Considerations for Endpoint Adjudication Committees – Regulatory Perspective

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Disclosure Slide

I have nothing to disclose, and the opinions expressed here are my own.
Objectives

• To discuss FDA’s cardiovascular and stroke endpoint definitions and cardiovascular data standards for clinical trials
• To discuss FDA’s current thinking on Endpoint Adjudication
• To discuss Best Practices for submission of clinical trial data to the Agency
Standardized Data Collection for Cardiovascular Trials Initiative (SCTI)
Key Events Leading to the Need for Standards in Cardiovascular Trials

• Endocrinologic and Metabolic Drugs Advisory Committee (July 2008)
• Diabetes Cardiovascular Guidance (December 2008)
• Advisory Committee Meetings (April 2009)
July 2008 Endocrinologic and Metabolic Drugs Advisory Committee

- Discussed the role of cardiovascular assessment in the premarketing and postmarketing settings
- Recommended requiring sponsors to conduct a long-term cardiovascular trial (VOTE: 14 “YES”, 2 “NO”)
  - If an anti-diabetic therapy demonstrated a concerning cardiovascular (CV) safety signal during Phase 2/3 development
  - OR
  - If no signal existed (and sponsor could not provide other equivalent evidence to rule out unacceptable cardiovascular risk)
Diabetes Cardiovascular Guidance - 1

• Final guidance published in December 2008
  – Guidance for Industry: “Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes”

• Identified HbA1c as the primary efficacy endpoint for glucose reduction

• Asked sponsors to demonstrate that new type 2 diabetes agents did not unacceptably increase cardiovascular risk
Pharmaceutical Manufacturers planning new clinical trials were also expected to

- Establish an independent cardiovascular endpoints committee to prospectively and blindly adjudicate major cardiovascular events (e.g., CV death, myocardial infarction, and stroke) during all phase 2 and 3 trials
- Ensure that phase 2 and 3 trials were appropriately designed and conducted so that a pre-specified meta-analysis of major CV events could be reliably performed
Pharmaceutical Manufacturers planning new clinical trials were also expected to

- Provide a protocol describing statistical methods for the proposed meta-analysis of all placebo-controlled trials, add-on trials, and active comparator trials
- Enroll patients at increased cardiovascular risk to ensure sufficient endpoint events to allow a meaningful estimate of risk
- Conduct trials longer than the typical 3 to 6 months duration to obtain enough events and to provide data on longer-term cardiovascular risk
## Diabetes Cardiovascular Guidance - 4

<table>
<thead>
<tr>
<th>UPPER BOUND OF 95% CI FOR RISK RATIO</th>
<th>CONCLUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.8</td>
<td>Inadequate to support approval</td>
</tr>
<tr>
<td>&gt;1.3 but &lt;1.8*</td>
<td>Postmarketing trial(s) needed to show definitively &lt;1.3</td>
</tr>
<tr>
<td>&lt;1.3*</td>
<td>Postmarketing cardiovascular trial(s) generally not necessary</td>
</tr>
</tbody>
</table>

CI=confidence interval
*with a reassuring point estimate
Advisory Committee Meetings (April 2009)

• Cardiovascular adverse events were not predefined or adjudicated during study conduct
• The patient population was not enriched for elevated CV risk (CV events were sparse)
• Limitations of retrospective analyses (Broad SMQ MACE, Custom MACE)
• Missing data (key data elements never collected)
Need for Data Standards

• To improve the quality and efficiency of cardiovascular trials
• To provide endpoint definitions so that events are clearly characterized by objective criteria and reported uniformly
• To standardize data collection to capture key data elements
• To simplify analyses of events within or across drug development programs or among different clinical trials and to more easily identify trends and other safety signals
March 2009 - First developed definitions and case report forms for the cardiovascular and stroke endpoints

May 2009 - Convened an internal meeting between the Division of Cardiovascular and Renal Products and the Division of Metabolism and Endocrinology Products (DMEP) to discuss MACE endpoints as well as definitions for key cardiovascular and stroke endpoint events in clinical trials

Discussed and refined these definitions with other stakeholders

July 2009 - Released draft definitions to PhRMA and requested their assistance in validating the definitions
Food and Drug Administration - 2

- September 2009 - Convened a public meeting of all major stakeholders to create the SCTI working group and to discuss these definitions as well as the need to standardize data collection for CV trials
- Over the next 6 years, the SCTI and FDA met numerous times, both publicly and internally, to review and refine the endpoint definitions for use in clinical trials and regulatory submissions
- Posted these definitions for public comment from November 2010 through January 2011 and again from March through April 2014.
Goals of the SCTI

• To create definitions and data standards for key cardiovascular and stroke endpoint events in clinical trials

• To integrate these data standards with
  – CDISC (Clinical Data Interchange Standards Consortium)
  • SDTM (Study Data Tabulation Model)

