Design Strategies to Improve the Feasibility of HABP-VABP Registration Studies

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"Some people think design means how it looks. But of course, if you dig deeper, it's really how it works..."
Steve Jobs

Since the 2009 Workshop……

* Draft guidance HABP/VABP (Nov 2010)
* 1st HABP/VABP Trius Advisory Board (May 2011)
* FDA Workshop "Inherent trade-offs in precision of estimates of efficacy and safety for a drug and practicality/feasibility of clinical trials" (Nov 2011)
* October 2012…….

The Objective is to Design a Study that Is feasible while Maintaining Scientific Integrity

What Are The Areas Where Trade –offs Are Acceptable?

Is There a Flexible Framework That Can Fit Most Situations?

Main Determinants of Study Feasibility in HABP/VABP

1. Primary outcome measure
2. Primary analysis set
3. Adjunctive therapy: Risk of confounding effect on target pathogens
4. NI margin
5. Prior antibiotic use

The Endpoint

* The "traditional": Clinical response
  * Ok in clinical medicine
  * "Weak" in clinical research: neither well defined nor reliable
* The "unambiguous": All cause mortality (ACM)
  * Clinically relevant, "Well defined" and "reliable"
* The "composite" endpoint
  * It depends on what's in it
  * Ability to set an NI margin?
* The "surrogate" for outcome
  * Are there any?

The Primary Efficacy Analysis Set

- Defines evaluable population for the primary outcome measure
  - Drives the size of the study
- Issue: no "gold standard" for the diagnosis of HABP/VABP
- May range widely from ITT to MITT
  - ITT: uncertainty that patients have the disease
    - Essentially clinically-based
    - Risk of misdiagnosis: Confounding underlying/concomitant conditions
  - Micro-ITT (MITT) : Essentially culture-based
    - False positive as many sites use endotracheal suction
    - Unlike in CABP, microbiology has inherent limitations in VABP
    - Questionable feasibility in global trials, particularly for narrow spectrum Abx or MDR pathogens
    - Impact of prior Abx on culture results
  - Modified-ITT (mITT) : clinically- and microbiologically-based

Can we trade off by redefining the primary analysis set as a modified ITT (mITT)?

* Objectives: define a primary analysis set where ITT > **mITT**> MITT
  * Goal: Strong plausibility that patients have the disease of interest in spite of some unavoidable level of uncertainty, as in the clinics
* Ingredients of an mITT
  * Solid clinical criteria:
    * Increased probability of correct diagnosis (Klompas et al, 2007) &
    * Ventilated patients with HABP and VABP &
    * Procalcitonin increased at baseline?
  * Microbiology: exclude patients with negative gram stain at baseline
    * **Positive respiratory culture at baseline in prespecified X % patients, with X adjusted based on expected size of ME population OR**
    * Positive *Gram stain* on baseline respiratory sample

The NI Margin

* Is a 10% NI margin too conservative?

* Is the NI margin another area where a “trade off” is possible?

In Summary

1. Investigate the disease in ventilated patients only
2. Keep the ACM as the primary outcome measure
3. Since no ***certainty*** in the diagnosis of HABP/VABP, focus on **high *plausibility*** of diagnosis

    Redefine the primary efficacy analysis set by defining a realistic though solid mITT analysis set instead of a too restrictive Micro-ITT set requiring a positive culture in all patients
4. Address the impact of confounding adjunctive therapy on study size
5. Can less conservative statistical approaches (i.e., NI>10%) be considered?