Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials

CSRC and MDEpiNet Thinktank Meeting

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

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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

UPPER BOUND OF 95% CI FOR RISK RATIO	CONCLUSION
>1.8	Inadequate to support approval
>1.3 but <1.8*	Postmarketing trial(s) needed to show definitively <1.3
<1.3*	Postmarketing cardiovascular trial(s) generally not necessary

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

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

July 28, 2015: Data Standards white paper published

2016

January 19, 2016: Discussion of CEC Results

February 2, 2016: SCTI Working Group Meeting

FDA Internal Meetings

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 4, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.12.018

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)

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*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.

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on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative

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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)
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- 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/system/files/all/standard/Draft%20Definitions%20for%20CDISC%20August%2020%2C%202014.pdf

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