• To create a FDA Data Warehouse of Clinical Trials
Stakeholders - 1

- FDA (CDER and CDRH)
- CDER Data Standards
- CDER Critical Path Initiative
- FDA Stroke Team
- Clinical Data Interchange Standards Consortium (CDISC)
- Health Level Seven (HL7)
- American College of Cardiology (ACC)
- Clinical Trials Transformation Initiative (CTTI)
- Association of Clinical Research Organizations (ACRO)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- Pharmaceutical Industry Representatives
Stakeholders - 2

• Beth-Israel Deaconess Medical Center
• Brigham and Women’s Hospital
• Case Medical Center
• Cleveland Clinic
• Duke Clinical Research Institute
• Harvard Clinical Research Institute
• Harvard Medical School
• Mount Sinai School of Medicine
• San Francisco VA Medical Center
• Scripps Translational Science Institute
• TIMI
• St. Louis University
• Yale University School of Medicine
Definitions

- Cardiovascular Death
- Non-Cardiovascular Death
- Undetermined Cause of Death
- Myocardial Infarction
- Hospitalization for Unstable Angina
- Transient Ischemic Attack and Stroke
- Heart Failure Event (includes hospitalization and urgent outpatient visits)
- Interventional Cardiology Definitions
- Peripheral Vascular Intervention
- Stent Thrombosis
Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials

Karen A. Hicks, H. M. James Hung, Kenneth W. Mahaffey, Roxana Mehran, Steven E. Nissen, Norman L. Stockbridge, Shari L. Targum, Robert Temple; on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative

TASK FORCE MEMBERS

Chairpersons: Karen A. Hicks, Kenneth W. Mahaffey, Roxana Mehran, Steven E. Nissen


With special thanks to Rhonda Bartley, Leanne Madre, and MariJo Mencini, Co-ordinators (Clinical Trials Transformation Initiative) and to Rachel E. Hartford, Anna Park, and Lori Anne Wachter, Co-ordinators (Food and Drug Administration).
Draft Definitions


http://www.cdisc.org/therapeutic
Clinical Data Standards

2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards)

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Data Standards

Standardized Data Collection for Cardiovascular Trials – Final Stages

• Formal testing of Definitions
  – Drs. Roxana Mehran and Stephen Wiviott
  – FDA Biometrics Team (Drs. Jim Hung, John Lawrence, Steve Bai)
  – CECs: 500 events
    • Cardiovascular Research Foundation (CRF)
    • Duke Clinical Research Institute
    • Thrombolysis in Myocardial Infarction Research Group
    • Brigham and Women’s Hospital Clinical Endpoints Center
    • Uppsala Clinical Research Centre, Uppsala Sweden
    • PERFUSE
Standardized Data Collection for Cardiovascular Trials Initiative: Summary

• Extensive volunteer effort
• The testing results will be discussed amongst the SCTI soon
• White papers on the definitions and testing results are planned for 2015/2016
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- Steven Steinhubl, M.D.
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- John Teerlink, M.D.
- Steve Wiviott, M.D.
Endpoint Adjudication: Regulatory Perspective
Successful Endpoint Adjudication

• The process for successful endpoint adjudication begins at the earliest stages of the development program
Elements of a Successful Development Program - 1

• Early interaction with the FDA
  – Pre-IND meeting

• Continued interaction with the FDA throughout the development program
Elements of a Successful Development Program - 2

- **Standard endpoint definitions**
  - Use SCTI’s definitions and data standards
  - Include in the Protocol, CEC Charter, and SAP (and should be identical)
- **Uniform capture of critical source documents** *(preferably at the time of the adverse event)*
- **Standard triggering process for investigator referral of endpoints to CEC for adjudication**
- **Standard process of adjudication**
- **Standard coding system to harmonize endpoints** *(e.g., MedDRA)*
  - Use same version of coding system within a particular trial (and preferably within an entire development program)
  - If upgrading within MedDRA, recode using the verbatim term
- **Quality data collection**
Elements of a Successful Development Program - 3

- FDA Review of proposed Phase 3 Protocols (either as a submission or a Special Protocol Assessment)
  - Protocol
  - Informed Consent
  - Statistical Analysis Plan
  - CEC Charter
  - DSMB Charter
  - Prespecify and define Endpoint Events and Events of Special Interest (and clarify which events will be adjudicated)
    - Investigator Endpoint Reporting Forms for these events
    - CEC Adjudication Forms
    - For each event, create a list of source documents that should be collected at the time of the event
  - Prespecify standardised MedDRA queries (SMQs) and other terms that will be used to search the Adverse Event Database in a clinical trial for other possible endpoint events that may require adjudication (“upgrades”)
Elements of a Successful Development Program - 4

• Adjudication
  – Blinded
  – Standardized Process
  – CEC Endpoint Adjudication Form
  – CEC Packets: Source documents and case report forms
    • CEC should have access to ALL pertinent source data that the Investigator sees in the setting of an event
  – Management of Disagreements
  – Necessary Expertise
    • Cardiologists, Interventional Cardiologists, Neurologist, Oncologist
  – Which Process is Best?
    • Requires further study
Adjudication

• Investigator-reported events
• CEC adjudicated events

Which process is best?
Withdrawal of Consent: Incorporate the following language into all protocols

• “Withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, e.g., medical records checks. Subjects requesting withdrawal should be informed that withdrawal of consent for follow-up will jeopardize the public health value of the study.

