ICH E17 Multi-Regional Clinical Trials

Dr Carole Légaré
Director, Office of Clinical Trials
Therapeutic Products Directorate
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Acknowledgement

- I would like to acknowledge
  - Robert O’Neil, FDA retiree, and
  - Aloka Chakravarty, FDA (co-authored by Yoshi Uyama and William Wang)

who provided some of the slides
Objectives

• Understand a brief history of how and why E17 was developed
• Review some important concepts from E17
• Discuss the Canadian perspective on implementation of E17
• Discuss the challenges relating to Multi-Regional Clinical Trials (MRCTs) from a regulatory perspective
International Council for Harmonization (ICH)

• ICH is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.
ICH E family of guidelines

E8 General Considerations for Clinical Trials

Design and analysis:
- E4 Dose-Response Studies
- E9 Statistical Principles for Clinical Trials
- E10 Choice of Control Group in Clinical Trials
- E17 Multi-Regional Clinical Trials

Conduct and reporting:
- E3 Clinical Study Reports
- E6 Good Clinical Practice

Safety reporting:
- E1 Clinical Safety for Drugs used in Long-Term Treatment
- E2A - E2F Pharmacovigilance
- E14 Clinical Evaluation of QT
- E19 Safety Data Collection

Populations:
- E5 Ethnic Factors
- E7 Clinical Trials in Geriatric Population
- E11-E11A Clinical Trials in Pediatric Population
- E12 Clinical Evaluation by Therapeutic Category

Genetics/Genomics:
- E15 Definitions in Pharmacogenetics/Pharmacogenomics
- E16 Qualification of Genomic Biomarkers
- E18 Genomic Sampling
The challenge

“To design product development programs that will meet the needs of health authorities around the world.”

Canada is the number two or three location globally for clinical trials of major pharmaceutical companies

Source: Girman, CJ and B Binkowitz Regulatory perspectives: different requirement/endpoints and needs for harmonization in MRCT for simultaneous global new drug development 2016
History of E17

ICH E5: Ethnic Factors in the Acceptability of Foreign Clinical Data

• Published in February 1998
• Addresses the intrinsic and extrinsic factors that could affect the results of clinical studies carried out in regions
• Established a framework for acceptance of foreign data (“bridging study”)

# ICH E5: Classification of Intrinsic and Extrinsic Ethnic Factors

<table>
<thead>
<tr>
<th>INTRINSIC</th>
<th>EXTRINSIC</th>
</tr>
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<tbody>
<tr>
<td>Genetic</td>
<td>Environmental</td>
</tr>
<tr>
<td>Physiological and Pathological Conditions</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Climate</td>
</tr>
<tr>
<td>(children-elderly)</td>
<td>Sunlight</td>
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<tr>
<td>Liver</td>
<td>Pollution</td>
</tr>
<tr>
<td>Kidney</td>
<td>Culture</td>
</tr>
<tr>
<td>Cardiovascular functions</td>
<td>Socioeconomic factors</td>
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<tr>
<td>Genetic polymorphism</td>
<td>Educational status</td>
</tr>
<tr>
<td>of the drug metabolism</td>
<td>Language</td>
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<tr>
<td>Genetic diseases</td>
<td>Medical practice</td>
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<tr>
<td>Race</td>
<td>Disease definition/Diagnostic</td>
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<tr>
<td>Height</td>
<td>Therapeutic approach</td>
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<td>Bodyweight</td>
<td>Drug compliance</td>
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<tr>
<td>ADME</td>
<td>Regulatory practice/GCP</td>
</tr>
<tr>
<td>Receptor sensitivity</td>
<td>Methodology/Endpoints</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Alcohol</td>
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<tr>
<td>Cannabis</td>
<td></td>
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<tr>
<td>Food habits</td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td></td>
</tr>
</tbody>
</table>

Source: ICH E5, modified by Wang, F.
History of E17

ICH E5 Q&A

• Published in June 2006
• Introduced the concept of MRCT using a common protocol
• General concepts on the interpretation of MRCT evidence
• Did not address planning or design
• Provided a definition for an MRCT:
  – A **multi-regional clinical trial** is a single study under “a common protocol that includes sufficient numbers of patients from each of multiple regions to reach a conclusion about the effect of the drug in all regions.”
Drug development has become a global enterprise in recent years

