



**Highlights from the  
PhRMA MRCT Key Issue Team  
& DIA MRCT Workshop**

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Merck and Co., Inc.*

**4<sup>th</sup> Seattle Symposium in Biostatistics:  
Clinical Trials**

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# 4 PhRMA MRCT KIT Workstreams

- PhRMA MRCT KIT chairs: B. Binkowitz, E. Ibia
- Workstreams:
  - Issues when endpoints/timepoints/etc. differ between health authorities (C. Girman)
  - Considerations when defining “region” (Y. Tanaka, C. Mak)
  - Consistency (H. Quan, J. Chen)
  - Survey of PhRMA companies MRCT practices (N. Scott)

# Consistency Team Publications

- Chen et al. Assessing consistent treatment effect in a multi-regional clinical trial: a systematic review. *Pharmaceutical Statistics* 2010;9:242–253.
- Quan et al. Assessment of consistency of treatment effects in multiregional clinical trials. *Drug Information Journal* 2010; 44:617–632.

# Consistency Team

- Ultimate goal of MRCT is the overall effect in the full study pop of the clinical trial
- Showing robustness & consistency of trt effects across regions deserves attention.
- Examined various definitions of “consistency”
- Recommends:
  - Address regional consistency at the design stage
  - Pre-specify “region” in protocol/analysis plan

# Consistency Team

- Ideally, all regions should be treated identically in the consistency definition
- Overall sample size plays a key role in examining consistency, and in fact it may not be possible to partition the regions to achieve desired power depending on the number of regions and the definition of consistency. Keep # of regions small.
- Don't conclude inconsistency without attempting to understand why
  - Multiplicity issues
  - Further exploratory analyses :Baseline characteristics, medical practice, and other intrinsic/extrinsic factors that may confound the results
  - Totality of the data/evidence
    - Overwhelming vs marginal overall effect
    - Consistency in other important endpoints and subgroups
    - External data (e.g., same class, same patient population, etc.)
  - Hill's criteria

# Issues when endpts/timepts/etc. differ between health authorities: Summary Recommendations

<b>Different Regional requirements</b>	<b>Potential handling in MRCT</b>
Different clinical endpoints as primary/co-primary	Pre-specify different primary or co-primary hypotheses in protocol, and describe separately in study report
Different timepoints for primary endpoint	Pre-specify different timepoints in primary hypothesis for different regions as long as blinded trial duration extends to longer duration If analysis done at earlier timepoint, need to consider later timepoint as supplemental information, or account for interim look Need to ensure trial integrity because of earlier unblinding.
Different non-inferiority margins	If trial size is sufficient for both margins, pre-specify different margins for different regions in protocol; describe separately in report
Different analytic populations or methods	Pre-specify differences in protocol and describe separately for different regions in report
Different study designs	Depending on magnitude of differences, can handle minor differences in MRCT by pre-specifying in protocol

## Issues when endpts/timepts/etc. differ between health authorities: Summary:

- Many different regional requirements for endpoints can be handled within MRCTs – recommend to proactively discuss discrepancies with Health Authorities as they arise
- Harmonized guidance from health authorities on handling or eliminating such discrepancies would be useful
- Guidances for specific therapeutic indications could be made more consistent where clearly different requirements exist
- If such regulatory requirement differences remain, pre-specifying such differences in protocols and/or data analysis plans is critical
- Team will provide published examples of trials, and cite examples from guidances, of discrepancies.

# Considerations when defining “region”

<b>Factors</b>	<b>Rationale</b>
Race and ethnicity	Surrogates for genomic issues and therefore a supposedly homogeneous, w.r.t. drug effects, group
Medical practice	Encompasses practices of treating a patient including local medicines, hospital treatment
Human Development Index	Surrogate for ability to provide and have access to the "latest" developments in health care (Adult literacy, GDP, Education, life expectancy)
Disease Epidemiology	Goes to the differing characteristics of the disease (including genomics/biomarkers) which are reflected by many of the issues on this list. Provides the background information that can indicate where disparate characteristics occur that will affect the planning, analysis and execution of the clinical trial.
Geographic proximity	The traditional idea of a region, yet still very fluid
Geopolitical / Institutional	Health Authority driven
Culture	Broad term to encompass common health practices, ethics, and behaviors that impact on a clinical trial that arise from within a common culture.



