Non-Invasive Central BP Monitoring: Improving Efficiency and Success of Drug Development

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Steven Kesten, MD
Chief Medical Officer, ATCOR Medical

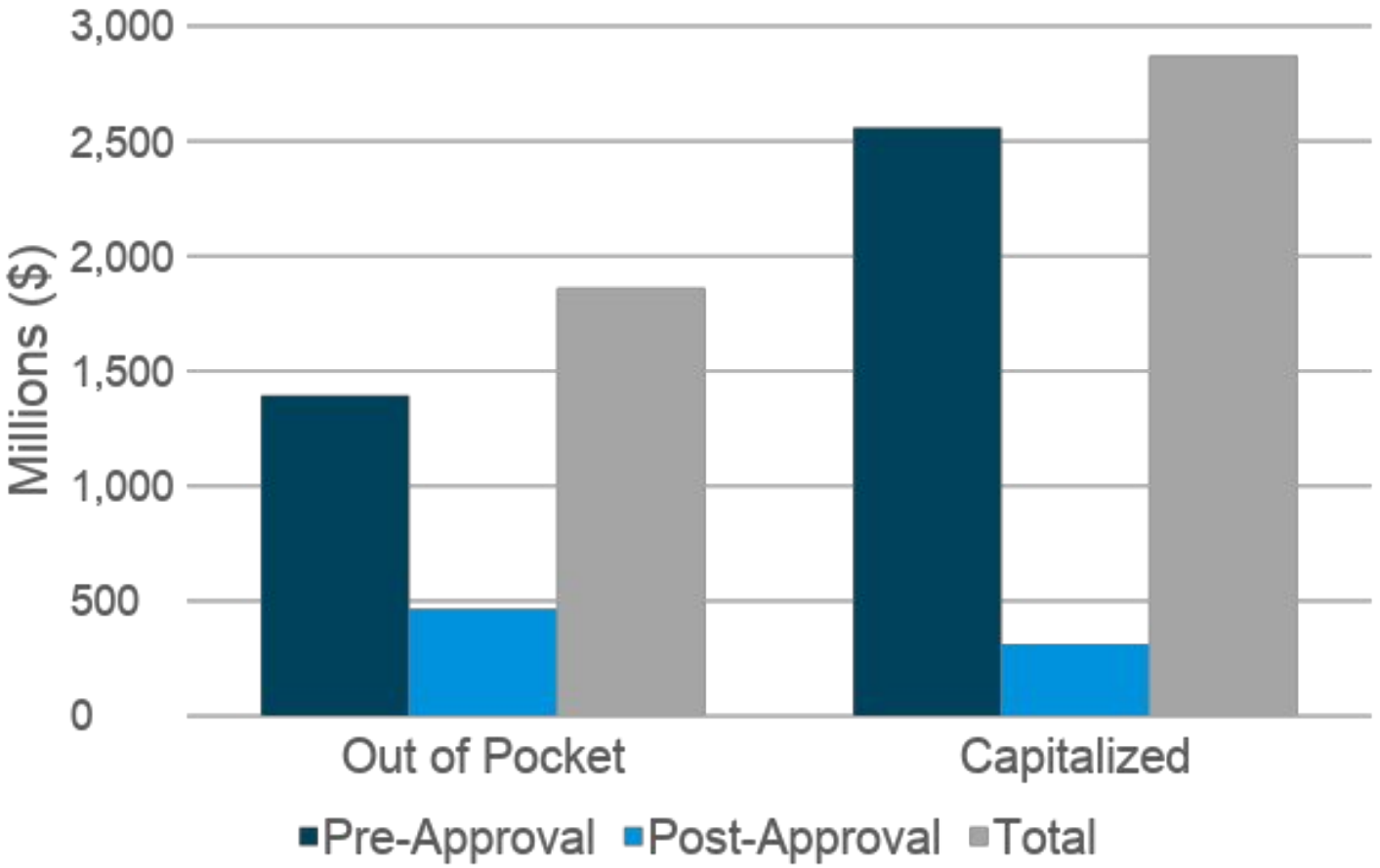
Objective of Presentation

To outline the rationale for integrating central aortic blood pressure (cBP) monitoring into clinical development programs where arterial pressure is a primary outcome (e.g., products for hypertension) or an important secondary outcome (e.g., products for heart failure, pulmonary hypertension, chronic kidney disease).

Background

Total Cost Per Drug Approval

Out of Pocket and Capitalized Cost Per Approved New Drug



DiMasi et al. Innovation in the pharmaceutical industry: new estimates of R&D costs. J Health Economics. 2016;47:20-33.