Multi-regional clinical trials (MRCTs) are conducted to provide data in support of regulatory submissions in different regions, including non-ICH regions

Regulatory agencies often face challenges in evaluating data from MRCTs for drug approval

However, there are currently no harmonized guidelines on designing or conducting MRCTs

An international guideline that harmonizes regulatory expectations about the use of MRCTs for global drug development will be useful to both sponsors and regulators
ICH E17

General Principles for Planning and Design of Multi-Regional Clinical Trials

• Promote conducting MRCT appropriately, especially focusing on scientific issues in planning/designing MRCTs
• Facilitate MRCT data acceptance by multiple regulatory agencies
ICH E17 guideline

ICH HARMONISED TRIPARTITE GUIDELINE

General Principles for Planning and Design of Multi-Regional Clinical Trials E17 (FINAL)

November 16th, 2017

- Started in June 2014
- Draft in June 2016
- Finalized in November 2017
7 Principles of Good MRCT Designs
(Simplified from the ICH E17 Step 4, Nov 2017)

1. Strategic use of MRCTs throughout drug development program

2. The intrinsic/extrinsic factors should be identified/examined early

3. MRCTs are planned under the assumption that the treatment effect applies to the entire target population, where strategic allocation of the sample size to regions allows a proactive evaluation

4. Pre-specified pooling of regions or subpopulations may help provide flexibility in sample size allocation, facilitate the assessment of consistency, and support regulatory decision-making

5. A single primary analysis approach should be planned so that it will be acceptable to all concerned regulatory authorities. A structured exploration to examine the consistency of treatment effects across regions and subpopulations should be planned

6. Ensuring high quality of study design and conduct in all regions is of paramount importance

7. Efficient communication among sponsors and regulatory authorities is encouraged at the planning stage of MRCTs
# Table of Contents of E17

**ICH Harmonised Guideline**

**General Principles for Planning and Design of Multi-Regional Clinical Trials**

E17  
ICH Consensus Guideline

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1.1. Objectives of the Guideline

- With the increasing globalization of drug development, it has become important that data from multi-regional clinical trials (MRCTs) can be accepted by regulatory authorities across regions and countries as the primary source of evidence, to support marketing approval of drugs (medicinal products).

- The purpose of this guideline is to describe general principles for the planning and design of MRCTs with the aim of increasing the acceptability of MRCTs in global regulatory submissions.

- The guideline addresses strategic program issues as well as issues that are specific to the planning and design of confirmatory MRCTs, and it should be used together with other ICH guidelines, including E5, E6, E8, E9, E10, and E18.
The Objectives of the E17 Guideline

1.1. Objectives of the Guideline

With the increasing globalisation of drug development, it has become important that data from multi-regional clinical trials (MRCTs) can be accepted by regulatory authorities across regions and countries as the primary source of evidence, to support marketing approval of drugs (medicinal products). The purpose of this guideline is to describe general principles for the planning and design of MRCTs with the aim of increasing the acceptability of MRCTs in global regulatory submissions. The guideline addresses strategic programme issues as well as issues that are specific to the planning and design of confirmatory MRCTs, and it should be used together with other ICH guidelines, including E5, E6, E8, E9, E10, and E18.
MRCTs and Global Drug Development

1. Independent strategy: Local trials
   - A region
     - PK
     - Exploratory clinical trials
     - Confirmatory clinical trials
     - Regulatory Review
     - Submission*
   - B region
     - PK
     - Exploratory clinical trials
     - Confirmatory clinical trials
     - Regulatory Review
     - Submission*

2. Global strategy: representative example of MRCTs
   - A region
     - Exploratory clinical trials ** Including pharmacology (PK/PD) study
     - Multi Regional Confirmatory Clinical Trials
     - Regulatory Review
     - Submission*
   - B region
     - No delay
     - Regulatory Review

Source: ICH E17
Relevance of ICH E6 (R2) to the planning, design and interpretation of a MRCT

