CLINICAL TRIALS TRANSFORMATION INITIATIVE

CTTI Recommendations: IND Safety Assessment and Communication

I. Upfront safety planning for a drug or biological development program

- At the beginning of a drug development program, sponsors should prospectively identify serious adverse events anticipated to commonly occur in the study population independent of drug exposure (e.g., myocardial infarction in elderly patients) or as manifestations of the disease being treated (including study endpoints).
    - Sponsors should use standardized terms for such anticipated serious adverse events throughout the drug or biological development program.
- In individual trial protocols, sponsors should specify that such anticipated serious adverse events will not be reported as individual IND safety reports. Rather, sponsors should plan to analyze the aggregate frequency of these events by treatment group during the development program.
    - Likewise, in keeping with current FDA guidance, sponsors should report study endpoints to FDA according to the protocol. Sponsors should not submit study endpoints as individual IND safety reports, except in the unusual case where evidence suggests a causal relationship between the drug and event (e.g., death due to anaphylaxis or hepatic necrosis).
- To effectively monitor the frequency of anticipated serious adverse events by treatment group, considering all ongoing and completed trials, sponsors need timely access to data, as would be afforded by electronic collection.

II. Implementation of safety assessment in clinical trials

- Sponsors should arrange for periodic evaluation of the totality of safety information in the drug or biological development program.
    - Sponsors should not wait until the time of new drug application (NDA) or biologic license application (BLA) submission to do such an integrated analysis.
    - The frequency of these analyses depends on the drug or biological product, the disease being studied, the stage of development, and the nature of the serious adverse events.
    - As comparisons of event rates in the overall study population relative to an external (e.g., historical) control are less sensitive than comparisons across treatment arms, unmasking of the serious adverse event may be required. However, it is imperative that all plans to incorporate unmasked data from ongoing trials ensure the

integrity of those trials. Primary efficacy endpoints should not be unmasked.
    - Unmasked analyses should be conducted by firewalled safety committees (internal or external to the sponsor) comprising members with clinical, safety, and biostatistical expertise who have, at most, minimal contact with members of the product's clinical development team and with those interacting with investigative sites.
- The FDA should issue additional guidance concerning mechanisms by which internal or external safety committees might notify appropriate individuals at the sponsor company of a safety signal in a way that balances the need to protect both patient safety and the integrity of an ongoing trial, if it were to be continued.
- When appropriate, sponsors should perform a meta-analysis of completed studies. In some cases, the meta-analysis might include unmasked data from ongoing studies.
    - To the extent feasible, analyses should preserve the randomization of the individual studies and account for differences in the study designs, the nature of control groups, and duration of exposure.
    - These analyses, intended to identify reportable serious adverse events, should not correct for multiplicity, nor should a specific *P* value be the criterion for reporting.
- The sponsor should develop a plan that allows incorporation into aggregate analyses the totality of data on the investigational product across its development program(s), including not only serious adverse events, but also laboratory results and other relevant measures.

III. Threshold for expedited reporting of anticipated events

- Sponsors should not submit serious adverse events that are prospectively identified as anticipated to occur in the study population as individual IND safety reports. Instead, sponsors should report such events in aggregate at the point in time when the totality of the data may suggest a causal relationship.

IV. Adverse events not pre-specified in the protocol

- For serious and unexpected adverse events that are not pre-specified in the protocol as anticipated (i.e., events that are presumably uncommon and/or not known to be strongly associated with drug exposure and are not study endpoints), a single case may meet the definition of a suspected adverse reaction, and sponsors should report these events in an expedited report as an individual event. Often, however, more than one occurrence of these specific types of events is necessary before the sponsor can judge that there is a reasonable possibility that the drug caused the event. If there is uncertainty or weak evidence of causality, sponsors could consider reporting these events as individual events via expedited reporting mechanisms to the FDA.

References

Archdeacon P, Grandinetti C, Vega J, et al. Optimizing Expedited Safety Reporting for Drugs and Biologics Subject to an Investigational New Drug Application. *Therapeutic Innovation & Regulatory Science* November 2013; 48(4): 413–419.

US Food and Drug Administration. Final Rule: Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm226358.htm

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- *CTTI's Executive Committee approved the recommendations.*
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