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Clinical Trial Success Rates

Clinical Trial Success Rates by Phase and Therapeutic Area*

Source	Phase 1 to Approval, %	Phase 2 to Approval, %	Phase 3 to Approval, %	FDA Submission to Approval, %
Therapeutic-area–specific rates				
Oncology	3.4	6.7	35.5	81.7
Metabolism and endocrinology	19.6	24.1	51.6	80.4
Cardiovascular	25.5	32.3	62.2	84.5
Central nervous system	15	19.5	51.1	82.2
Autoimmune and inflammation	15.1	21.2	63.7	80.3
Ophthalmology	32.6	33.6	74.9	80.4
Infectious disease	25.2	35.1	75.3	84.9
Other	20.9	27.3	63.6	80.4

*adapted from Wouters et al

Given the modest probability of success from Phase 1 to 3, opportunities for improving development program decision making and increasing the probability of success should always be considered.

Wouters et al. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. JAMA. 2020;323(9):844-853. doi:10.1001/jama.2020.1166

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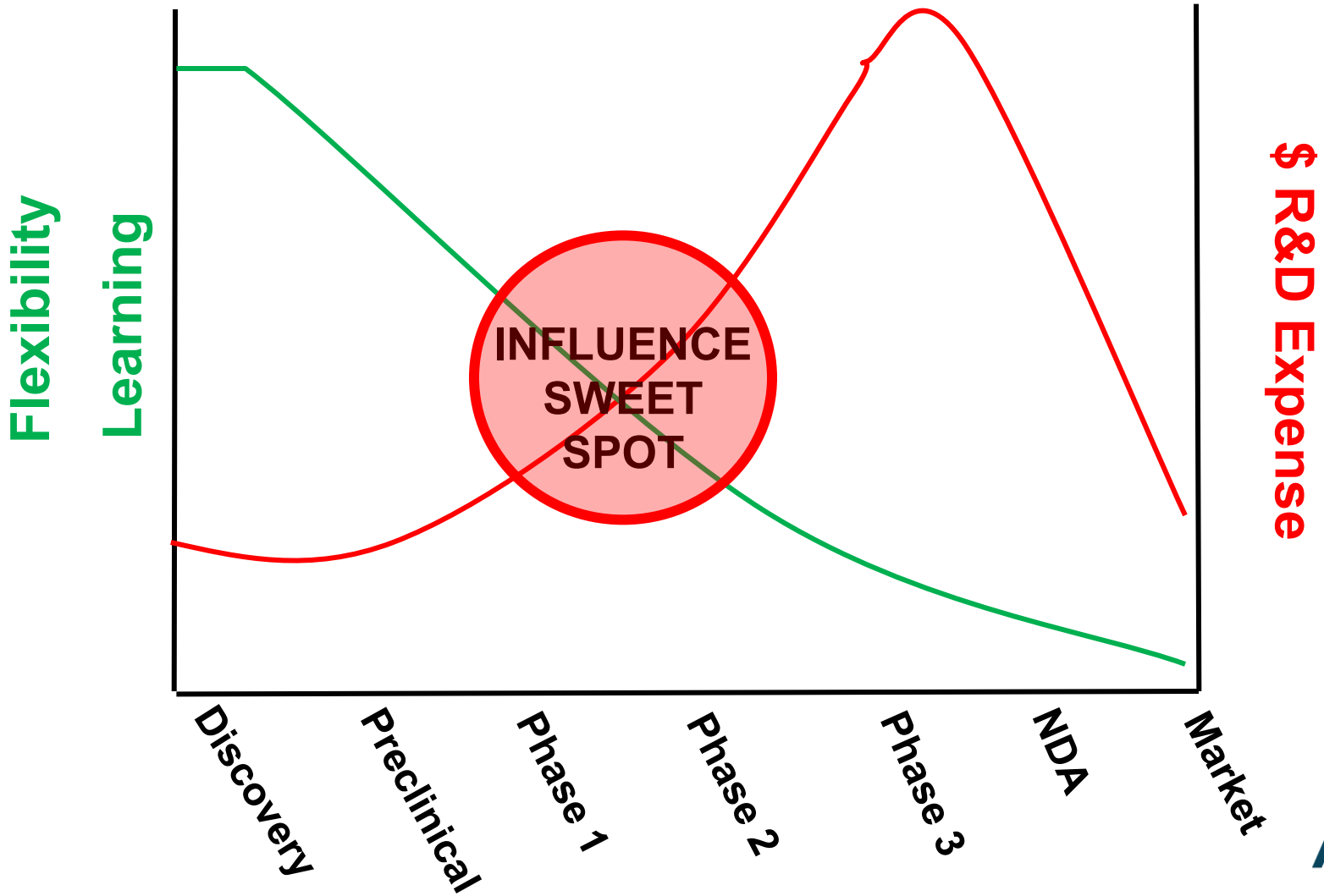
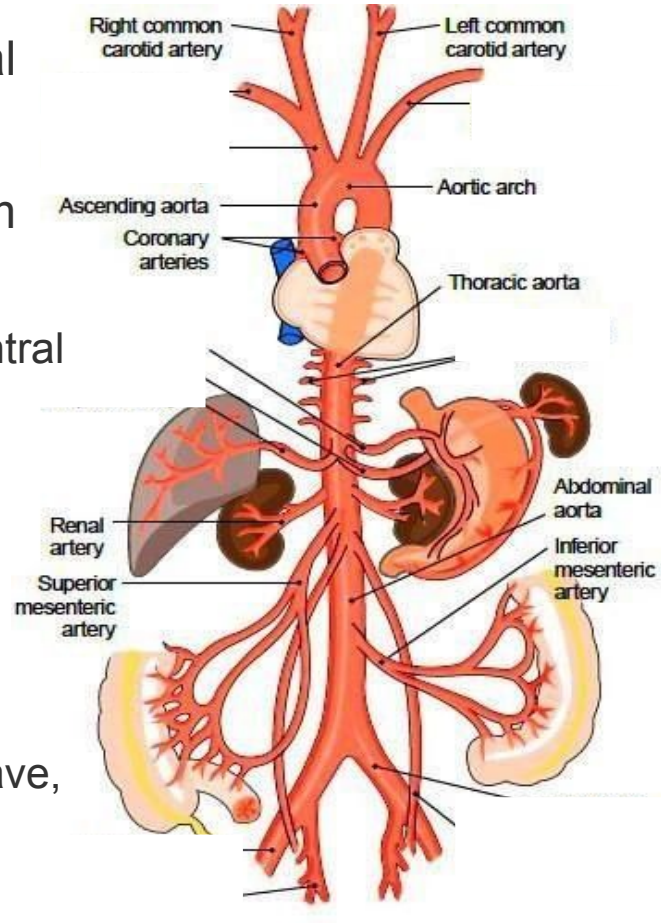
Phase II: Critical Time Point