• Planning involves being aware of how it all fits together in terms of assuring quality study data that supports evidentiary standards:
  – Appropriate choice and training of investigators and the site team
  – Understanding the planned protocol, how to implement it, and the consequences in study quality resulting from study conduct
  – Reviewing and evaluating the study results, understanding systematic and chance variation in treatment responses and the impact of biases (unblinding, missing data) on the strength of conclusions and evidentiary support
  – Auditing and inspecting study data for compliance, validity and quality and sources of uncontrolled variability

Source: Robert O’Neil
2.2.1 Pre-consideration of Regional Variability and its Potential Impact on Efficacy and Safety

• At the planning stage, regional variability, the extent to which it can be explained by intrinsic and extrinsic factors, and its potential to influence the study results, should be carefully considered in determining the role MRCTs can play in the drug development strategy.

• The intrinsic and extrinsic factors important to the drug development program should be identified during the planning stage of an MRCT
2.2.2 Subject Selection

• In MRCTs, subject selection should be carefully considered to better understand and possibly mitigate potential sources of regional variability and their impact on trial results.

• Clear and specific inclusion and exclusion criteria, that are acceptable and can be applied across regions, should be included in the protocol.

• To harmonise subject selection, uniform classification and criteria for diagnosis of the disease or definition of the at-risk population should be implemented, such as the use of relevant guidelines for disease definitions.
2.2.3 Selection of Doses for Use in Confirmatory MRCTs

- It is important to execute well-planned early development programs that include PK and/or PK-PD studies of applicable parameters, in order to identify regional differences which may impact dose selection.

- The dose regimens in confirmatory MRCTs (based on data from studies mentioned above) should in principle be the same in all participating ethnic population.

- If earlier trial data show a clear difference in dose-response and/or exposure-response relationships for an ethnic population,
  - it may be appropriate to use a different dosing regimen, provided that the regimen is expected to produce similar therapeutic effects with an acceptable safety margin, and provided it is scientifically justified in the study protocol
  - Prospective careful planning of assessment strategies where different doses are used should be tailored to each case and described in the analysis plans
2.2.4 Choice of Endpoints

- The primary endpoint should be relevant to the target population.
- An ideal clinical trial endpoint is one that is clinically relevant, accepted in medical practice (e.g., by regulatory guidance or professional society guidelines) and sufficiently sensitive and specific to detect the anticipated effect of the treatment.
- The primary endpoint should be acceptable to all concerned regulatory authorities.
- The primary endpoint of MRCTs should be one for which experience is already available in the participating regions.
2.2.5 Sample Size Planning

• The key consideration for sample size planning, is ensuring sufficient sample size to be able to evaluate the overall treatment effect
  – under the assumption that the treatment effect applies to the entire target population, particularly to the regions included in the trial.

• Two additional factors are particularly important in the MRCT setting
  – the size of the treatment effect that is considered clinically relevant to all regions in the trial
  – the expected variability of the primary outcome variables based on combining data across regions.
2.2.5 Sample Size Planning

- The MRCT should be planned to include an evaluation of the consistency of treatment effects among regions, consistency is defined as a lack of clinically relevant differences.

- If clinically relevant differences among regions are observed, then the MRCT provides a unique opportunity for additional learning about the factors that may explain these differences.

- Regional allocation should have a scientific basis (rather than arbitrary targets)
  - should support the evaluation of consistency
  - should provide the information needed to support regulatory decisions
2.2.5 Sample Size Planning
Pooled Region and Pooled Subpopulation

Science based strategic pooling can bring efficiency and knowledge to enable regulatory decision making.

- **Pooled Region**
  - Pooling subjects across geographical regions, countries or regulatory regions based on a commonality of extrinsic and/or intrinsic factors.

- **Pooled Subpopulation**
  - Pooling subsets of the subjects across geographical regions and regulatory jurisdictions, who share one or more key intrinsic or extrinsic factors.
2.2.6 Collecting and Handling of Efficacy and Safety Information

• **Adherence to GCP is critical** for any clinical trial to meet its stated objectives
  – particularly important in an MRCT, because of the coordination required to conduct a trial in diverse geographic regions.

• **Methods of collecting and handling efficacy and safety information** should be standardized across participating regions.

