Endpoint Adjudication Best Practices for NASH trials

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Disclosures

Employee of ACI Clinical

ACI Clinical specializes in providing independent endpoint adjudication committees (EAC/CEC) and data monitoring committees (DMC) services.

Financial Disclosures related to ACI Clinical:

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"Fine, tell him he's going to make it.
We'll just have to agree to disagree."

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Agenda

- **Background of adjudication of cardiovascular endpoints in Diabetes trials**
- **Adjudication of CV and Hepatic endpoints in NASH**
- **Best Practices in Adjudication**

The Beginning

- **Endpoint adjudication established a regulatory path forward when there was uncertainty surrounding the validity of reported endpoints**

- **Rosiglitazone Story…**

- **“insofar as the findings of Nissen and Wolski represent a valid estimate of CV events, rosiglitazone represents a major failure of the drug-use and drug-approval processes in the US”**

Psaty and Furberg NEJM 2007

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment

Guidance for Industry

C. Phase 3 Development Considerations

This section addresses phase 3 drug development for treatment of noncirrhotic NASH with liver fibrosis, which includes clinical trials intended to support a marketing application.

for such liver enzyme elevations. Sponsors should establish an expert committee to adjudicate cases that meet protocol-defined criteria for hepatic decompensation events and possible cases of drug-induced liver injury.

- Given the growing evidence of a link between NAFLD and cardiovascular disease, cardiovascular safety should be adequately monitored in clinical trials. FDA encourages sponsors to establish an expert committee to adjudicate cases that meet protocol-defined criteria for major adverse cardiac events.

CSRC Think Tank – White paper

Centralized adjudication of cardiovascular end points in cardiovascular and noncardiovascular pharmacologic trials: A report from the Cardiac Safety Research Consortium

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This white paper provides a summary of presentations and discussions at a cardiovascular (CV) end point adjudication think tank cosponsored by the Cardiac Safety Research Committee and the US Food and Drug Administration (FDA) that was convened at the FDA's White Oak headquarters on November 6, 2013. Attention was focused on the lack of clarity concerning the need for end point adjudication in both CV and non-CV trials: there is currently an absence of widely accepted academic or industry standards and a definitive regulatory policy on how best to structure and use clinical end point committees (CECs). This meeting therefore provided a forum for leaders in the fields of CV clinical trials and CV safety to develop a foundation of initial best practice recommendations for use in future CEC charters. Attendees included representatives from pharmaceutical companies, regulatory agencies, end point adjudication specialist groups, clinical research organizations, and active, academically based adjudicators.

The manuscript presents recommendations from the think tank regarding when CV end point adjudication should be considered in trials conducted by cardiologists and by noncardiologists as well as detailing key issues in the composition of a CEC and its charter. In addition, it presents several recommended best practices for the establishment and operation of CECs. The science underlying CV event adjudication is evolving, and suggestions for additional areas of research will be needed to continue to advance this science.

This manuscript does not constitute regulatory guidance. (Am Heart J 2015;169:197-204.)

Best Practices in Adjudication

Table II. Recommendations for cardiovascular end point committees best practices

1. Prospective approach to adjudication;
2. Independent voting processes;
3. Comprehensive search strategy for potential CV events (eg, MedDRA searches);
4. Standardized event definition CRFs (optional);
5. Adjudication of CV events when an unanticipated safety signal arises in a clinical development program;
6. At least 3 CEC members with knowledge of the geographic variations of care represented in the trial;
7. CEC independence from sponsor;
8. Consideration of risk-based or adaptive adjudication models

Abbreviation: *MedDRA*, Medical Dictionary for Regulatory Activities.

Seltzer et al. Centralized adjudication of cardiovascular end points in cardiovascular and noncardiovascular pharmacologic trials: A report from the Cardiac Safety Research Consortium. AHJ 2015.

Regulatory expectations of adjudication

- **A process which adds transparency and rigor to, and eliminates variability in clinical trial results**

- **Experts in the area of clinical relevance making endpoint decisions in a systematic, reproducible manner**

Critical Features for Best Practices in Adjudication

- **Case detection**
- **Case preparation**
- **Case decision**
- **Committee composition**

Case Detection

“Cast a Wide Net”

- **SMQ driven**
- **Medical oversight**
- **Triage process**

Case preparation

- **Minimize “not assessable” cases**
- **Demonstrate to regulators the data that was provided to adjudicators**
  - Core minimal data set

Case decision

- **Independent voting**
- **“Real time” voting**
- **Minimize variability**

"DR. WILLIAMS WILL BE WITH YOU SHORTLY. HE'S CONSULTING WITH A COLLEAGUE."

Best Practices for Committee Composition

- **Putting together the right committee**
  - Expertise
  - Actively practicing
  - Clinical trial experience
  - Knowledge of geographic variability in clinical practice
  - Number of members

CEC Charter

- **Exact definitions of endpoints**
- **Standard processes by which the cases to be evaluated will be selected**
- **Data to be presented to the adjudicators**
- **Voting Rules**
- **Decision Rules**
- **Expertise of committee members**

So when is endpoint adjudication a good idea?

- **When it is "required"**
  - CV endpoints in DM trials
  - CV endpoints in NASH trials
  - Hepatic endpoints in NASH trials
- **When it is "suggested"**
- **When the investigators specialty differs from the specialty of the endpoint**
- **When there is potential for significant bias**
- **Studies with small numbers**

Conclusions: Adjudication for NASH

- **Scientific Rigor**
  - Reduce variation and possibility of bias
  - Higher level of expertise
  - Reproducibility
- **Decrease Regulatory Risk**
  - Reduced perception of Conflict of Interest
  - Justification for Regulatory Decision Making
  - Transparency
- **FDA guidance**
  - Cardiovascular events
  - Hepatic events

Thank you

Q&A