Non-Invasive Measurement of Central Aortic BP

- Central pressures directly impact organs and are generally more highly correlated with end-organ damage and clinical outcomes compared to brachial (peripheral) pressures
- Central pressures can be captured non-invasively through pressure wave form analysis (PWA)
  - Transforms the data from peripheral arterial BP waveforms into an evaluation of central aortic pressures
  - PWA corrects for pressure wave amplification in the upper limb
- Key variables produced by PWA:
  - Central aortic systolic and diastolic pressures
  - Central aortic pulse pressure (systolic minus diastolic pressure)
  - Augmentation pressure (difference between (a) reflected wave added to incident wave, and (b) incident pressure during systole)
  - Augmentation index (augmentation pressure divided by the pulse pressure)



The SphygmoCor® XCEL System

Dual Arterial Pressure Monitoring System

- Utilizes a cuff placed on the patient's brachial artery
- Obtains brachial BP followed by measurement of central aortic pressures
- Records brachial BP and brachial pressure waveform
- From this, derives the central aortic pressure waveform at the heart
- Provides physiological data including:
  - Central blood pressures (systolic & diastolic)
  - Augmentation Pressure (AP)
  - Augmentation Index (AIx)
  - Subendocardial Viability Ratio
- The **only** FDA cleared medical device for full arterial waveform features in all adults

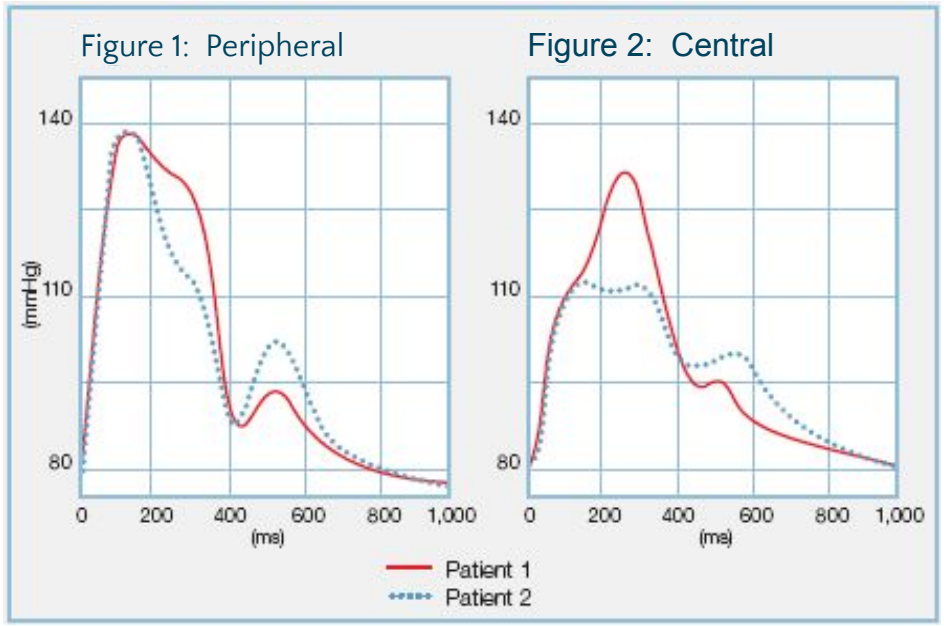
AP: the additional pressure that wave reflection makes to the systolic arterial pressure obtained by measuring the reflected wave coming from the periphery to the center.
AIx: AP divided by pulse pressure ×100.

