JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
PUBLISHED JOINTLY BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION AND
AMERICAN HEART ASSOCIATION, INC.

VOL. 71, NO. 9, 2018

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials

Karen A. Hicks, MD,[a,*,†] Kenneth W. Mahaffey, MD,[b,†] Roxana Mehran, MD,[c,†] Steven E. Nissen, MD,[d,†] Stephen D. Wiviott, MD,[e] Billy Dunn, MD,[f,*] Scott D. Solomon, MD,[g] John R. Marler, MD,[f,*] John R. Teerlink, MD,[h] Andrew Farb, MD,[i,*] David A. Morrow, MD, MPH,[e] Shari L. Targum, MD, MPH,[a,*] Cathy A. Sila, MD,[j] Mary T. Thanh Hai, MD,[k,*] Michael R. Jaff, DO,[l] Hylton V. Joffe, MD, MMSc,[m,*] Donald E. Cutlip, MD,[n] Akshay S. Desai, MD,[g] Eldrin F. Lewis, MD, MPH,[g] C. Michael Gibson, MD, MS,[o] Martin J. Landray, PhD,[p] A. Michael Lincoff, MD,[d] Christopher J. White, MD,[q] Steven S. Brooks, MD, MBA,[r] Kenneth Rosenfield, MD,[s] Michael J. Domanski, MD,[t] Alexandra J. Lansky, MD,[u] John J.V. McMurray, MD,[v] James E. Tcheng, MD,[w] Steven R. Steinhubl, MD,[x] Paul Burton, MD, PhD,[y] Laura Mauri, MD, MSc,[z] Christopher M. O'Connor, MD,[aa] Marc A. Pfeffer, MD, PhD,[g] H.M. James Hung, PhD,[bb,*] Norman L. Stockbridge, MD, PhD,[a,*] Bernard R. Chaitman, MD,[cc] Robert J. Temple, MD,[dd,*] on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI)

ABSTRACT

This publication describes uniform definitions for cardiovascular and stroke outcomes developed by the Standardized Data Collection for Cardiovascular Trials Initiative and the U.S. Food and Drug Administration (FDA). The FDA established the Standardized Data Collection for Cardiovascular Trials Initiative in 2009 to simplify the design and conduct of clinical trials intended to support marketing applications. The writing committee recognizes that these definitions may be used in other types of clinical trials and clinical care processes where appropriate. Use of these definitions at the FDA has enhanced the ability to aggregate data within and across medical product development programs, conduct meta-analyses to evaluate cardiovascular safety, integrate data from multiple trials, and compare effectiveness of drugs and devices. Further study is needed to determine whether prospective data collection using these common definitions improves the design, conduct, and interpretability of the results of clinical trials. (J Am Coll Cardiol 2018;71:1021–34) Published jointly by the American College of Cardiology Foundation and American Heart Association, Inc.

From the [a]Division of Cardiovascular and Renal Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA), Silver Spring, Maryland; [b]Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, California; [c]Division of Cardiology, Icahn School of Medicine at Mount Sinai, New York, New York; [d]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio; [e]TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts; [f]Division of Neurology Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA), Silver Spring, Maryland; [g]Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts; [h]Section of Cardiology, San Francisco Veterans Affairs Medical Center and School of Medicine, University of California San Francisco, San Francisco, California; [i]Division of Cardiovascular Devices, Center for Devices and Radiological Health (CDRH), United States Food and Drug Administration (FDA), Silver Spring, Maryland; [j]Neurological Institute, University Hospitals-Cleveland Medical Center, Cleveland, Ohio; [k]Office of Drug Evaluation II, Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA), Silver Spring, Maryland; [l]Department of Medicine, Harvard Medical School, Boston, Massachusetts; [m]Division of Bone, Reproductive and Urologic Products, Office of Drug Evaluation III, Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA), Silver Spring, Maryland; [n]Cardiology Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; [o]Cardiovascular Division, Department of Medicine, Harvard Medical School, Boston, Massachusetts; [p]Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), University of Oxford, Oxford, United Kingdom; [q]Department of Cardiology, Ochsner Clinical School, New Orleans, Louisiana; [r]Brooks Medtech, LLC, Reisterstown, Maryland; [s]Vascular Medicine and Intervention, Corrigan Minehan Heart Center, Massachusetts General Hospital, Boston, Massachusetts; [t]Peter Munk Cardiac Centre, University Health Network/Mount Sinai Hospital, University of

