

FNIH Update for CTTI

Biomarkers Consortium HABP/VABP Working Group

August 29, 2013



Charge

- At FDA's request, this Working Group has been constituted to provide recommendations to support FDA's goal of articulating scientifically rigorous and clinically relevant HABP/VABP drug development guidance that is also feasible for sponsors to implement in terms of both financial cost and time.

Working Group Goal

- Identify potential changes to study design and analysis that could improve the feasibility—while retaining reliability, scientific validity, and meaningfulness for patients, caregivers, and clinicians—of HABP/VABP registrational clinical trials based on an NI design.

Working Group Processes

- Evaluate the medical literature to determine those signs, symptoms, and measures of function that are clinically relevant to treatment outcome;
- Identify feasibility constraints imposed by clinical trial requirements other than the primary endpoint;
- Determine whether it is possible to identify non-mortality endpoints, for use as the primary endpoint or as part of a composite primary endpoint;
- Use hypotheses generated based on the medical literature followed by examination of data from modern-day clinical trials, to focus specifically on defining the variables in such endpoints and quantifying a treatment effect on how patients feel and/or function.

Interim Considerations

- Despite the clinical trial feasibility issues raised by current FDA Guidance, WG participants are comfortable with all-cause mortality (ACM) as an endpoint, especially for VABP, if trial feasibility could be addressed by changing other parameters of study design.
- Outstanding questions for use of ACM include timing of its assessment
- One concern with ACM is its lower incidence in registrational trials versus “real life”. It is hypothesized that making exclusion criteria less restrictive, and thereby increasing the severity of illness in the enrolled population, has the potential to facilitate enrollment.

Interim Considerations

- For VABP sample size estimation and analyses, when mortality is $\geq 15\%$ on the active control, a risk-difference metric with an NI margin of 10% could be used.
- For HABP, a clinically meaningful endpoint of symptom improvement plus survival for non-ventilated patients could be based on the historical data for CABP, for which there is a large treatment effect to day 7 of therapy.
- There was some concern that mortality and other differences between HABP and VABP suggest these are different diseases, meaning that combining both in a single trial could raise methodological issues.

Interim Considerations

- A number of candidate changes to other aspects of trial design (e.g., primary analysis set) were identified as promising potential approaches to improving feasibility, while maintaining scientific validity.
- The WG remains very interested in evaluating the potential application of alternative endpoints (e.g., improved oxygenation) for VABP and considering how they could be evaluated and qualified as endpoints.

Current Activity

- The WG is examining the data from a single HABP/VABP trial, contributed in kind, to understand the data that are available (e.g., prevalence of respiratory symptoms at trial enrollment and their severity, mortality rate over time).
- FDA has conducted an analysis of trials in its database to explore some of the initial FNIH hypotheses.
- A formal statistical analysis plan is being drafted, after which data from a number of HABP/VABP trials contributed in kind will be analyzed .
- Results and conclusions will be submitted to FDA.

Conclusions

- The FNIH WG will make evidence-based recommendations on potential changes to HABP/VABP study design and analysis that could improve the feasibility—while retaining reliability, scientific validity, and meaningfulness for patients, caregivers, and clinicians—of registrational clinical trials based on an NI design.
- FNIH hopes its efforts will be complementary to those of CTTI, which is exploring other approaches to improve trial feasibility.