Brachial Pressure Differs from Central Pressure

Brachial Cuff Pressure vs. Central Aortic Pressure

Two patients with SIMILAR BRACHIAL CUFF pressures (Figure 1), but with significantly DIFFERENT CENTRAL/AORTIC arterial pressure waveforms (Figure 2).

- The difference in waveform shapes, due to differences in arterial stiffness and the effects of wave reflections, effects the aortic but not the brachial systolic and pulse pressures



Brachial and Central Aortic Pressure Measurements are Not Redundant and Provide Clinically Relevant and Complimentary Information

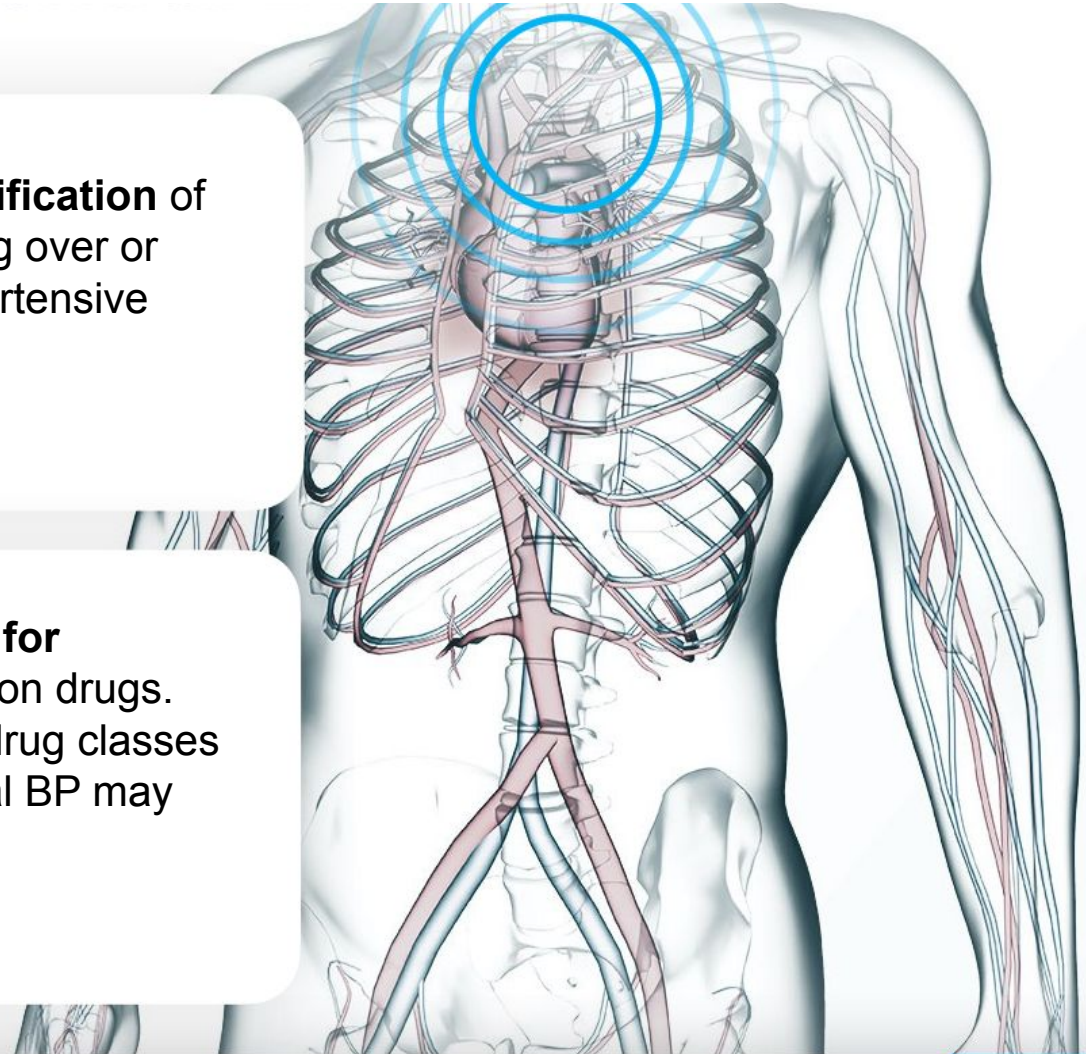
Why Central Waveforms and Central BP?

1. **Additional risk determination** of hypertension and CV related diseases, such as stroke, CKD, pre-eclampsia. Central systolic BP is independently predictive of CV events.

2. **Closer reflection of CV risk** than brachial BP – studies indicate predictive superiority of central over brachial BP. Elevated central BP predicts CV events, mortality, and organ damage (e.g., LVH, intima-medial thickness, reduced GFR).

