

Cardiac Endpoint Adjudication

Synopsis of the November 6, 2013 of the FDA/CSRC Think Tank Meeting held at the FDA

An FDA/CSRC sponsored Think Tank was convened at the FDA White Oak Headquarters on November 6th, 2013 to discuss the issues surrounding Cardiovascular (CV) endpoint adjudication in cardiovascular trials as well as CV endpoint adjudication in non-cardiovascular trials. Key issues included the lack of clarity about when CV endpoint adjudication is needed and how it is most appropriately conducted, so that CV endpoint adjudication does not unnecessarily or erroneously consume sponsor and investigative site resources. Although we eventually hope to codify indications and taxonomy for CV adjudication as well as establish a framework for risk-based endpoint adjudication, the purpose of this FDA/CSRC Think Tank was to examine the current state of the art and determine areas of consensus. To accomplish this goal, the day was separated into four separate topic areas in which the issues of CV endpoint in CV trials and non-CV trials were independently addressed.

Session 1: Why do we need CV Endpoint Adjudication Committees (CECs)

There was general agreement that CECs, if done well, provide an independent systematic process of evaluation of events, greater reproducibility, and therefore, greater reliability. There was consensus that this greater reliability was more necessary in the case of complex or subjective endpoints in large or global trials, and when there was a tendency for site under-reporting or when there was a possibility of site unblinding. The group agreed that CV Endpoint Adjudication was especially helpful in non-CV trials as there is usually significant discordance between the CEC and site investigators. Finally, there was also agreement that there was no 'standard' CEC process and this is an area for further exploration and definition.

There was not consensus, however, about the use of CECs in CV trials. Data was presented which suggest, that in the case of CV trials, hazard ratios were not changed by the presence of adjudication, nor are treatment effects. FDA regulators seem interested in CEC if, compared to the investigative site judgment, it brings accuracy or precision to the endpoint or can be demonstrated to add an indicator of reliability or quality; however, data showing does not appear to be robust. In contrast, EMA regulators, because they do not handle raw data, are more reliant on judgments made by CECs and DSMBs. Some felt that this was evidence that CECs in CV trials were an unnecessary burden. Others contested the methodology and also asked if perhaps we were seeing a Hawthorne effect-- the concordance in these trials was specifically because there was a CEC. On the other hand, there did seem to be general agreement that CECs were helpful in defining the true incidence rate of CV events.

Session II: Event Identification and Ascertainment Strategies

This session was intended to bring to light the current methods used to cast a 'wide net' to detect potential CV events. The discussion and presentation focused on current methods, strengths and weaknesses, and future directions. There was general agreement that compared to a post-hoc analysis, prospective CV event evaluation is advantageous in reducing bias and improving data collection. As far as how wide a net, serious AEs have more data than non-serious events. There is a perception that site investigators under report, so systemic strategies to identify potential events are critical, especially in CV trials of non-CV drugs. Strategies include screening AE and SAE databases, MedDRA codes, manual review of withdrawals or medications, etc. If PIs are educated about endpoints and what is expected at the investigative site, endpoint adjudication activities will likely be more efficient. In the future, sampling strategies for unlikely events may reduce adjudication caseload and the emerging data from patient registries may be able to offer other methodologies than traditional CECs to assure the accuracy of endpoints. Work is already underway to include standardized endpoint definitions as part of the emerging EHR infrastructure.

Session III: Clinical Development and CV Endpoints- Potential Impact on Adjudication Strategies:

This session was devoted to exploring some of the more practical aspects of CV endpoint adjudication. There was consensus that the level of detail for adjudication of endpoints in CV and Non-CV trials will be different (for example, type of MI vs MI yes or no). There was also agreement that there are basic criteria that define a standardized CV endpoint that need definition regardless of the type of trial and they can be standardized. As far as the protocol goes, the rationale for adjudication should be stated and the adjudication definitions should be included so investigative sides are knowledgeable about them. Regarding the CEC itself, there seemed to be consensus that at least 3 adjudicators were necessary, independent voting was superior than consensus opinion, and adjudicator geography should be representative of clinical trial enrollment.

Areas for further discussion include non-CV trials where there is a small number of events, but a large database. Some argued that lack of biologic plausibility precluded adjudication. Others argued that in non-CV trials the actual rate and effect is unknown, so adjudication is necessary to, in fact, rule out plausibility especially with global differences in diagnostic criteria. Still others felt that if the demonstrated rate was within the margin of error of underlying population rate, there was no need to adjudicate whereas others felt that the specificity of clinical trials precludes the knowledge of the actual event rate. As far as the CEC itself, there was disagreement about when to use an internal vs an external CEC (i.e. what is the definition of independence) and whether the fellow-attending model at the same institution is inferior to three completely independent experts. Clearly, more data on adjudication methodologies is needed.

Session IV: Adjudication: Practical Aspects and Future Directions:

There was general agreement that every event does not need adjudication. Risk-based approaches, sampling approaches, and adaptive approaches can be used as cost-effective models when appropriate. Although we don't know what is the optimal degree of precision for determination of an 'event', we need to define an acceptable degree of imprecision and we need to begin working with more standardized definitions.

There was some discussion around how endpoint adjudication might additionally be used as risk-mitigation strategy. Although best practices currently don't exist, the group felt they should as well as a 'use case' framework in which to test these best practices.