Regulators and sponsors need to continually assess the risk-benefit of medical products throughout the life-cycle. When a safety issue is identified in a development program the issue is addressed prospectively in the program safety analysis plan with a goal to combine the data across studies. In the absence of large-scale confirmatory studies on the safety of products it is necessary to synthesize the available scientific evidence.

A regulatory information synthesis (RIS) includes the systematic review and a meta-analysis, if appropriate to combine data across studies. Guidance on best practices for RIS enhances transparency, objectivity, reproducibility, consistency and interpretation. RIS is an important tool in safety evaluation and is one of several sources of evidence that is considered in support of risk-benefit decisions in the regulatory setting.

Those who have suggestions or comments regarding this topic may communicate via E-mail to: meta_analysis_guidance@fda.hhs.gov

FEATURED TOPICS
- Best Practices for Information Synthesis
- Format and Content of a Protocol for Safety Information Synthesis
- Minimizing Bias in Information Synthesis
- Dealing with Heterogeneity
- Analytical Considerations for Sparse Data
- Bayesian and Frequentist Analytical Strategies
- Meta-analysis of a Class of Products
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Type of Activity: Knowledge

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LEARNING OBJECTIVES

At the conclusion of this meeting, participants should be able to:

• Summarize key principles for conducting rigorous information synthesis of evidence from randomized controlled trials for safety evaluation
• Develop and implement a review protocol for a regulatory information synthesis
• Identify appropriate methodologies and considerations for dealing with heterogeneity in meta-analysis of sparse data from randomized controlled trials
• Develop a prospective plan to collect, analyze and combine drug safety data to assess an anticipated risk in a drug development program

WHO SHOULD ATTEND

Professionals involved in:

• Biostatistics
• Clinical research
• Compliance
• Data analysis
• Drug Safety and Pharmacovigilance
• Epidemiology
• Labeling
• Medical Information
• Quality assurance/Quality control
• Regulatory affairs
• Risk management

DAY ONE | THURSDAY, MARCH 10

THEME: BEST PRACTICES IN DESIGN AND CONDUCT OF INFORMATION SYNTHESIS OF RANDOMIZED TRIALS FOR PRODUCT SAFETY EVALUATION

7:30–8:30 AM CONTINENTAL BREAKFAST AND CONFERENCE REGISTRATION

8:30–8:45 AM OPENING REMARKS AND PRELIMINARIES

C. George Rochester, MA, PhD, RAC
Associate Office Director for Safety Assessment
Office of Biostatistics
CDER, FDA

WELCOME AND INTRODUCTION OF KEYNOTE SPEAKER

ShaAvhreé Buckman, MD, PhD
Director, Office of Translational Sciences
CDER, FDA

8:45–9:30 AM KEYNOTE ADDRESS

Janet Woodcock, MD
Director
Center for Drug Evaluation and Research, FDA

9:30–10:30 AM

Best Practices for Regulatory Information Synthesis for Medical Product Safety Evaluation: Overview, Challenges and Opportunities

SESSION CHAIRPERSON

Stephen E. Wilson, DrPH, CAPT, USPHS
Director, Division of Biometrics III
CDER, FDA

This session is intended to provide an overview of the major themes and concepts to be proposed in the draft guidance on “Best Practices in Regulatory Information Synthesis of Randomized Controlled Trials for Product Safety Evaluation.” This guidance will address synthesis of evidence from randomized controlled trials and not observational studies. This session will highlight the aspects of a systematic review and meta-analysis to assess moderate effects in the presence of sparse data. Challenges and opportunities to embrace best practices to support rigorous information synthesis for regulatory decision making will be highlighted.
C. George Rochester, MA, PhD, RAC  
Associate Office Director for Safety Assessment  
Office of Biostatistics  
CDER, FDA

SESSION SPEAKER

10:30–10:45 AM MORNING REFRESHMENT BREAK

10:45 AM–12:15 PM
Format and Content of a Protocol for Safety Information Synthesis

SESSION CHAIRPERSON

Eric Frimpong, PhD  
Mathematical Statistician, Office of Biostatistics  
CDER, FDA

This session will focus on the format and content of a review protocol for an information synthesis for safety. It should be standard practice to prepare a protocol before conducting a regulatory information synthesis, similar to how a protocol is formulated for a clinical trial, especially since the synthesis is a complex process. Protocol amendments documenting unforeseen changes to the protocol can be made. In the prospective case, ideally, the protocol program safety analysis plan is devised prior to generating data from the individual studies. Key hypotheses to be tested are pre-specified as well as the primary analytic strategy, sensitivity and exploratory analyses. The protocol is more crucial for a retrospective synthesis as it may depend on available data that were not necessarily generated to support the scientific question under consideration. Subject level data is critical to facilitate the range of analyses and quality checks needed to support regulatory decisions.