• **It is also important to provide standardised training for investigators and study personnel** in each region
  – before initiating the trial in that region - ensures that the trial objectives are met through standardised implementation of the study protocol.
2.2.8. Selection of Comparators

- The choice of control groups should be considered in the context of the available standard therapies, the adequacy of the evidence to support the chosen design, and ethical considerations.

- Comparators in MRCTs should in principle be the same in all participating regions.

- The justification (including safety considerations) for the use of an unapproved drug should be described in the protocol based on scientific information, treatment guidelines and other relevant documents.
2.2.9. Handling Concomitant Medications

- In general, **drugs used concomitantly** with the investigational drug **should be the same** throughout the regions to the extent possible,
  - but there may be **some differences** in the drugs and/or doses actually used due to variations in medical practices
  - this **could be acceptable** if not expected to substantially impact trial results.

- In circumstances where approved drugs are **combined** with an investigational drug, **the same dosage regimen in all regions should generally be applied**.

- If required by protocol, concomitant medications that are **not approved** in a region should have their use **justified** based on scientific information, treatment guidelines and other relevant documents
Impacts of E17 guideline

• Earlier access to innovative therapies
  – Synchronize clinical drug development across different regions

• Avoid duplication
  – Reduce the need for region specific studies and bridging studies

• Promote international harmonization
  – A globally harmonized approach to drug development should be considered first

• Provide better evidences for drug approval in each region
  – Incorporate latest knowledge and experience from regions into one trial

Source: Robert O’Neil
ICH E17 Future Work Plan
(Based on discussion at the Geneva Meeting)

• Form an E17 Implementation Working Group (IWG)
  – The final concept paper is now under discussion at the management committee of ICH

• Training materials describing practical cases for which E17 guideline apply will facilitate the understanding of contents and promote harmonized implementation of this guideline

• In the process of finalization of the training materials, the necessity of formal Q&As will be discussed.
Types of MRCTs

• Very large trials with objective and semi-objective outcomes, such as cardiovascular / diabetes trials involving thousands of subjects, hundreds of sites, many countries and regions, and multiple categories of subgroups of subjects classified in multiple ways – often long term time to event outcomes

• Mid-size trials of drugs to treat symptomatic outcomes using scoring and rating scales, such as in major depressive disorders, and schizophrenia – maybe more difficult to interpret

• Trials of acute exposure, short term (2 week) outcomes (anti-infectives)

• Prevention vs. treatment trials

• Superiority trials (show a difference), non-inferiority trials (no placebo)  

Source: Robert O’Neil
Explanations for variation in differential treatment effects

- Trial assigned dose does not agree with actual dose taken (TOPCAT)
- A confounding factor is responsible as an effect modifier for the observed differential treatment effects (PLATO)
- Systematic factors that are unmeasured but may be responsible for differential treatment effects – reason unknown (LEADER)
- A statistical chance occurrence, not explained by any observed factors

Source: Robert O’Neil
The PLATO Trial

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and R. for the PLATO Investigators*

Statistics in Biopharmaceutical Research

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/usbr20

Comment: The PLATO Trial Case Study

Joshua Chen a & Hui Quan b
a Merck Research Laboratories, Rahway, NJ, 07026
b Sanofi, Bridgewater, NJ, 08807
Published online: 12 Jun 2013.

Statistics in Biopharmaceutical Research

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/usbr20

Statistical Evaluation and Analysis of Regional Interactions: The PLATO Trial Case Study

Kevin J. Carroll a & Thomas R. Fleming b
a Independent Statistical Consultant, 79 Albany Road, Bramhall, Cheshire, SK7 1NE, UK
b Department of Biostatistics, University of Washington, Seattle, WA
Accepted author version posted online: 25 Mar 2013. Published online: 12 Jun 2013.
The PLATO trial

- Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes
- Ticagrelor is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor P2Y12 that has a more rapid onset and more pronounced platelet inhibition than clopidogrel.
- In patients who have an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non–procedure-related bleeding.

