CTTI Recommendations: Optimizing Operational Efficiency for Data Collection in Hospital Acquired Bacterial Pneumonia (HABP)/Ventilator Acquired Bacterial Pneumonia (VABP) Trials

If the investigational drug has been previously studied in a similar patient population at the same dose and duration, it should be possible to tailor and potentially simplify the amount of safety data collected and recorded for HABP/VABP trials. Prior to study initiation, sponsors should discuss the use of supportive data to justify streamlined data collection with the appropriate regulatory authorities. The term "data collection" used throughout these recommendations refers to the recording of specific, relevant data in the Case Report Form (CRF), not the comprehensive collection of data captured as part of routine clinical care.

The European Union (EU) and United States (US) regulatory framework already allow for simplification of data collection in order to maintain a balance between eliminating nonessential data and collecting sufficient data to allow adequate characterization of a drug's safety profile as part of the overall benefit-risk assessment.

These recommendations address the amount of safety data collection in HABP/VABP trials.

1. General recommendations for safety data collection:

- Data collection can be streamlined in HABP/VABP trials by capturing and recording data that is most relevant to the principal trial objectives. When streamlined safety data collection is planned, a meeting with the appropriate regulatory authorities should be held prior to the start of the study.
- Focus data collection on pre-specified, relevant clinical outcomes.
- Reporting of serious adverse events (SAEs) should occur according to applicable regulatory requirements (see links to relevant US and EU documents and CTTI recommendations).

2. Data collection for adverse events (AEs):

- The protocol should clearly pre-specify adverse events (AEs) that will be recorded in the CRF:
    - All serious adverse events (SAEs)
    - Unexpected AEs (serious and nonserious)
    - AEs leading to discontinuation of study drug or dose modification

- AEs of special interest (i.e. based on drug class, pre-clinical and phase 1 findings)

- The protocol should clearly pre-specify and provide ample rationale for AE data that is thought to be appropriate for either abbreviated collection or omission from recording in the CRF, including:
  - Nonserious AEs not associated with drug discontinuation: These may be events that are well characterized in this patient population from previous trials for other indications. The extent to which observations collected as part of routine care in the intensive care unit (ICU) are recorded in the CRF should be limited for nonserious AEs.
  - History and physical exams:
    - Create robust inclusion/exclusion criteria to target the relevant trial population so that additional medical history should not be required unless such medical history is relevant to a patient's ongoing concomitant medications or routine care. Additional medical history requirements may be discussed with the appropriate regulatory authorities.
    - The protocol should include criteria on when recording of certain assessments (e.g., physical exams and vital sign measurements) become critical during the study.
    - More targeted physical examinations may be acceptable.
  - Vital signs, patient-reported symptoms, or investigator-observed symptoms:
    - To reduce inconsistencies in naming conventions, use of standardized Medical Dictionary of Regulatory Activities (MedDRA) queries is encouraged when possible.
    - If disease conditions are clearly defined by associated signs and symptoms, individual observations that comprise a disease entity can be captured as the unified condition. For example, if safety data is being collected every third day, symptoms, signs, and hemodynamic measurements such as an increase in basal serum creatinine, a decrease in creatinine clearance, urine output of less than 400-500 mL/day, or the need for renal replacement therapy (RRT) could be captured collectively in the CRF as "Acute Kidney Injury." However, in order to ensure consistency in reporting, it is suggested that such terms are prospectively defined (e.g. in the protocol or clinical data dictionary) so that investigators and reviewers clearly understand what is meant by their use.

3. Clinical laboratory data:

- Laboratory data recorded in the CRF should be relevant to the drug or drug class under investigation and based on target organs of known toxicity.

- Routine laboratory reporting in the CRF should be focused on those measurements relevant to the trial; examples include:
    - Consider only recording laboratory values if they exceed pre-specified minimal clinically important differences (MCID) during specified time intervals, which are pre-defined in the protocol.
    - Record laboratory values at pre-specified intervals if they involve target organs of known toxicity (e.g., liver function tests to be recorded at pre-specified intervals rather than daily).
    - Routine vital signs or electrolyte/arterial blood gas or other laboratory abnormalities may be omitted from recording in the CRF unless certain values are pre-specified in the protocol as relevant to the disease state and/or trial drug.

4. Concomitant medications:

- Record in the CRF only relevant concomitant medications as pre-specified in the protocol, examples being:
    - Drugs or drug classes that may interact with the investigational drug (e.g., based on drug class, pre-clinical, and phase 1 findings).
    - Antibacterial drugs which have a spectrum of activity that overlaps with the investigational drug.
- Recording co-medication for patients on sedation drips for mechanical ventilation can be cumbersome since doses are titrated and changed frequently. This could be simplified to “days on/off.”

- *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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