10:45–11:15 AM
SESSION PRESENTER

Libero Marzella, MD  
Medical Team Leader  
Division of Medical Imaging and Hematology Product  
Office of New Drugs (OND)  
Office of Oncology Drug Products (OODP)  
CDER, FDA

11:15–11:45 AM
PANELISTS

Andreas Brückner, MS  
Principal Statistician  
Bayer-Schering Pharma  
Germany

Robert J. Temple, MD  
Deputy Director for Clinical Science  
CDER, FDA

Harry A. Seifert, MD  
Executive Director, Safety Evaluation & Risk Management  
GlaxoSmithKline Biologicals

11:45–12:15 PM OPEN DISCUSSION

12:15–1:30 PM NETWORKING OPPORTUNITY AND LUNCHEON

1:30–3:00 PM
Definition, Adjudication and Harmonization of Endpoints

SESSION CHAIRPERSON

Simone Pinheiro, ScD, MSc, MA,  
Lead Interdisciplinary Scientist, Epidemiologist  
Division of Epidemiology  
Office of Surveillance and Epidemiology  
CDER, FDA

This session will focus on the potential limitations of meta-analyses of randomized clinical trials related to definition and adjudication of endpoints. Accuracy of endpoint ascertainment is essential in the conduct of meta-analyses to inform regulatory decisions. Lack of a-priori endpoint definitions poses difficulties in the proper identification of outcomes of interest. Additional challenges are encountered in harmonization of endpoints, or derivation of composite endpoints, across clinical trials. Whether or not standardized coding dictionaries are employed similarly across trials impacts one’s ability to adjudicate clinically meaningful endpoints. Finally, the role of patient-level data in meta-analyses will be discussed to facilitate exploration of the data to assess study quality and support analyses beyond the primary summary measure estimates.

1:30–2:00 PM
SESSION PRESENTER

Karen Hicks, MD  
Medical Team Leader  
Division of Cardiovascular & Renal Products  
Office of New Drugs, CDER, FDA

2:00–2:30 PM
PANELISTS

Janet Witos, PhD  
President  
Statistics Collaborative, Inc

Sharon Hertz, MD  
Deputy Director, Division of Anesthesia, Analgesia and Rheumatology Products  
CDER, FDA

Kelly Posner, PhD  
Director, Center for Suicide Risk Assessment (CSRA)  
Columbia University New York State Psychiatric Institute

Steve Snapinn, PhD  
Vice President, Global Biostatistical Science  
Amgen, Inc.

2:30–3:00 PM OPEN DISCUSSION

3:00–3:30 PM AFTERNOON REFRESHMENT BREAK
Meta-analysis has been subject to criticism because of the obvious problems associated with combining studies from multiple sources. This session will focus on strategies that can be used to minimize bias in the context of a meta-analysis. Understanding which biases may be obscuring a safety issue or which will magnify a safety signal is to be discussed, whether data is from individual patients or aggregated at some level. The magnitude of a difference in adverse event rates across treatment arms may be impacted by: the choice of blinded or open label studies, how much missing data there is, whether there is differential loss to follow-up or pattern dropouts and discontinuations, as well as inconsistent lengths of follow-up across studies. The conduct of each study is also relevant including how key safety endpoints are adjudicated. Failure to define safety endpoints consistently among studies will impact the quality of a meta-analysis. Concerns over the completeness of the studies to be included including publication bias or omission of failed studies also need to be considered. The panel will discuss what features ought to be addressed for a prospectively planned meta-analysis and then separately what concerns should be addressed if a meta-analysis is planned where some or all of the studies have already been completed.
Such comparisons across subclasses may need to rely on the use of indirect comparisons, so this area will be considered in the session, as well. Other issues include whether or not to combine data across indications. Dose may vary across indications for the same compound, or there may be physiologic reasons to suspect that susceptibility to an adverse event may vary. There will almost always be a theoretical interest in making comparisons across drugs within a class, but small numbers will typically limit the ability to draw firm inferences from such comparisons. (Otherwise, a class-level analysis would not have been needed in the first place.)

Finally, in some situations, there may be large outcomes studies as well as collections of smaller studies. Part of this session will focus on understanding how these two data sources may complement each other, and on how results from these two sources may (or may not) have differed in some prominent examples in the past.

Mark Levenson, PhD  
Deputy Division Director  
Division of Biometrics VII  
Office of Biostatistics  
CDER, FDA

Panelists:
Joseph Cappelleri, PhD, MPH  
Senior Director  
Pfizer Inc  

Jesse Berlin, ScD  
Vice President for Epidemiology  
Johnson and Johnson Pharmaceutical Research & Development LLC  

Evelyn Mantari, MD, MS  
Clinical Safety Reviewer  
Division of Neurology Products  
CDER, FDA

10:30–10:45 AM MORNING BREAK

10:45 AM–12:15 PM  
Considerations for the Analysis of Sparse Data

Session Chairperson:
Scott W. Miller, PhD  
Mathematical Statistician  
Division of Biostatistics, CDRH, FDA

Rare event meta-analysis poses some unique analytical challenges and adds another layer of complexity to information synthesis. First, classical inferences for meta-analysis which rely on large sample approximations may not be appropriate in rare event setting. Second, certain serious adverse events are often sparse, leading to zero events being observed in some patient groups for some studies therefore making the evaluation of a drug effect difficult to quantify. Third, the choice of meta-analysis methods may have an unexpected influence on the results. Special consideration should be given to choice of summary measure, fixed effects vs. random effects models, continuity corrections and statistical methods when handling zero events. In addition, sensitivity analysis assessing robustness of the results is crucial because results may be sensitive to statistical and non-statistical aspects. In this session, the issues with rare event meta-analysis will be presented and analytical considerations in such a setting will be discussed by an expert panel.