Source: NEJM 2009; 361:1045-1057
# PLATO Trial

<table>
<thead>
<tr>
<th>Region</th>
<th># patients</th>
<th># events Tic</th>
<th># events Clop</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia/Australia</td>
<td>1714</td>
<td>95</td>
<td>116</td>
<td>0.80</td>
</tr>
<tr>
<td>Central/South America</td>
<td>1237</td>
<td>91</td>
<td>104</td>
<td>0.86</td>
</tr>
<tr>
<td>Europe/Africa/Middle East</td>
<td>13859</td>
<td>576</td>
<td>712</td>
<td>0.80</td>
</tr>
<tr>
<td>North America</td>
<td>1814</td>
<td>102</td>
<td>82</td>
<td>1.25</td>
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</table>

The most pronounced initial observation explaining the regional differences in outcome was that of a potential treatment interaction between aspirin (ASA) and study treatment, such that higher-dose aspirin was associated with comparatively unfavorable outcomes for ticagrelor.

Further analyses suggested that US subjects who received ASA 81mg had numerically better outcomes than those on 325mg.

Source: FDA Advisory Committee
Regulation of clinical trials: Division 5 of the *Food and Drug Regulations*

**Two overarching objectives**

- Strengthen protections for human research subjects
- Increase R & D investment in clinical trials in Canada
Canadian situation – clinical trial application review

• Regulations state that a sponsor may not sell or import the drug for a clinical trial if:
  
  – There is insufficient information to assess the risks of the drug or the trial
  – The use of the drug for the purpose of the clinical trial endangers the health of a clinical trial subject or other person
  – The clinical trial is contrary to the best interests of a clinical trial subject
  – The objectives of the clinical trial will not be achieved
Canadian situation - drug review

• In Canada, drug review is focused on:
  – Quality, safety and efficacy of the drug
  – There must be substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended *FDR, C.08.002(2)(h)*

• Acceptance of foreign clinical trial data
  – No requirement for clinical trials to have been conducted in Canada, BUT
  – Trials must have been conducted under GCP (ICH E6)

• Benefits of MRCT for Canada
  – Canada has a diverse population (27% minorities)
Regulatory role in providing advice for MRCT

• The sooner the better
  – Before clinical trial application
    • pre-CTA meeting
  – During clinical trial application
    • Issuance of Information Requests
    • Statistical consult

• Consider:
  – ICH Guidelines
  – *Food and Drug Regulations*
  – Practice guidelines
  – Advice that may have been provided by the FDA or EMA
  – Principles of quality by design
Examples where Canada has requested specific changes to MRCT protocols

• Canadian Product Monograph has stricter approach in terms of:
  – Dose interruption/discontinuation guidance in the presence of a specific health condition
  – Duration of contraception after the last dose

• Insufficient information to support use in a specific population
  – Exclusion of a specific age group
MRCT and global drug development

• More patients available for recruitment
  – And more treatment-naïve patients
• Potential for generalization of findings
• Allows for more rapid access across countries
• Avoids duplication
• Promotes international harmonization
• Builds up capacity and infrastructure globally
Issues/challenges to be considered in decision to run an MRCT

• Clinical
  – Disease epidemiology
  – Intrinsic/extrinsic factors

• Statistical
  – Methods for subgroup analysis
  – Predefining “region”

• Operational
  – Technological standards
  – Translation

• Regulatory
  – Different regulatory requirements
  – Different clinical trial approval times

• Ethical

Clinical issues: Disease epidemiology

• MRCTs best suited for:
  – Rare diseases present globally
  – Common diseases present globally
• Is it the same disease in all regions?
  – Same bacterial/viral strain?
  – Same DNA cancer mutation?
  – Same clinical form?
• Is the disease definition the same in all regions?
• Beyond disease prevalence, need to consider
  – Stage of the disease
  – Previous treatments
Clinical issues: Number of drugs taken by individuals with established cardiovascular or cerebrovascular disease by country economic status

Clinical issues: Healthcare system/ Medical practice

• Is the disease diagnosed and treated in the same way across regions?
  – Different clinical practice guidelines?
  – Can the same comparator be used in all countries?
• Access to the same diagnostic modalities across regions?
  – Especially when sophisticated equipment is needed to monitor a patient
• Applicability of measurement tools across regions?
  – Especially when using “standardized” questionnaires that may be influenced by cultural factors
• Different criteria for hospitalization?
  – Can impact “seriousness” designation of an adverse reaction
Cultural factors

