Large "Simple" Trials: A Reviewer's Perspective

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Disclaimer

- The views expressed in this talk represent my opinions and do not necessarily represent the position of the FDA.

SHARP & JUPITER

- Timing of protocol development relative to approval
- Blinded trials designed to test superiority of a treatment
- Data collection largely targeted to answer the primary clinical questions
- Inclusion/exclusion considerations
- Designs informed by *specific* safety concerns
- Successful follow-up

Review Experience

- Efficacy focus: CV events & various sensitivity analyses related to these outcomes
- Safety
  - Reviewers successfully obtained additional detail from the sponsors when necessary
  - Substantial postmarketing experience accumulated while these trials were ongoing
  - Reviewers did not feel limited by the absence of "traditional" safety laboratories
- Both trials successfully led to changes in labeling

Experience with "Simply Sufficient" Trials

- Several examples in lipid and obesity arena, both pre-market and post-market
- *Review* experience limited to superiority trials at present
- Focus on key questions
  - What's needed for robust determination of efficacy?
  - What unique features of the trial population, dose, formulation, etc. may call for special attention to specific efficacy and/or safety issues?
  - Have safety issues been generally consistent across other trials or drugs in class?
  - Consider what questions you may have if the trial were to "fail" and prospectively collect data that may help to inform the next trial (or drug). Could this be done in a randomly selected subset of subjects?

Experience with "Simply Sufficient" Trials

- Targeted approach to AE collection
  - Non-serious AEs that do *not* lead to drug interruption, discontinuation, or dose modification should be less of a concern at the time a "large simple trial" is considered.
  - Are there specific AEs of concern with chronic therapy that a long-term, large trial could help to better describe?
- Although reducing the amount of "extraneous" data during follow-up may be entirely appropriate, cast a wider net for baseline characteristics.
- Reviewers may be concerned about underreporting of AEs/endpoints as the time between study visits widens. Include methods to keep subjects engaged.

Summary

- Designs elements that categorize SHARP & JUPITER as large "simple" trials did not substantively affect their review.
- Collaboration with the review division as such a protocol is being developed is strongly recommended.
- Helpful for protocols to explicitly highlight what *will not* be collected and the rationale.
- "Simple" trials are not simple to implement. They provide an opportunity to focus increased attention on the quality of data that *are* collected: subject retention, endpoint assessment, capture of important safety data.