Session Presenter
Estelle Russek-Cohen, PhD  
Acting Director, Division of Biostatistics and Epidemiology  
CBER, FDA

11:15–11:45 AM  
Panelists
William H. DuMouchel, PhD  
Chief Statistical Scientist  
Oracle Health Services.

A. Russell Localio, JD, MA, MPH, MS, PhD  
Associate Professor of Biostatistics at HUP  
University of Pennsylvania SOM

Lee-Jen Wei, PhD  
Professor of Biostatistics  
Department of Biostatistics  
Harvard University

Brenda Crowe, PhD  
Research Advisor  
Eli Lilly and Company

11:45–12:15 PM OPEN DISCUSSION

12:15–1:30 PM NETWORKING OPPORTUNITY AND LUNCHEON

1:30–3:00 PM  
Dealing with Heterogeneity

This session will cover different approaches for dealing with heterogeneity in meta-analyses, from identification and quantification through strategies to ensure valid inference from study level and subject level characteristics. Specifically we will discuss fixed and random effects, multiplicity, cumulative meta-analyses. Frequentist and Bayesian approaches to address heterogeneity will be discussed.

Session Chairperson
Ram Tiwari, PhD  
Associate Director, Office of Biostatistics  
CDER, FDA

1:30–2:00 PM  
Session Presenter
Scott Berry, PhD  
President and Senior Statistical Scientist  
Berry Consultants

2:00–2:30 PM  
Panelists
Amy Xia, PhD  
Head, Global Safety and Independent Biostatistics  
Global Biostatistical Science  
Amgen, Inc.

Robert J. Temple, MD  
Deputy Center Director for Clinical Science  
CDER, FDA

Stephen Grant, MD  
Deputy Division Director  
Division of Cardiovascular and Renal Products  
OND, CDER, FDA

2:30–3:00 PM OPEN DISCUSSION

3:00–3:30 PM AFTERNOON REFRESHMENT BREAK
Uses of Information Synthesis for Regulatory Decision Making

SESSION CHAIRPERSON
C. George Rochester, MA, PhD, RAC
Associate Office Director for Safety Assessment
Office of Biostatistics
CDER, FDA

In product safety evaluation, the increasing volume, complexity, quality of information and, the lack of thorough reporting in the medical literature, make it hard to integrate the scientific information that is needed to support good decisions. Regulatory decisions are based on the totality of the evidence on a product or class of products. Subsequent to an information synthesis, regulators, sponsors, healthcare providers and other stakeholders face a substantial challenge in applying a decision framework that considers the best available evidence. The results of meta-analyses of clinical trials have to be considered against findings from observational studies, experience with a product class, populations for which the product is intended and the natural history of disease. This session will focus on the incorporation of multiple sources of information to inform complex regulatory decisions. An expert panel will provide perspectives on how results from information synthesis are used in product regulation.

SESSION PRESENTER
Robert J. Temple, MD
Deputy Center Director for Clinical Science
CDER, FDA

3:30-4:45 PM

Panelists
Gerald Dal Pan, MPH, MD
Director, Office of Surveillance and Epidemiology
CDER, FDA
Douglas Throckmorton, MD
Deputy Director
Regulatory Programs
Office of the Center Director
CDER, FDA
Mary H. Parks, MD
Director, Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation (ODE) II
Office of New Drugs (OND)
CDER, FDA
Robert O’Neill, PhD
Director
Office of Biostatistics
CDER, FDA

Next Steps and Path Forward

C. George Rochester, MA, PhD, RAC
Associate Office Director for Safety Assessment
Office of Biostatistics
CDER, FDA

4:45–5:00 PM

5:00 PM WORKSHOP ADJOURNED

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DIA/FDA Best Practices for Regulatory Information Synthesis of Randomized Controlled Trials for Product Safety Evaluation
Event #11011 • March 10-11, 2011
DoubleTree Hotel and Executive Meeting Center, Bethesda, MD, USA

Contact Information
Event Information: Contact Constance Burnett at the DIA office by telephone 215.293-5800, fax 215.442.6199 or email Constance.Burnett@diahome.org.

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Registration fee includes refreshment breaks, luncheons, and reception (if applicable), and will be accepted by mail, fax, or online.

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Cancellations must be in writing and be received by the cancellation date above. Registrants who do not cancel by that date and do not attend will be responsible for the full registration fee paid. Registrants are responsible for canceling their own hotel and airline reservations. You may transfer your registration to a colleague at any time but membership is not transferable. Please notify DIA of any such substitutions as soon as possible. Substitute registrants will be responsible for nonmember fee, if applicable.

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