• HIV prevention trial in African women
  – ~90% of women indicated they had not missed a dose of medication
  – Only 30% of plasma samples showed detectable level of the study drug
  – Faced with these results, many women admitted not taking the medication

Source: Saag, MJ  *NEJM* 2015; 372: 564-566
Ethical issues

• “Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).” (ICH E6)

• MRCTs must adhere to the ethical principles of autonomy, beneficence, non-maleficence, justice and clinical equipoise

• Post-trial access to the trial drug
  – Is there a plan to market the drug in the countries where the trial is being conducted?
  – Will participants who responded continue to have access until drug is marketed?

Regulatory issues

• Different time lines for approval of clinical trial applications in different countries

• Regulators may request specific changes in protocol for their jurisdiction

• Ability to inspect foreign trials used to support new drug submission
Design elements

Different healthcare systems may not agree on:

• Primary endpoint to be used to evaluate a patient’s response to a treatment for a specific disease (e.g. patient-reported outcome vs clinical outcome)
• Definition of endpoint
• Appropriate time point to assess the endpoint

Other design elements:

• Non-inferiority margin
• Study design
Selected clinical trial design elements in MRCT

• Consider regional differences and their potential impact

• Study population
  – Clear, specific inclusion/exclusion criteria
  – Uniform criteria for diagnosis of the condition
  – Use of validated tools (e.g. biomarkers)

• Dose selection
  – Explore PK/PD differences across regions before confirmatory trial

Source: ICH E17
Selected clinical trial design elements in MRCT

• Primary endpoints
  – Clinically relevant, accepted in medical practice in all regions
  – Sufficiently sensitive and specific to detect the anticipated effect of the treatment
  – May require precise and uniform definitions

• Selection of comparator
  – Should in principle be the same in all participating regions
  – Based on scientific and other relevant information
  – Should ideally be approved in all participating regions

Source: ICH E17
To what extent would the following differences in regulatory requirements impact the MRCT design?

<table>
<thead>
<tr>
<th>Different requirement</th>
<th>Impact on MRCT</th>
</tr>
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<tbody>
<tr>
<td>Endpoint</td>
<td>Need different hypotheses within protocol; need larger sample size</td>
</tr>
<tr>
<td>Time point for measuring response</td>
<td>Different time points may require different sample size. Cannot unblind and continue unless has a DSMB</td>
</tr>
<tr>
<td>Experimental design- minor differences</td>
<td>Pre-specify in protocol and report by region</td>
</tr>
<tr>
<td>Experimental design- major differences</td>
<td>May need different trials</td>
</tr>
<tr>
<td>Non-inferiority margin</td>
<td>Seek agreement on the most scientifically valid margin or power the trial for the tightest non-inferiority bound</td>
</tr>
</tbody>
</table>

Source: Girman, CJ et al *Drug Information Journal* 2011; 45:587-594
Recommendations to improve MRCT quality

• Ensure adequate training of clinicians and site personnel involved in trials
• Perform regular monitoring of site performance
• Consider central review of all or part of the trial data
• Develop a library of well-studied clinical trial tools (questionnaires, rating scales) whose features in international trials are known
• Increase use of biomarkers to reduce diagnostic heterogeneity in globalized trials
  – Also useful to objectively measure response

Source: Global Clinical Trials for Alzheimer’s disease, 2014, Bairu and Weiner Editors
Reporting of MRCTs

- ICH-E3: Structure and Content of Clinical Study Report

  - “For a multicentre study, where appropriate, data display and analysis of individual centres should be included for critical variables to give a clear picture of the results at each site, especially the larger sites”.

  - “Any extreme or opposite results among centres should be noted and discussed, considering such possibilities as differences in study conduct, patient characteristics, or clinical settings”.


Challenges with interpreting MRCT results

In general, results are consistent between regions. When inconsistencies are observed they may be due to:

- Random variation
- Inaccuracies in diagnosis or stage of disease
- Intrinsic/extrinsic factors
- Inconsistencies in study conduct

Thank you