# Considerations when defining “region”

- Region does not necessarily have to be geographical or political.
- Different factors should be considered depending on therapeutic area / disease state.
- **“Region” should be pre-defined (with justifications)**
  - **How these definitions are accounted for in the study design should be noted with the pre-definition**
  - **how region will be analyzed should be pre-specified in the planning stage (stratification, consistency method should be integral in the design).**

# Considerations when defining “region”

- This workstream has conducted a comprehensive review of ACM minutes over the past 2 year, searching for “region” discussions.
- Targeted literature search on this topic conducted
- Findings across literature and ACM minutes:
  - Pre-definition is rare, and justification more rare
  - Post-hoc definitions more common, lack justification
  - Vast majority of of definitions are geographically based, even with evidence of differences crossing geography.
  - Geography is often defined by health authority
- Details in the forthcoming publication

# PhRMA Survey of MRCT Practices

- Greater, region independent, standards to guide the conduct of **all** trials
- Greater cross-regulatory collaboration to align:
  - Therapeutic area specific requirements
  - Safety data requirements
  - Logistics of drug import / export

# PhRMA Survey of MRCT Practices

- Processes and enforcement to achieve standardization:
  - Centralized quality management plans
  - Global monitoring guidelines (consider PhRMA white paper on acceptable approaches for risk-based clinical trial monitoring: “PhRMA BioResearch Monitoring Committee: Perspective on Acceptable Approaches for Clinical Trial Monitoring”, Drug Information Journal, Vol. 44, No.4, July 2010)
  - Guidelines to restrict and manage when protocol amendments may be utilized

# Next Steps for the MRCT KIT

- Publication of work from each workstream / position papers
- Working with DIA to publish the proceedings from the DIA MRCT meeting
- Session at 2011 conferences (e.g. DIA/FDA Stat Forum April 2011), proposal for 2011 FDA/Industry Statistics Workshop
- Pending further sanctioning from PhRMA, we would have additional objectives for:
  - more work on trial and data quality
  - collaborating with academia, perhaps a “missing data” NAS type of effort?



# **Brief Highlights from the DIA MRCT Workshop**

**October 26-27, 2010**

9:00-9:45 AM SESSION 1: PLENARY KEYNOTE ADDRESS

### Keynote Speaker

Towards the Definition of Appropriate Globalization in Clinical Trials:  
the Case for Transparent Cooperation

#### Robert M. Callff, MD

Vice Chancellor for Clinical Research  
Duke University Medical Center  
Director, Duke Translational Medicine Institute

9:45-10:45 AM SESSION 2 – PART 1

### Perspectives on Multiregional Clinical Trials (MRCTs): FDA, EMA, Health Canada, and Industry

SESSION CHAIRPERSON

#### Mike Ward

Manager, International Programs Division  
Therapeutic Products Division  
Health Canada

This keynote panel discussion will address broad questions that cover multiregional clinical trial (MRCT) conduct including the current state; data monitoring committees, data quality, integrity and human subject protection; potential barriers to MRCT data acceptability and address heterogeneity of results with ability to verify source data; perspective on CROs and other service providers involved in MRCTs and last, regulatory harmonization to facilitate efficient conduct of MRCT.

#### Panelists

##### Leslie Ball, MD, CAPT, USPHS

Director, Division of Scientific Investigations  
Office of Compliance, CDER, FDA

##### Fergus Sweeney, PhD

Head of Sector, Compliance and Inspections  
European Medicines Agency, European Union

##### Agnes V. Klein, MD, DrPH

Director, Centre for Evaluation of Radiopharmaceuticals  
and Biotherapeutic Products  
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Duke University Medical Center  
Director, Duke Translational Medicine Institute

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Director, Centre for Evaluation of Radiopharmaceuticals  
and Biotherapeutic Products  
Health Canada

##### Mark Paxton, PhD

Associate Vice President, International Regulatory Affairs,  
Pharmaceutical Research and Manufacturers of America  
(PhRMA)

##### Ian Marschner, PhD

Professor, Statistics  
Department of Statistics  
Macquarie University, Australia

##### Diana Zuckerman, PhD

President, National Research Center for Women & Families

12:00-1:00 PM NETWORKING OPPORTUNITY AND LUNCHEON

# Highlights from DIA MRCT Workshop

## Sessions 1 and 2

### ■ Dr. Califf

- urged for reaching sensible standards for global trials as that would have a huge positive impact on development and deployment of effective therapies
- we need the regulators to facilitate.
- electronic medical records and a learning medical system could foster such standards.
- Transparent "coopetition" is a key element of MRCT (define intended purpose of the trial, ensure registration, predefine a plan for quality in conduct and interpretation of the trial).



