

Standard End Point Definitions in Cardiovascular Trials

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***On behalf of the Standardized Data Collection
for Cardiovascular Trials Initiative***

CDISC Webinar

Friday, November 19, 2010

1:00 p.m. – 2:00 p.m.

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

- 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 end point for glucose reduction
- Asks sponsors to demonstrate that new type 2 diabetes agents do not unacceptably increase cardiovascular risk

March 2009

- **Draft proposal for cardiovascular end points, definitions, and case report forms**
- **Internal and external discussion on best path forward**

Advisory Committee Meetings (April 2009)

- **Cardiovascular adverse events were not prespecified or predefined**
- **Missing data (key data elements never collected)**
- **Limitations of retrospective analysis (Broad SMQ MACE, Custom MACE)**
- **Cardiovascular adverse event rates appeared to be low (low risk populations)**

Why Data Standards?

- To improve the quality and efficiency of cardiovascular trials
- To provide end point 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

Standardized Data Collection for Cardiovascular Trials Initiative: Goals

- Standardized Definitions
- Standardized Data Collection/Case Report Forms
- Integrate with
 - CDISC (Clinical Data Interchange Standards Consortium)
 - SDTM: Study Data Tabulation Model
 - HL7 (Health Level 7, Inc.)
- FDA Data Warehouse of Cardiovascular Trials

Stakeholders - 1

- **FDA (CDER, CDRH, Office of Women's Health)**
- **CDER Data Standards (Jay Levine, Ana Szarfman)**
- **Critical Path Initiative (Leonard Sacks)**
- **Academia**
- **American College of Cardiology (ACC) (James Tchong, Dan Roman, Maria Isler, Susan Fitzgerald)**
- **Association of Clinical Research Organizations (ACRO) (Doug Peddicord, Christine Clark, Jean Morgan, Barbara Tardiff)**

Stakeholders - 2

- **Clinical Data Interchange Standards Consortium (CDISC) (Bron Kisler, Rebecca Kush, Chris Tolk, Brian McCourt (DCRI))**
- **Clinical Trials Transformation Initiative (CTTI) (Judith Kramer, Martin Landray)**
- **Health Level 7, Inc. (HL7) (Charles Jaffe)**
- **NHLBI (Mike Domanski)**
- **Pharmaceutical Research and Manufacturers of America (PhRMA) (Alan Goldhammer)**
- **Pharmaceutical Industry Representatives (Paul Burton (J & J), and Yale Mitchel (Merck))**

Academia

- Cleveland Clinic (Drs. Steve Nissen, Mike Lincoff)
- Duke Clinical Research Institute (Drs. Ken Mahaffey, Chris O'Connor, James Tchong)
- Mount Sinai School of Medicine (Dr. Roxana Mehran)
- Harvard Clinical Research Institute (Drs. Don Cutlip, Laura Mauri)
- Harvard Medical School (Dr. Michael Jaff)
- TIMI (Drs. Steve Wiviott, David Morrow, Ben Scirica)
- Brigham and Women's Hospital (Drs. Scott Solomon, Akshay Desai, Eldrin Foster Lewis, Marc Pfeffer, John McMurray (Glasgow, Scotland))
- St. Louis University (Dr. Bernard Chaitman)
- Yale University School of Medicine (Dr. Alexandra Lansky)
- Beth-Israel Deaconess Medical Center (Dr. C. Michael Gibson)

Neurology Working Group

- **FDA Stroke Team**
 - **Drs. Billy Dunn, John Marler, Heather Fitter, and Kachikwu Illoh**
- **Cathy Sila, M.D. (Case Medical Center)**

Definitions

- **Cardiovascular Death**
- **Non-Cardiovascular Death**
- **Myocardial Infarction**
- **Hospitalization for Unstable Angina**
- **Stroke**
- **Coronary Revascularization Procedures**
- **Peripheral Revascularization Procedures**
- **Heart Failure Requiring Hospitalization**
- **Stent Thrombosis**

Standardized Data Collection for Cardiovascular Trials

- **July 22, 2009: Draft definitions released**
- **September 11, 2009: Meeting of Major Stakeholders**
- **February 5, 2010: Internal Working Group Meeting**
- **March 26, 2010: Meeting of Major Stakeholders**
- **Multiple meetings with FDA Senior Management**
- **Ongoing communication with the Universal Definition of MI Working Group**

Standardized Data Collection for Cardiovascular Trials – Next Steps

- Posting of Definitions on CDISC website (November 17, 2010) for 30 days of public comment
 - Links to definitions provided to professional societies to facilitate comments
- Formal testing of Definitions (Drs. Roxana Mehran and Stephen Wiviott)
- Creation of Standardized Case Report Forms for Cardiovascular End Point Events
- Integration with CDISC / HL7

Standardized Data Collection for Cardiovascular Trials – Other Steps

- FDA is working with ACC and other professional societies to harmonize ACC and CDISC data elements
(Dr. Chris Cannon)
 - Goal is for data to be CDISC ready for submission
- Sentinel Initiative

Acknowledgements

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- Steve Grant, M.D. (DCRP)
- Jim Hung (Director, 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. , Hylton Joffe, M.D., M.M.Sc, Ilan Irony, M.D. (DMEP)
- Rachel Hartford, RPM (DMEP)/Lori Wachter, RN, BSN, OCN Project Manager (DCRP)/ Anna Park, R.Ph Project Manager (DCRP)
- Chuck Cooper, M.D. (OTS/OB/DBVI)
- FDA Stroke Team (Billy Dunn, M.D., John Marler, M.D., Heather Fitter, M.D., Kachikwu Illoh, M.D.)