• “Subjects who withdraw should be explicitly asked about the contribution of possible adverse events to their decision to withdraw consent, and any adverse event information elicited should be documented.

• “Preferably the subject should withdraw consent in writing and, if the subject or the subject’s representative refuses or is physically unavailable, the site should document and sign the reason for the subject’s failure to withdraw consent in writing. The informed consent for the study should note that although a subject is free to leave the study and stop taking study medication, the investigators hope the patient will remain for follow up status evaluations.”
Missing Data

• There should be none!
• Obtain Vital Status as well as primary endpoint and major secondary endpoint data on all subjects in the trial
Case Report Form

• Include detailed information on history of current or prior cancer (including skin cancer)
  – Type of cancer
  – When diagnosed
  – How diagnosed
  – Operative and Pathology reports
  – How treated (e.g., medications – total dose/duration)
Definition of Myocardial Infarction

• Use the Universal Definition of MI and the 99th percentile of the upper reference limit (troponin and CKMB)
• Include the reference ranges
Prespecify Statistical Analyses

- Primary Analysis
- Secondary Analyses
- Exploratory Analyses
- Subgroup Analyses
Event Coding

• Systematic Sorting or Indexing of Data (Standardization)
• Used for Retrieval, Analysis, and Comprehension of Data
MedDRA Structure (Version 13.1)

- System Organ Class (SOC) (26)
- High Level Group Term (HLGT) (335)
- High Level Term (HLT) (1,709)
- Preferred Term (PT) (18,919)
- Lowest Level Term (LLT) (68,661)*
- Standardised MedDRA Queries (SMQ) (84)

*The lowest level term is the closest to the verbatim term
MedDRA: Preferred Terms and System Organ Classes

• A PT can be classified in > 1 SOC
• There is 1 primary SOC
  – The rest of the SOCs are secondary
  – Prevents a PT from being represented more than once in data retrieval
Verbatim Terms

• Definition
• Mapped to LLT
• Legacy Data Conversion: process of taking data coded with an older terminology and coding it into MedDRA
  – Best to recode verbatim terms to MedDRA rather than use the original coded term from older terminology—otherwise, could end up with different Preferred Terms
• If you only have a preferred term, the quality of the coding cannot be verified. Need LLT.
Verbatim Term and Final Adverse Event Coding

• Provide a SAS dataset with subject IDs, dates of onset, and the original and final Adverse Event (AE) terms for all adverse events. Include records for AEs that have been deleted.
Best Practices for Submission of Clinical Trial Data to the FDA
NDA Submissions: Red Flags for FDA

• Investigator-Reported Results and CEC-Adjudicated Results go in opposite directions for the primary endpoint and major secondary endpoints

• Investigator Description of Event is different from the CEC description of Event OR there is disagreement about an event amongst CEC reviewers

• Original Verbatim Term is mapped to a completely different final adverse event or endpoint
Sponsor Check-List for NDA Submission

• Clinical End Points Committee Charter and any modifications
• Statistical Analysis Plan with any modifications
• Minutes from the DSMB Meeting and results of all interim analyses
• Original Protocols for Studies and all Amendments
• Entire CEC packets with all source documents, all queries, and results of queries for the adjudicated end points
Sponsor Check-List for NDA Submission

• Paginated Define Files for All Data Sets
• Randomization Code
• Case Report Forms for all deaths and discontinuations due to adverse events (at least)
• SAS dataset with, for each visit for each subject, subject ID, visit #, visit date, including unscheduled visits and hospitalizations (listed separately)
Sponsor Check-List for NDA Submission

- SAS dataset with, for each subject, subject ID, date of last subject visit, date of withdrawal of consent, type of withdrawal of consent, the date of the last patient contact and type of contact, and the date of the last f/u information and source of information
  - Informed Consents
  - Vital Status

- SAS dataset with, for each event submitted to the CEC for each subject, subject ID, date of event, type of event, investigator description, and CEC adjudications (for each reviewer and final)
Sponsor Check List for NDA Submission

• SAS dataset with subject IDs, dates of onset, and the original and final AE terms for all adverse events. Include records for AEs that have been deleted, if any.

• SAS data sets for
  – All investigator-reported events
  – All CEC adjudicated events
  – All investigator-reported events that were also adjudicated as the same events by the CEC
  – “Downgrades”
  – “Upgrades”

• All raw data
Summary – Endpoint Adjudication

- Interact early with the FDA (PIND) and as frequently as necessary during the development program
- Use the SCTI cardiovascular and stroke endpoint definitions and data standards
- Submit Phase 3 Protocols and all pertinent documents to FDA for review PRIOR to study initiation
- Prespecify and define as much as possible (endpoint definitions, events of special interest, statistical analyses)
- Uniformly capture critical source data at the time of the event
- Use a standard process of adjudication/necessary expertise
- Avoid missing data – follow-up all patients for vital status and for the primary endpoint and major secondary endpoint events
Thank you