

CTTI RECOMMENDATIONS: STREAMLINING PROTOCOL ELEMENTS FOR HOSPITAL-ACQUIRED BACTERIAL PNEUMONIA (HABP)/VENTILATOR-ASSOCIATED BACTERIAL PNEUMONIA (VABP) TRIALS

Clinical trials to evaluate the efficacy and safety of new antibacterial drugs for HABP/VABP are challenging to conduct and expensive, and there are a very limited number of clinical trials of new drugs for this indication in progress or planned. CTTI has identified overcoming enrollment challenges as critical to conducting HABP/VABP trials. Other, more general, principles should also be considered as significant opportunities for improving the efficiency and feasibility of HABP/VABP trials while maintaining patient safety and scientific validity.

1. Informed Consent:

- HABP/VABP trial subjects are critically ill and some may have limited capacity to provide informed consent at the time of trial recruitment. Due to such challenges, CTTI recommends: making the informed consent process as streamlined as possible.

One strategy may be training research and hospital staff on the challenges typically faced with obtaining consent from the HABP/VABP patient population, with an emphasis on best practices for obtaining consent from these seriously ill, incapacitated patients and their legally authorized representatives (LAR).

- To facilitate enrollment as soon as possible after the diagnosis of HABP/VABP, CTTI recommends that further studies are conducted to investigate whether patients and their LARs could be identified and approached at an earlier time. For example, such further research could examine the feasibility of:
 - A *general acceptability approach*: where all potential HABP/VABP patients are engaged while they are not critically ill and are of sound mind to discuss their **general** views on trial participation. These views can be recorded so that family members and legal representatives are aware of them should the patient become eligible for a trial.
 - A *targeted approach* to investigate whether it is possible to effectively identify patients as being at particularly high risk for developing HABP/VABP with a view to:
 - i) Informing / educating patients **specifically** about HABP/VABP trials at a time when they are not incapacitated and can have a more meaningful discussion regarding the benefits and risks for

study participation. Patients' LARs should be involved in these conversations.

- ii) Obtaining consent through patients' LAR, should they become eligible for the HABP/VABP trial but unable to consent themselves.
- iii) Facilitating earlier trial enrollment to minimize pre-study antibacterial drug therapy and provide a better assessment of the efficacy of the investigational drug.

2. Protocol Design:

- In order to help sponsors focus on the study activities essential to the safety of trial participants and the reliability of study results, CTTI has issued ["Quality by Design" recommendations](#) across disease areas.

Specific strategies to reduce excessive data collection in HABP/VABP trials have been proposed in the CTTI Recommendations for "Optimizing Operational Efficiencies for Data Collection in Hospital Acquired Bacterial Pneumonia/Ventilator Associated Bacterial Pneumonia Trials."

- The list of exclusion and inclusion criteria should be succinct and restricted to those that are **essential** to address the scientific objectives of the trial and minimize risks to study participants. Rationale: To maximize the applicability and generalizability of the trial results to the broadest possible population.

One approach may involve including immunosuppressed patients or patients with additional comorbidities in the trial. Where this may give rise to concerns about the effect of chance imbalances of baseline comorbidities between treatment arms on the interpretation of trial results, stratifying at randomization or analysis by co-morbidity(s) may be appropriate.

- CTTI encourages further research to explore expanding the less than 24 hour prior effective antibacterial therapy allowance to 48 hours prior to enrollment such as prospective collection of data to assess the effect of 0, 24, 36, and 48 hours of prior effective antibacterial drug therapy on clinical outcome. Rationale: one of the leading causes of screen failures is the adherence to the 24-hour time window advised by current US and EU guidance.
- CTTI recommends simultaneous testing of new diagnostics and biomarkers in a clinical trial evaluating the safety and efficacy of a new antibacterial drug. Where this is potentially applicable, CTTI encourages sponsors to dialog with regulators regarding trial design.

One strategy may be to evaluate the experimental diagnostic as a secondary endpoint in a study of the efficacy and safety of a new antibacterial drug.

- CTTI recognizes that a single HABP/VABP trial conducted by a sponsor may be used for registrational purposes for more than one regulatory authority worldwide

and recommends consulting with each authority to ensure its suitability prior to initiating the trial

3. Use of a Central Institutional Review Board (IRB):

- In order to accelerate IRB approval and pre-study procedures, [CTTI recommends the use of a central IRB](#) in multi-center trials. CTTI defines a central IRB as a single IRB of record to which sites cede all regulatory responsibility for scientific oversight and integrity of the protocol from initial review to termination of the research, including review of informed consent.

4. Trial Outcomes and Efficacy Endpoints:

- FDA Draft Guidance recommends a primary endpoint based on survival or a primary endpoint based on survival and no disease-related complications (“mortality plus”). Sponsors interested in this second option are encouraged to discuss with regulators the disease-related complications and pre-specified follow-up time that would be included in the endpoint definition.
- The use of concomitant antibacterial drugs should be addressed in the protocol and investigator training. To the extent possible, the concomitant antibacterial drug should not have antibacterial activity similar to the investigational drug. Based on clinical improvement, de-escalation of concomitant antibacterial drug therapy should be encouraged. The rationale for the use of concomitant antibacterial drug therapy should be recorded on CRFs to facilitate patient-level assessment at the time of study analysis to determine clinical success or failure.

▶ *These recommendations are based on results from the [Streamlining HABP/VABP Trials Project](#).*
▶ *CTTI's [Executive Committee](#) approved the recommendations.*
▶ *Released in August 2016*

References

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