Next Steps

Brian McCourt

Associate Director, Clinical Research Informatics
Clinical Data Integration
Duke Clinical Research Institute

Standardized Data Collection for Cardiovascular Trials Initiative: Goals



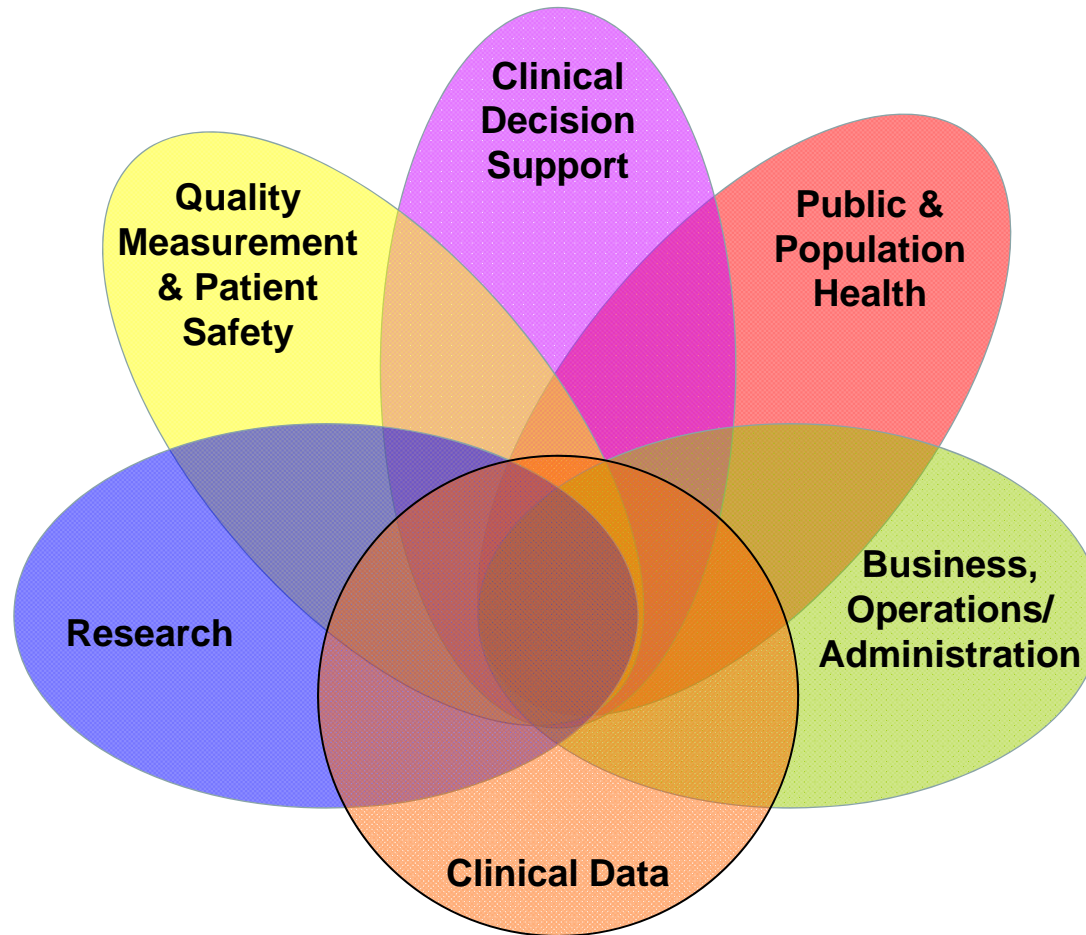
Sept
2011

- Standardized Definitions
- Standardized Data Collection/Case Report Forms
- Integrate with
 - CDISC (Clinical Data Interchange Standards Consortium)
 - SDTM: Study Data Tabulation Model
 - HL7 (Health Level 7, Inc.)
- FDA Data Warehouse of Cardiovascular Trials

Key Considerations

- **Standard end point definitions are critical, but not sufficient to meet the quality, efficiency or analysis objectives**
- **End point data is clinical data, standardize at the source**
- **Coordinate various cardiology standards efforts to collaboratively produce a single set of work products**

Collect Once, Repurpose Many Times



Don Mon, AHIMA

Collaborating Organizations

- American College of Cardiology Foundation (ACC)
- Clinical Data Standards Interchange Consortium (CDISC)
- Duke Clinical Research Institute (DCRI)
- Duke Translational Medicine Institute (DTMI)
- US Food and Drug Administration (FDA)
- Health Level Seven (HL7)
- National Cancer Institute (NCI)
- National Cardiovascular Research Infrastructure (NCRI)

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Work Products

	Healthcare	Research
Use cases and patient scenarios	Cardiovascular Domain Analysis Model	
Data elements and clinical definitions		
Activity diagrams		
Information model		
Healthcare (HL7 RIM) representation	HL7	
Sample data collection forms		CDISC
CDISC (CDASH, SDTM) representations		CDISC
Electronic metadata publication (NCI EVS/caDSR)	HL7 and CDISC	

Process & Milestones

- Identification and development of common data elements
 - CV CDASH Domains, Related artifacts
 - Preparatory work started, growing CDISC & HL7 activity
- CDISC Public Comment
 - Target: 2nd Quarter 2011
- HL7 Ballot (Cardiology DAM, R2)
 - Target: September 2011 Ballot Cycle
- Publish Metadata (NCI EVS/caDSR)

Standardized Data Collection for Cardiovascular Trials

Coming Soon