3. **More accurate identification** of patients that are being over or undertreated for hypertensive related disorders.

4. **Additional precision for targeting** of prescription drugs. Differential effects of drug classes on brachial and central BP may occur.



Rationale for Incorporating Central Aortic BP Monitoring in Clinical Development Programs

Confirmation of Hypertension at Baseline

- Clinical trials specify optimal BP measurement procedures (e.g., quiet room, sitting upright, multiple measurements).
  - However, suboptimal implementation may occur or be influenced by unrecognized subject factors.
  - Inaccurate baseline values can invalidate all post-intervention results within a subject; therefore, confirmation and confidence in baseline BP is essential.
- Inclusion/exclusion criteria based on threshold values may be improved in terms of subject qualification by considering central BP.
- Examples:
  - *Scenario A: Concurrent elevation in brachial and central BP – confirmed hypertension*
  - *Scenario B: Minimal/borderline elevation in brachial BP that minimally satisfies inclusion criteria (e.g., subject must have Stage 2 hypertension). Elevation of central BP confirms acceptability. Low central pressure suggests that the subject may not be an optimal candidate.*
  - *Scenario C: Substantial divergence between brachial and central BP. Consider differential effect of intervention, which can be evaluated (pre-specified in SAP).*

Avoiding Misleading Information Due to White Coat Hypertension (baseline & follow-up)

- White coat hypertension is extremely common.
- Procedures outlined in clinical trial protocols and investigator training will decrease but unlikely to eliminate the phenomena. Central BP can provide informative information.
- Examples:
  - *Scenario A: brachial BP elevated, central BP is normal or low.*
  - *Scenario B: brachial BP is significantly higher than baseline at follow-up visit, while central BP is the same as baseline visit.*

Confirmation of Blood Pressure Values at Follow-Up

- Previous issues apply equally to follow-up (post-enrollment visits) measurements.

- Examples (particularly for end-point visit) :
  - *Scenario A: Large differences in absolute values.*
  - *Scenario B: Discordant changes from baseline in cBP and pBP values (e.g., no change in pBP but decline in cBP).*
    - *Implication: Therapeutic intervention may be having a differential effect*
    - *Documented in previous trials comparing drugs in different classes. Without cBP, a false interpretation (e.g., no efficacy) could be concluded, when a true drug effect exists.*

Endpoints for Evaluation of Therapeutic Effect

- Central BP may distinguish thresholds or associations with end-organ damage that might not be observed within a given brachial BP range.
  - Central BP provides additional and potentially independent information regarding risk of end-organ damage (or probability of reduced risk) and clinical outcomes.
  - Such data can be utilized in clinical trial design.
- Example:
  - *Scenario: Drug in phase 2 shows minimal change in brachial BP that does not provide adequate information for assessment of go/no go decision.*
    - *A clear effect (or absence of effect) on central BP allows for a more informed decision as to whether to proceed with additional phase 2 studies or to proceed to phase 3.*

Informing Dose Selection During Phase II

- Often 3 to 5 doses are evaluated in phase 2 in order to proceed with 1 to 2 doses in phase 3.
- Decisions in phase 2 can be considered the “sweet spot” in terms of decisions to proceed into phase 3.
  - Phase 2 dose-ranging studies generally not powered for detecting difference among active doses.
  - Surrogate endpoints (often multiple endpoints) are utilized in phase 2 studies.
  - In addition to dose, decisions may involve dose frequency (e.g., daily or bid).

Additional information from central aortic pressures permits more informed decision regarding:

a. confirmation of therapeutic effect when the effect and effect size is unclear or imprecise
b. magnitude of therapeutic effect
c. different therapeutic effect than anticipated
d. signals as to expected adverse effects (e.g., hypotension)
e. duration of effect

Improved decisions: stopping development, additional phase 2, or moving to phase 3.

Information for Safety Evaluation

- Overtreatment (e.g., development of hypotension) may lead to:
  - Symptoms without clinical consequences (presyncope)
  - Syncopal episodes with falls
  - End-organ damage (e.g., stroke, syncope, myocardial ischemia, elevated creatinine).
- Studies have documented worsening of end-organ function and increasing adverse events (including death) associated with more aggressive treatment and low blood pressure.
- Episodic and infrequent hypotension may only occur in a small subset that are predisposed (e.g., elderly, unrecognized autonomic dysfunction, left and right ventricular failure) and could lead to (a) failure to achieve regulatory approval or (b) prominent labeling (warnings, precautions, contraindications).
- Central BP data can provide early signals and evidence that may determine that a higher dose should either be considered or not be brought forward into phase III.

Prescribing Information

- The FDA encourages companies to identify population characteristics and responses to interventions that improve the overall benefit-risk profile of therapeutics.
- Endpoints related to the primary endpoint have been and can be included in prescribing information.
- Such information may lead to decisions that optimize patient dosing (increase/decrease) that improves efficacious and safe use of the product.
- Companies that include informative central BP data in phase III trials will be at an advantage over those that have not.

