Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials
CSRC and MDEpiNet Thinktank Meeting

Washington, D.C.
Friday, March 11, 2016

Karen A. Hicks, MD
Medical Officer
Division of Cardiovascular and Renal Products (DCaRP),
Center for Drug Evaluation and Research (CDER),
U.S. Food & Drug Administration
On behalf of the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI)
Disclosure Slide

The opinions expressed here are my own.
Background

- 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 pre- and post-approval settings for drugs and biologics developed for the treatment of Type 2 DM

- Voted (14 “Yes,” 2 “No”) to require sponsors to either
  - conduct a long-term cardiovascular trial if an anti-diabetic therapy did not demonstrate a concerning cardiovascular (CV) safety signal during Phase 2/3 development
  - or
  - provide other equivalent evidence to rule out an unacceptable CV 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”

- Identifies HbA1c as the primary efficacy endpoint for glucose reduction

- Asks sponsors to demonstrate that new type 2 diabetes agents do not increase cardiovascular risk unacceptably
Diabetes Cardiovascular Guidance - 2

- Recommends that
  - Independent Committee prospectively and blindly adjudicates major cardiovascular events
  - Phase 2/3 designs permit a pre-specified meta-analysis of major cardiovascular events
  - Trials include patients at increased risk for cardiovascular disease
  - Trial duration(s) exceed 6 months to ensure a sufficient number of events and to provide long-term data
## Diabetes Cardiovascular Guidance - 3

<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 events had not been predefined or adjudicated during study conduct
- Risk estimates for MACE identified through a post-hoc selection of PTs in MedDRA and SMQs
- Patient population was not enriched for elevated CV risk (events were sparse)
- Missing data (key data elements never collected)
Why 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 analysis of events in drug development programs or among different clinical trials and to more easily identify trends and other safety signals
SCTI - Goals

- To create uniform definitions and data standards for key cardiovascular and stroke endpoint events in clinical trials
  - CDISC (Clinical Data Interchange Standards Consortium)
    - Study Data Tabulation Model (SDTM)

- To create a FDA Data Warehouse of Clinical Trials
Definitions

- Cardiovascular Death
- Non-Cardiovascular Death
- Undetermined Cause of Death
- Myocardial Infarction (Universal Definition)
- Hospitalization for Unstable Angina
- Stroke and Transient Ischemic Attack
- Heart Failure Event
- Percutaneous Coronary Intervention
- Peripheral Vascular Intervention
- Stent Thrombosis
Timeline

2008
July 1-2, 2008: Endocrinologic & Metabolic Drugs Advisory Committee

December 2008: FDA’s Diabetes Cardiovascular Guidance

2009
March 2009: First Draft of CV and Stroke Endpoint Definitions (FDA)

April 2009: (2) Endocrinologic & Metabolic Drugs Advisory Committee Meetings

July 2009: Draft CV and Stroke Endpoint Definitions released to PhRMA

September 11, 2009: SCTI Meets at FDA for First Public Meeting

2010 - 2012
February 5, 2010: SCTI Working Group Meeting

March 26, 2010: SCTI Public Meeting

November 17, 2010 – January 31, 2011: Definitions posted on CDISC Website for Public Review

March 28, 2011: SCTI Working Group Meeting

February 12, 2012: SAP and Definitions for Testing

FDA Internal Meetings

2013 - 2015
Adjudication of Clinical Events and FDA’s Analysis of Results

March - April 2014: Data Standards posted on ACC/AHA website for Public Review

December 29, 2014: Data Standards paper published electronically

February 2, 2016: SCTI Working Group Meeting

2016
January 19, 2016: Discussion of CEC Results

February 2, 2016: SCTI Working Group Meeting
ACC/AHA 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)

Writing Committee Members*

Karen A. Hicks, MD, FACC, Chair*
James E. Tcheng, MD, FACC, Vice-Chair
Biykem Bozkurt, MD, PhD, FACC, FAHA
Bernard R. Chaitman, MD, FACC
Donald E. Cutlip, MD, FACC
Andrew Farb, MD, FACC*
Gregg C. Fonarow, MD, FACC, FAHA
Jeffrey P. Jacobs, MD, FACC
Michael R. Jaff, DO, FACC
Judith H. Lichtman, MPH, PhD

Marian C. Limacher, MD, FACC, FAHA
Kenneth W. Mahaffey, MD, FACC
Roxana Mehran, MD, FACC, FAHA
Steven E. Nissen, MD, MACC, FAHA
Eric E. Smith, MD, MPH, FAHA
Shari L. Targum, MD, FACC*

*The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the U.S. Food and Drug Administration.
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

Future Directions

- MDEpiNet – Registries
- Electronic Health Records – Clinical Trials
Acknowledgements

- Stanford University School of Medicine (Dr. Ken Mahaffey)
- Mount Sinai School of Medicine (Drs. Roxana Mehran, Mike Domanski)
- Cleveland Clinic (Drs. Steve Nissen, Mike Lincoff)
- Duke Clinical Research Institute (Dr. James Tcheng)
- Beth-Israel Deaconess Medical Center (Dr. C. Michael Gibson)
- Brigham and Women’s Hospital (Drs. Scott Solomon, Akshay Desai, Eldrin Foster Lewis, Marc Pfeffer, John McMurray (Glasgow, Scotland))
- Case Medical Center (Dr. Cathy Sila)
- Inova Heart & Vascular Institute (Dr. Chris O’Connor)
- Harvard Clinical Research Institute (Drs. Don Cutlip, Laura Mauri)
- San Francisco VA Medical Center (Dr. John Teerlink)
- Scripps Translational Science Institute (Dr. Steve Steinhubl)
- St. Louis University (Dr. Bernard Chaitman)
- TIMI (Drs. Steve Wiviott, David Morrow, Ben Scirica)
- Yale University School of Medicine (Dr. Alexandra Lansky)
Acknowledgements

- Robert Temple, M.D. (CDER)
- Ellis Unger, M.D. (ODE-I)
- Norman Stockbridge, M.D., Ph.D., Shari Targum, M.D., Ana Szarfman, M.D., Ph.D., Jay Levine (DCaRP)
- Jim Hung, Ph.D., John Lawrence, Ph.D., Steve Bai, Ph.D. (Division of Biometrics I)
- Andrew Farb, M.D., Bram Zuckerman, M.D., Steve Brooks, M.D., Ken Cavanaugh, M.D. (CDRH)
- Mary Parks, M.D. (ODE-II)
- Hylton Joffe, M.D., M.M.Sc (DBRUP), Ilan Irony, M.D. (CBER), Leonard Sacks, M.D. (OMP)
- Rachel Hartford, RPM (DMEP)/Lori Wachter, RN, BSN, OCN Project Manager (DCaRP)/ Anna Park, R.Ph Project Manager (DCaRP))
- FDA Stroke Team (Billy Dunn, M.D., John Marler, M.D., Heather Fitter, M.D., Kachikwu Illoh, M.D.)
- CDISC
- Health Level 7
- Clinical Trials Transformation Initiative (CTTI)
- Critical Path / Data Standards
- Association of Clinical Research Organizations
- Industry (Paul Burton, M.D., Yale Mitchel, M.D.)
Standardized Data Collection for Clinical Trials

Now Here

Coming Soon
Draft Definitions


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

http://ac.els-cdn.com/S0735109714074841/1-s2.0-S0735109714074841-main.pdf?_tid=180e3f72-e64b-11e5-831c-00000aacb35d&acdnat=1457564770_57f858d9a29b75d5a4fe86038b24be2f
Thank you