2011 CSRC Mini-symposium II: Do we need Thorough BP Studies?
--Industry View

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Current paradigm

- BPs routinely recorded pre-clinically and clinically, often at supratherapeutic doses
- If a signal emerges, or if there is a mechanistic reason why an elevated BP is expected, BP effects can be studied more thoroughly
- Do we miss signals during development?
  - Are there drugs that did not display a BP signal in pre-clinical and clinical studies that were later found to have a concerning effect?
- Does the current approach need to be improved?
  - Better technology (eg ABPM) to improve accuracy/precision?
    - "In my view, a better question regarding ABPM is whether *all* systemically available drugs intended for chronic use merit a careful assessment of their effects on vital signs by ABPM." --Norman Stockbridge, DIJ, 2011; 45:567.
  - Use of alternative BP parameters (central BP rather than peripheral)?
  - More frequent monitoring? More patients?
  - Thorough BP study?
    - What is a TBP study and how does it differ from thoroughly studying BP?

Thorough BP vs TQT—what do we mean by TBP?

- Do we need a positive control?
- What effect size is clinically relevant?
- How do we frame the statistical hypothesis?
- ECGs not routinely done during development
  - TQT study may be only time that QT is measured
- BPs are routinely recorded throughout development

What drug-induced BP increase is concerning?

- As little as 1-2 mm Hg BP increase in a large population over time may lead to adverse events
  - Evidence largely based on data from antihypertensive trials in hypertensive patients
  - To what extent can these data be extrapolated to small drug-induced BP increases in non-hypertensive patients?
- Would an important BP signal that is missed during development be captured by a TBP study?
- Implications of a drug-induced BP increase require context
  - Duration of therapy
    - Short course vs long duration
  - Risk-benefit ratio
    - Cancer therapy vs treatment of seasonal allergy
  - These don't argue for or against instituting TBP studies, they simply influence how one deals with a drug-induced increase

What can we detect during development?

Many ways of asking this from statistical perspective.

Assumptions:

- SD=14 mmHg (ABP will be lower)
- Power=80%
- Alpha=10%
- Parallel arm, 1:1 drug:placebo (or comparator)

Detectable BP ↑(mmHg)	1	2	3	4	5
N per group	1768	443	197	111	71

- If SD=11 mmHg, sample sizes will decrease by 38%
- If power=90%, sample sizes will increase by 46%

<u>Conclusions</u>

- BP should be more thoroughly studied when there is a signal (mechanistic, pre-clinical, or clinical)
- Depending on the definition of a TBP study, it is not clear that routine TBP studies would provide greater clarity