Regulatory Approval and Post-Approval Communication

- Incorporation of novel endpoints from central BP that are clinically and physiologically related to the primary outcome of a development program (e.g., hypertension, heart failure), especially for phase 3 clinical trials, provide opportunities for regulatory agency discussions
- *Examples:*
  - *Supportive data and intended utility of the central BP variables*
  - *Competitive advantages relative to other compounds (including within the same drug class)*
  - *Post-approval communications*
- If such variables are prespecified in a successful development program leading to regulatory approval, external communication of central BP results can be disseminated within regulatory guidance and expectations

Incorporating Central Aortic Pressure – Summary

Incorporation of PWA into product development clinical trials for cardiovascular disease (particularly hypertension) has the following advantages:

- Confirmation of hypertension at baseline and the precision (and reliability) of the value.
- Confirmation of blood pressure values at follow-up.
- Additional endpoints for evaluation of therapeutic effect.
- Informing dose selection during phase 2 dose-ranging trials.
- Minimizing misleading information due to white coat hypertension.
- Improved patient selection and benefit-risk evaluation.
- Providing supportive and potentially pivotal data improving the likelihood of regulatory approval.
- Information from central BP may be incorporated into the prescribing information.
  - Assisting in decisions that optimize patient dosing – efficacious and safe product use.
- Increasing opportunities for competitive advances with post-approval communication.

Non-Invasive Central Aortic BP: Remote Patient Monitoring and Decentralized Clinical Trials

Decentralized Clinical Trials – Dual Arterial Monitoring

"DCTs—also termed "direct-to-participant trials" or "virtual" studies— are characterized by less dependence on traditional research facilities or specialist intermediaries for data collection. DCTs leverage "virtual" tools, such as telemedicine, sensory-based technologies, wearable medical devices, home visits, patient-driven virtual health care interfaces, and direct delivery of study drugs and materials to patients' homes."

Van Norman GA. Decentralized Clinical Trials. The Future of Medical Product Development? JACC 2021;6:384-7.

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Non-Invasive Dual Arterial BP Monitor Devices

