Challenges and Opportunities of Bayesian Adaptive Trials & Beyond:

Where Do We Go From Here?

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CHALLENGES of Bayesian Adaptive Trials and Beyond

- Widespread misconceptions and Lack of knowledge of Bayesian methods
- Low receptivity to change from Frequentism/p-values
- Need for user-friendly software that also teach
- Adaptive trials are operationally difficult
  - Require more upfront planning for adaptations
  - Difficult to estimate needed clinical supplies (i.e. cannot tell you upfront how many of each treatment/dosage may be needed)
- Lack of consensus procedure for establishing prior probabilities for “borrowing information” from previous trials & other sources, and for regulatory approval decisions based upon drawing from prior trials

OPPORTUNITIES for Bayesian Adaptive Trials & Beyond- I

- Education and training in Bayesian methods, and development of teaching tools (video's, apps, short-courses at various levels)
- Next generation user-friendly Bayesian software
- Novel employment of post-approval Bayesian updating of safety registries, grounded in prior knowledge (from small trials during the pre-approval phases, other sources).
- Applicability of Bayesian Networks in drug development

Points to consider I (S. Ruberg)

- The world is more and more adaptive ... with real-time decision-making ... by algorithms. Look at Google, any modern factory (Ford) or logistic facility (Amazon, FedEx), autonomous vehicles, the emerging artificial pancreas
- The clinical development world needs to adopt these approaches. As data accumulate over the course of a long, large trial, preplanned algorithms analyze it (using models and probability statements), results are checked against decision rules and the trial is adapted to the best dose, in the right patients etc
- We can no longer afford to live in a world in which we embark on large, long, blinded trials in which we wait until the end of the trial to decide "yeah or Nay." Our adaptations at this point are most often one or two interim looks at the data ... and for the most part, trials proceed to their intended sample size and duration. This is not financially sustainable.

Where do we go from here?

- **THINK BIG.**
- Imagine Ph 3 trials with continuous decision-making on the question of "does the drug work?", updated weekly via a Bayesian probability.
- Imagine the *entire drug development program* with continuous decision-making on the questions of "does the drug work and how to make it safe?", updated weekly via a Bayesian probability.
- Safety documented Post-approval via Bayesian updating of Registry Data
- Require designers of frequentist trials to provide operating characteristics from a Bayesian perspective.

Where do we go from here?

- **START SMALL.**
- Implement Opportunities list
- Push further with Rare Disease / Orphan Drugs
- Use routinely for Non-inferiority trials
  - The door is open in the FDA Guidance

Where do we go from here?

- ***MOVE FAST!***
- Build on seamless Ph 2/3 trials
  - A path has been blazed (i.e. Yaning's presentation)
- Propose Bayesian approaches for Phase 3 with FDA and other regulators.
- Embrace the Points-to-Consider list