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ISSN 0735-1097/$36.00

https://doi.org/10.1016/j.jacc.2017.12.048

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

ACS = acute coronary syndrome

AHA = American Heart Association

AMI = acute myocardial infarction

CABG = coronary artery bypass graft surgery

CEC = clinical events committee

CK = creatine kinase

cTn = cardiac troponin

CV = cardiovascular

ESC = European Society of Cardiology

HF = heart failure

hs-cTn = high-sensitivity cardiac troponin

MI = myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

SCTI = Standardized Data Collection for Cardiovascular Trials Initiative

UDMI = Universal Definition of Myocardial Infarction

URL = upper reference limit

This publication describes uniform definitions for cardiovascular (CV) and stroke outcomes developed by the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI) and the U.S. Food and Drug Administration (FDA). The FDA established the SCTI in 2009 to simplify the design and conduct of clinical trials intended to support marketing applications. Specifically, the FDA convened the SCTI based on the need for standardization following the FDA's publication in December 2008 of the guidance for industry titled "Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" (1) and in response to a growing interest in developing a universal medical vocabulary for CV and stroke outcomes. The SCTI includes representatives from academia, professional societies, the Clinical Data Interchange Standards Consortium (CDISC), Health Level 7 International, the Clinical Trials Transformation Initiative, pharmaceutical and CV device manufacturers, and the FDA, including the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health (Online Appendix 1 and SCTI Contributors). A major limitation in comparing outcomes among trials within and across drug and device development programs has been the lack of uniform definitions for key endpoint events. Pre-specified endpoint definitions that are characterized by objective criteria and reported uniformly can help address this problem. Drafts of the SCTI's CV and stroke outcome definitions have been available in the public domain since 2009 ("Standardized Definitions for Cardiovascular Outcomes Trials: Draft Recommendations," dated July 22, 2009 and discussed at the public meeting on September 11, 2009). SCTI posted these definitions for public comment on the CDISC website from November 2010 through January 2011 and on the American College of Cardiology (ACC)/American Heart Association (AHA) website from March through April of 2014 (2).

The goal of this document is to provide a framework of definitions for CV and stroke outcomes in clinical trials to assess the safety and effectiveness of a particular treatment (Online Appendixes 2 to 12). These definitions are based on published medical data; clinical and research expertise; published definitions and guidelines; and SCTI's interpretation of specific laboratory tests, diagnostic tests, and imaging techniques.

All definitions have limitations and will not be satisfactory in every case. Some flexibility in applying the proposed definitions may be necessary to address the specific population being studied, intervention under investigation, duration of follow-up, and disease process. Outcome measures appropriate for a particular trial may vary according to the type and objectives of the clinical trial itself, the therapeutic

Toronto, Toronto, Ontario, Canada; [u]Department of Internal Medicine, Section of Cardiology, Yale School of Medicine, New Haven, Connecticut; [v]Institute of Cardiovascular & Medical Sciences, BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland; [w]Division of Cardiovascular Medicine, Duke University Medical Center, Durham, North Carolina; [x]Division of Digital Medicine, Scripps Translational Science Institute, La Jolla, California; [y]Cardiovascular and Metabolism Medical Affairs, Janssen Pharmaceuticals Inc., Titusville, New Jersey; [z]Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [aa]Division of Cardiology, Inova Heart & Vascular Institute, Falls Church, Virginia; [bb]Division of Biometrics I, Office of Biostatistics, Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA), Silver Spring, Maryland; [cc]Center for Comprehensive Cardiovascular Care, St. Louis University School of Medicine, St. Louis, Missouri; and the [dd]Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA), Silver Spring, Maryland. *The findings and conclusions in this report are those of the author and do not necessarily represent the official positions of the U.S. Food and Drug Administration (FDA). [†]Chairpersons. Dr. Mahaffey has received research grants or contracts in support of research projects from Afferent, Amgen, Apple Inc., AstraZeneca, Cardiva Medical Inc., Daiichi, Ferring, Google (Verily), Johnson & Johnson, Luitpold, Medtronic, Merck, Novartis, Sanofi, St. Jude, and Tenax; has provided consultancy or other services for Ablynx, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cardiometabolic Health Congress, Elsevier, GlaxoSmithKline, Johnson & Johnson, Medergy, Medscape, Merck, Mitsubishi, Myokardia, Novartis, Oculeve, Portola, Radiometer, Springer, Theravance, UCSF, and WebMD; and has equity in BioPrint Fitness. Dr. Mehran has received personal fees for serving on the Executive Committees of Janssen Pharmaceuticals and Osprey Medical Inc.; has served on the Data and Safety Monitoring Board (DSMB) of Watermark Research Partners; has served as a consultant to Medscape, The Medicines Company, Boston Scientific, Merck, Cardiovascular Systems, Inc., Sanofi USA, Shanghai BraccoSine Pharmaceutical Corp., and AstraZeneca; has equity stock options in Claret Medical Inc. and Elixir Medical Corporation; and her institution has received research funding from Eli Lilly/Daiichi-Sankyo, Bristol-Myers Squibb, AstraZeneca, The Medicines Company, OrbusNeich, Bayer, CSL Behring, Abbott Laboratories, Watermark Research Partners, Novartis Pharmaceuticals, Medtronic, AUM Cardiovascular, Inc., and Beth Israel Deaconess Medical Center. Dr. Nissen consults for Boeringher Ingelheim, Vivus, Medtronic, Novartis, Novo Nordisk, Shire, Sanofi-Regeneron, Janssen, CiVi Biopharma, and Takeda but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction; his institution (the Cleveland Clinic Center for Clinical Research) receives funding to perform clinical trials from Abbvie, AstraZeneca, Amgen,