# Highlights from DIA MRCT Workshop

## Sessions 1 and 2

### ■ Mark Paxton

- harmonization efforts of APEC
- PhRMA SGD activities
- both address barriers to contribute to drug lag in East Asia

### ■ Dr. O'Neill

- expressed surprise at the lack of published research into MRCT, especially with the rapid expansion of this type of design.
- "trust factor" involved with MRCT and therefore:
- called for building quality into the design
- returning to the first principles of study design including blinding, randomization and avoidance of skewed consent withdrawal.

# Highlights from DIA MRCT Workshop

## Sessions 1 and 2

### ■ Dr. Ball

- made the point that outsourcing leads to uncertainty on the part of regulators
- quality should be built into the trial as poor quality cannot be inspected out.
- briefly described what FDA is doing, including a pilot program on joint-inspection inspection with EMA, outreach to industry, shift to real-time monitoring and inspection, and developing a risk model to help the Agency.

### ■ Dr. Sweeney

- called for a network of regulators to tackle the issues of data from MRCT
- International ethical and data quality standards
- reinforced global International clinical development plan addressing common needs and separate medical needs

### ■ Dr. Klein

- informed the audience that Health Canada and FDA have already made a significant attempt to harmonize

# Highlights from DIA MRCT Workshop

## Sessions 1 and 2

### ■ Dr. Marchner

- stated that MRCTs can benefit from considering expected regional differences during study design and documenting these expectations in the analysis plan or design paper

### ■ Dr. Zuckerman

- called on sponsors to think clearly and creatively about what is in the trials for the benefit of patients from ethical and community perspectives.

PANELISTS

**Cynthia GIrman, ScD**

Senior Director, Epidemiology, Merck Research Laboratories

**Ian Marschner, PhD**

Professor, Statistics, Department of Statistics  
Macquarie University, Australia

**Fergus Sweeney, PhD**

Head of Sector, Compliance and Inspections  
European Medicines Agency, European Union

**David L. DeMets, PhD**

Professor of Statistics and Biostatistics  
Chair, Department of Biostatistics and Medical Informatics  
University of Wisconsin

**Mark Paxton, PhD**

Associate Vice President, International Regulatory Affairs  
Pharmaceutical Research and Manufacturers of America (PhRMA)

**Francois Bompert, MD**

Vice President, Medical, Access to Medicines Department  
sanofi-aventis, France

**Agnes V. Klein, MD, DrPH**

Director, Centre for Evaluation of Radiopharmaceuticals  
and Biotherapeutic Products  
Health Canada

**Robert T. O'Neill, PhD**

Director, Office of Biostatistics  
Office of Translational Sciences  
CDER, FDA

# Highlights from DIA MRCT Workshop

## Session 10

- **Dr. Sweeney** was of the view that the issue of data acceptability can be resolved from the regulatory perspective taken into consideration ethical and scientific frameworks. There is a need to carefully think through these as well as the differences in guidelines.
- **Dr. O'Neill** called for:
  - more discussion at the critical stage on what constitutes sources of variability, including an understanding of the knowns and unknowns about trial locations.
  - Noted that clinical trials are now driven by industry, as opposed to past academic drivers (e.g. NIH)

# Highlights from DIA MRCT Workshop

## Session 10

- **Dr. Marschner** called for a guidance on analysis of MRCT.
- **Dr. Klein** called for increased discussion and collaboration among regulators.
- **Dr. Bompert** noted image problem about clinical trials in developing countries and pointed out that addressing the challenges of MRCT can help improve the image.

# Highlights from DIA MRCT Workshop

## Session 10

- **Dr. DeMets** emphasized training.
- **Dr. Girman** urged a increased transparency, more harmonized guidances (e.g., therapeutic guidances), need for progress in finding a rational approach to defining region.
- **Dr. Binkowitz** noted some concrete recommendations from the workshop including
  - quality plan, pre-defining region, the concept of SMART auditing and statistical quality monitoring
- In general - Calls for involvement of academia, funding, improvement in CT infrastructure in the US.

# Highlights from DIA MRCT Workshop

## Session 10

- **Dr. O'Neill (FDA)** stated he wasn't sure if industry was the right group to drive the issue.
  - called for an institution with accountability to lead the effort.
  - noted that FDA has a lot of data in their database that can be explored but need to capture the attention of key stakeholders.
- Mike Ward noted that the APEC model should be examined and that there was a role for ICH.