XXX and YYY are given in combination to female volunteers
The effect of XXX and YYY in the Treatment of mild to moderate hypertension in Salt-Sensitive Subjects	Phase II / Clinical Pharmacology setting	Compare the effects of XXX and YYY on blood pressure and urinary ANP in subjects with salt-sensitive hypertension
A placebo-controlled, crossover study evaluating the effects of XXX on insulin resistance in subjects with hypertension	Phase II / Clinical Pharmacology setting	To demonstrate that XXX in comparison with placebo will increase the insulin sensitivity index after 4 weeks of therapy in patients with Stage 1 or Stage 2 hypertension and historical evidence of insulin resistance.
A Randomized comparison of XXX and YYY formulations of ZZZ relative to placebo in patients with borderline to mild/moderate hypertension	Phase II / Clinical Pharmacology setting	To compare a sustained release XXX with an immediate release XXX in terms of safety and pharmacokinetics

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Case Study: CNS Development

- Background
  - Compound in early phase, initial identification in increase in BP
  - Unclear if the BP increase resolves based upon PK/PD response
  - ABPM Primary endpoint
  - Goal to identify both immediate BP response to compound as well as response over extended period of time and steady state
- ABPM Benefit
  - Used both as an in patient - time matched PK/PD as well as 24 hour circadian profile

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Case Study: CNS Development

- 48 healthy volunteers
- 2 period cross-over design
- ABPM sessions scheduled based upon known steady state and beyond – 3 per period with a baseline at the start of each period
- Analysis of 24 hour mean systolic and diastolic as well as mean day and nighttime

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Summary

- Focus on the basics – Clinic BP
  - Cuff selection
  - BP assessment environment
  - Device validation
  - Patient population
  - *Question* – use of sites own automated device or standardized automated device provided to the site for a study
    Question – Calibration of devices
- Open for discussion:
  - Number of BP readings and averaging
  - Cuff standardization (small, medium, large, X-Large)
  - Is electronic capture of clinic BP an advantage over BP value transcription
  - Where does central BP monitoring fit into cardiac safety (versus efficacy)
- Recognized benefit of ABPM in off-target effect
- Take home message:
  - for BP evaluation look at the continuum across development phases
  - Recognize that the technologies are complimentary and can be implemented within a single study
  - Request input on BP expectations from Cardiorenal team

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Supporting – backup slides

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Standard Office Blood Pressure Evaluation

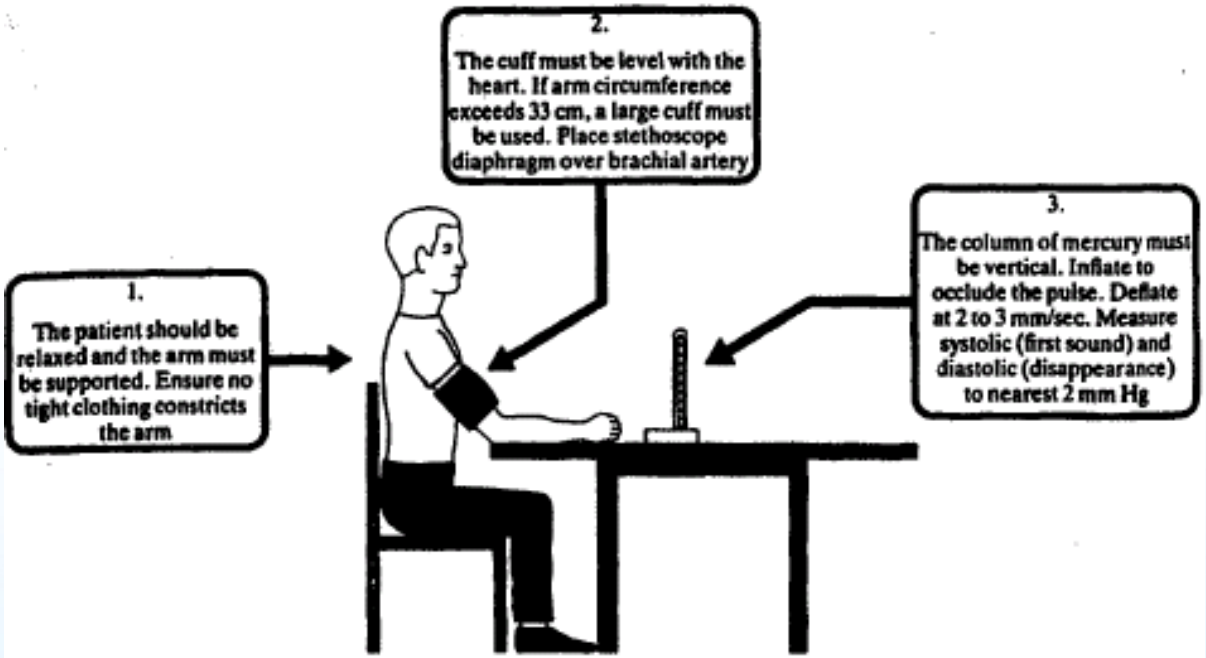

Figure 2.7. Technique of blood pressure measurement recommended by the British Hypertension Society. (Reproduced with permission from British Hypertension Society. *J Hypertens* 1985;3:293.)

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What is working / What can we do better / What is developing

- **What is working**
- Consistency
- Standardization
- Device validation
- "Organic" focus on BP methodology and endpoint consideration
- Ambulatory Blood Pressure Monitoring
  - Implementation across clinical trial phases and indications
- Education – awareness within clinical trial environment

- **What can we do better**
- Awareness of BP evaluation based on
  - Patient population
  - Device validation
  - When is ascultatory evaluation appropriate?
  - Decision tree of BP methodology based on BP signal
  - ***Cuff circumf. standardization***
  - Determine clinic based protocol
    - triplicate vs. single
    - orthostatic evaluation
    - Number of cycles of BP
- **What is developing**
  - Remote patient monitoring
  - Combination devices
  - Cross therapeutic awareness – it's not just hypertension research
  - Blood pressure variability

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Benefits of Automated Office and Home BP

- Additional tool in clinical trial blood pressure evaluation and monitoring
  - Assist in identification of white coat hypertensive patient
  - Remove variability that is generated by human/auscultatory bias
  - Good correlation between ABPM and automated home BP – Not a substitute but a compliment to ABP
- Accuracy of data collection – remove transcription errors (electronic home BP) Adaptive clinical trial design
  - Allows for earlier identification trends in blood pressure response
  - May allow for earlier endpoint identification

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Benefits of ABPM and T-SMBP

- Additional tool in clinical trial blood pressure evaluation and monitoring
  - Remove variability that is generated by human/auscultatory bias
  - Good correlation between ABPM and automated home BP/T-SMBP – Not a substitute but a compliment to ABP
- ABPM – large sample around a 24 hour period
- T-SMBP – large sample over an extended period of time (months)

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