SphygmoCor

Clinic

Pulse

Home & Clinic

CONNEQT Band

Ambulatory

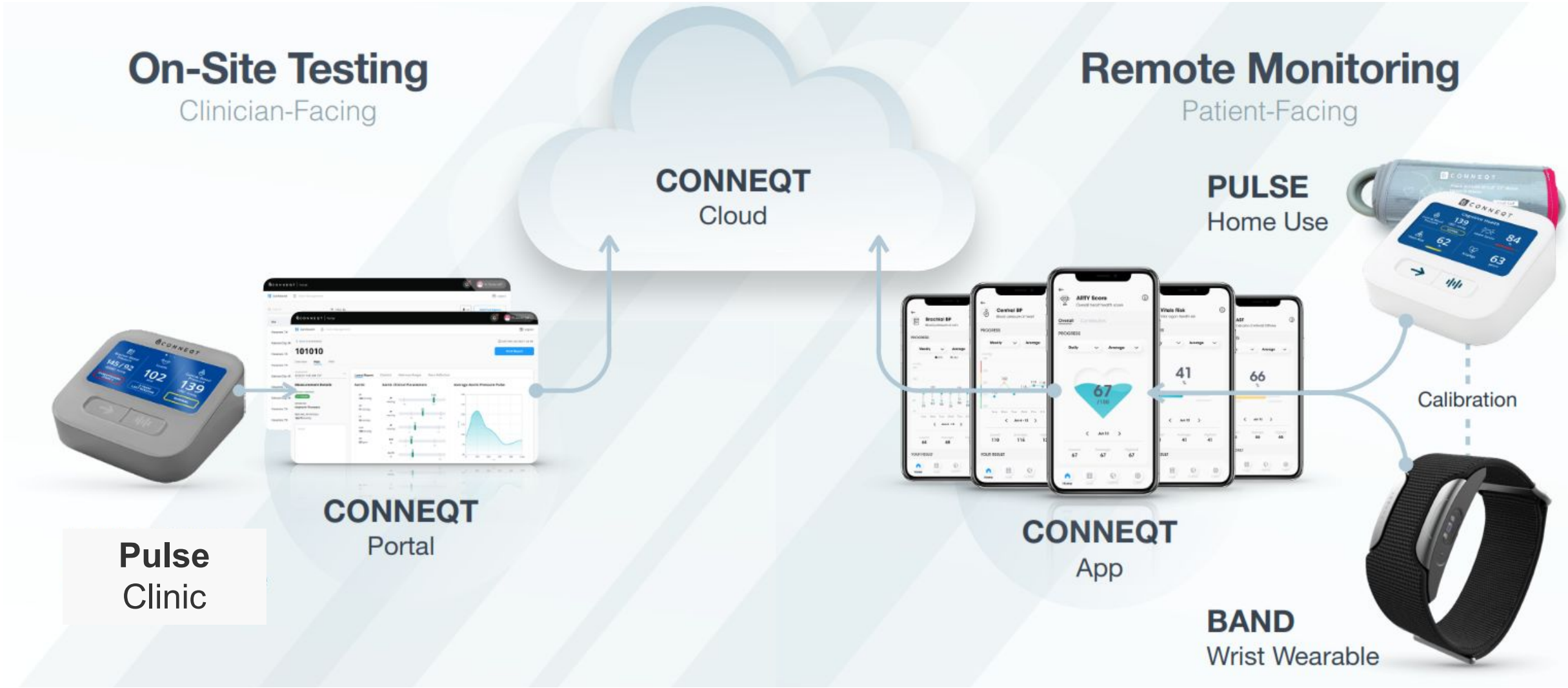
ATCOR

CONNEQT Band

- Incorporates photoplethysmography (PPG)* sensor algorithms for advanced arterial health monitoring
- First dual PPG sensor wearable incorporating both a radial and side sensor.
- Pairs with CONNEQT app for advanced analytics of individual health data.

*Photoplethysmography (PPG) – Measurement of blood flow or blood pressure by optical means (typically involving measurement of changes in the transmission or scattering of light created by blood flow in a part of the body).

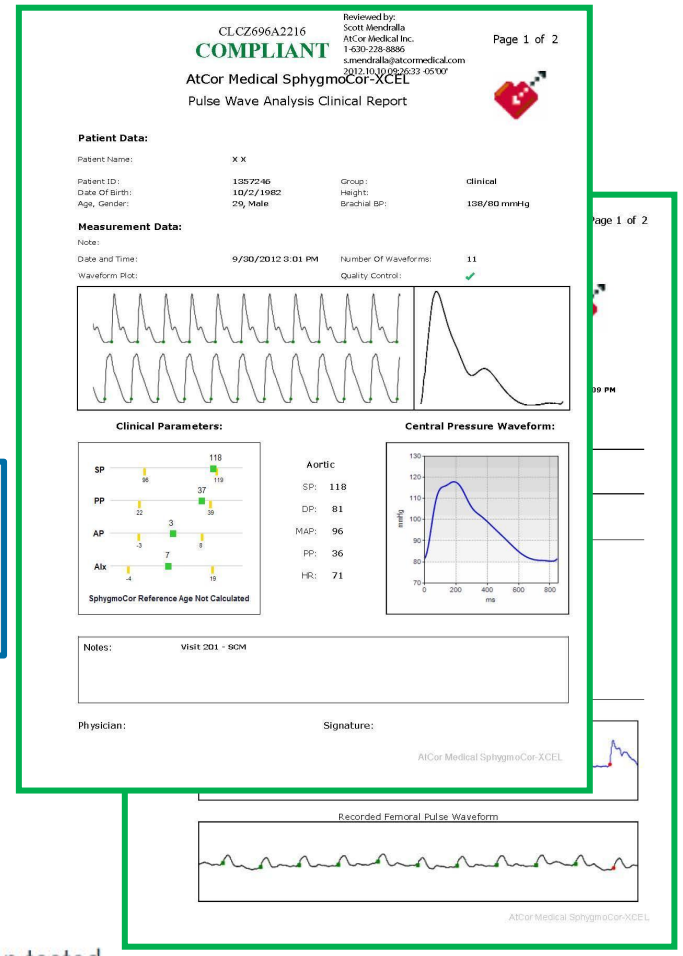
CONNEQT Ecosystem



Clinical Trial Services Overview

- System configuration
- Study Manual Development
- Protocol Design Assistance
- Investigator Meeting/Site training
- Data Management & Transfers
- Quality Control / Overread of Waveforms
- Report Generation
- Equipment Return & Archiving

Pulse Wave Analysis
Pulse Wave Velocity
24-hour ABPM



All "**Top 20 Hospitals**" use SphygmoCor technology to measure central blood pressure (cBP)

8 out of Top 10 Pharma companies have used SphygmoCor technology in their clinical trials

Over **11,000 patients** have been tested with SphygmoCor technology in pharmaceutical trials

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Studies Incorporating ATCOR Technology and Clinical Trial Services

Summary

New Paradigm of Incorporating Central Pressures: Not a New Concept

Analogies to Advancement in Medical Evaluation

- Fasting blood glucose followed by introduction of HbA1C.
- Electrocardiograms followed by introduction of echocardiogram.
- COPD Guidelines: FEV_1 only, followed by incorporation of COPD exacerbations.

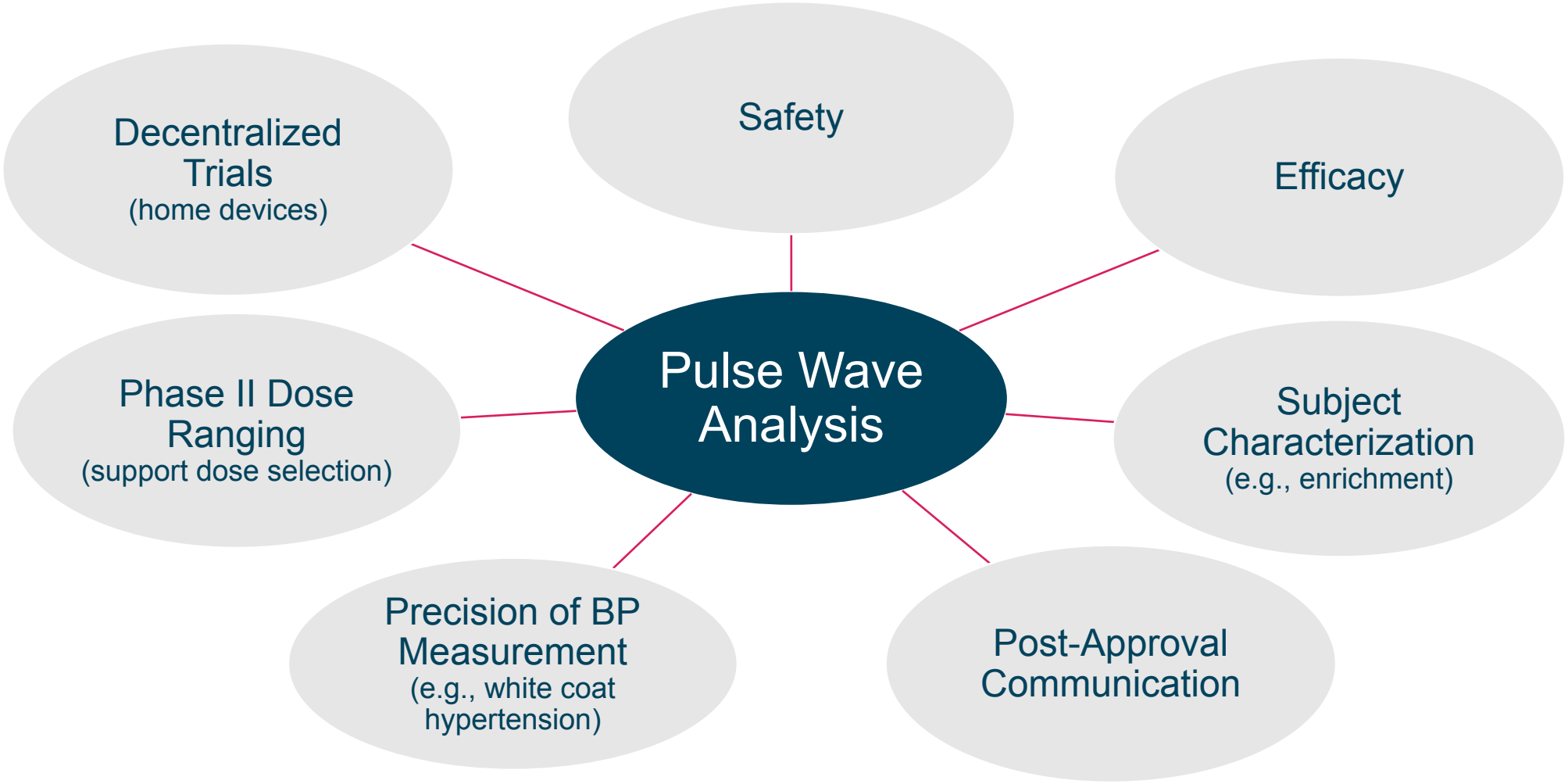
Every-Day Analogies

- 2-factor identification.
- Dead-bolt lock in addition to regular latch and lock.

Common Sense Practice of Medicine

- BP measurement needs to be correct and confirmed.
- Both brachial and central aortic BP should be considered as part of management of all patients requiring blood pressure management.

Incorporating PWA Can Improve Success and Efficiency of Drug & Device Development for Vascular Health



Conclusions

- For products targeting cardiovascular disease, incorporation of central aortic BP measurement and monitoring into clinical trials can improve key decisions during development (go/no go, endpoints, population characteristics, benefit-risk profile, dosing, etc.) and enhance the likelihood of both regulatory and commercial success.

- Based on current technology, the availability of a non-invasive dual arterial pressure measurement system, the compelling clinical rationale and the clinical published research, incorporation of central aortic BP monitoring into clinical trials, which is complementary to continued reliance on brachial BP monitoring should be considered for drug and medical device development programs for hypertension and other cardiovascular disorders.

ATCOR Medical

For Further Information:

ATCOR MEDICAL
184 Shuman Blvd,
Suite 515, Naperville
IL 60563 USA
Telephone: +1 (630) 228-8871
Fax: +1 (815) 336-5953
Email: skesten@cardiex.com

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