Clinical Trials: Assessing Safety and Efficacy for a Diverse Population

Panel 2: Participant diversity in clinical trials participants

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12/2/2015
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Disclaimer

The views and opinions expressed in the following slides are those of the individual presenter and are not necessarily representative of Merck & Co., PhRMA, The SCT MRCT Consistency Expert Group, or even my future self.
Multi-Regional Clinical Trials

Outline

- There is much in common between the issues of diversity and MRCTs
- But a MRCT does not automatically include a “diverse” population
- Consistency of effects depends on where you are standing, as does diversity
- Common Solutions (It’s the Design)
Multi-Regional Clinical Trials

What is a MRCT?

A single trial, under a single protocol, conducted in more than 1 region.
What is a Region?
A big area of the planet earth most often defined by geography, to include groups of different countries, often but not always, based on proximity (e.g. a continent or part of a continent).
What is a Region?

World Health Organization Member States are grouped into 6 WHO regions:

African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region.
What is a Region?
A surrogate for something believed to be more homogenous than the overall trial, that we are really interested in, based on intrinsic and extrinsic factors.
Clinical Trials: Assessing Safety and Efficacy for a Diverse Population

Problem statement: Some medical interventions do not have uniform effects across diverse patient populations represented in the United States, and it can be challenging to identify differences in effects across groups. This uncertainty leads to regulatory challenges for approval and monitoring of interventions. The aim of this workshop is to address the scope of potential ethnic/racial subgroup issues based on current evidence and to discuss methodologic approaches to addressing these issues. The workshop will focus on evidence from clinical trials and other data sources to address potential heterogeneity across large and diverse populations.
Problem statement: Some medical interventions do not have uniform effects across diverse patient populations represented multiple regions, and it can be challenging to identify differences in effects across regions. This uncertainty leads to regulatory challenges for approval and monitoring of interventions. One aim of MRCT research is to address the scope of potential ethnic/racial subgroup issues based on current evidence and to discuss methodologic approaches to addressing these issues. Such research focuses on evidence from clinical trials and other data sources to address potential heterogeneity across large and diverse populations.
Regional Differences?

Olanzapine - Schizophrenia in Adolescents and Bipolar I Disorder (Manic or Mixed episodes) in Adolescents. FDA AC, June 9, 2009.
PLATO Trial: Overall result of primary endpoint favored ticagrelor over Clopidogrel (HR=0.84; 95% C.I.=0.77-0.92; p-value=0.0003)

Source: Sponsor presentation at CV and Renal Drugs Ad Comm Meeting July, 2010
Regional Differences?

Psychopharm: naltrexone in Prevention of relapse in recently-detoxified opioid dependent patients

- 1 Russian trial: N=250 (126 Naltrexone, 124 Placebo)
- Are results applicable to the American population?
- A specific FDA Concern (From AdComm):
  - The rate of adverse event reporting was distinctly lower in the Russian study compared to the completed studies in the U.S. .... perhaps due to cultural factors.
  - Type of Opioid dependence appear different (more than twice of heroin use in Russia (US 42.6% vs Russia 88.4%).
Regional Differences?

Psychopharm: naltrexone in Prevention of relapse in recently-detoxified opioid dependent patients

- 1 Russian trial: N=250 (126 Naltrexone, 124 Placebo)
- Are results applicable to the American population?

- FDA’s General Concern (quote from the ADCOMM):
  “… not a data integrity or quality concern, but a concern about whether ethnic factors might render the Russian results inapplicable to the American population in some way. Although the term “ethnic factors” frequently refers to physical or genomic differences, in this case we are primarily concerned with the cultural and societal differences, the differences in the medical care system and the available treatment alternatives, … “.
Multi-Regional Clinical Trials

• In an MRCT, consistency of regional results is in the eye of the beholder
• Similarly, diversity is in the eye of the beholder

• There is a part of this that is subjective, depending on where you are standing
• Goal: make subgroup results less subjective

How do you assess subgroup findings?
The MRCT Expert Group Recommends following Hill’s Principles including:
1. The rule of chance/strength of association
2. The biologic gradient
3. Consistency (internal/external) – internal consistency through visual evidence
4. Confounding
5. Coherence/plausibility.
Multi-Regional Clinical Trials

• A MRCT is conducted under a single protocol.
• Because it is multi-regional, not necessarily “diverse”
• Even if the trial population appears to satisfy local needs for “diversity”, a deeper look may show lack of applicability.
Challenges of subgroup analyses in multinational clinical trials: Experiences from the MERIT-HF trial

Hans Wedel, PhD,a David DeMets,c PhD, Prakash Deedwania, MD, PhD,d Björn Fagerberg, MD, PhD,b Sidney Goldstein, MD,c Stephen Gottlieb, MD,f Ake Hjalmarson, MD, PhD,b John Kjekshus, MD, PhD,g Finn Waagstein, MD, PhD,b and John Wikstrand, MD, PhD,b on behalf of the MERIT-HF Study Group Göteborg, Sweden, Madison, WIs, Fresno, Calif, Detroit, Mich, Baltimore, Md, and Oslo, Norway
## Multi-Regional Clinical Trials

### MERIT-HF trial

*Am Heart J 2001;142:502-11*

**Table I.** Number of randomized patients and some baseline characteristics per country and overall in the 2 randomization groups

<table>
<thead>
<tr>
<th>Country</th>
<th>Meto CR/XL</th>
<th>Plac</th>
<th>Meto CR/XL</th>
<th>Plac</th>
<th>Mean EF</th>
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*EF, Ejection fraction; Meto, metoprolol; Plac, placebo.*
# Multi-Regional Clinical Trials

## MERIT-HF trial

<table>
<thead>
<tr>
<th>Country</th>
<th>On furosemide (%)</th>
<th>Dose of furosemide (mg)</th>
<th>On enalapril (%)</th>
<th>Dose of enalapril (mg)</th>
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<td>65.2</td>
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</table>

ACE, Angiotensin-converting enzyme; Meto, metoprolol; Plac, placebo.
Conclusions Just as we must be extremely cautious in overinterpreting positive effects in subgroups, even those that are predefined, we must also be cautious in focusing on subgroups with an apparent neutral or negative trend. We should examine subgroups to obtain a general sense of consistency, which is clearly the case in MERIT-HF. We should expect some variation of the treatment effect around the overall estimate as we examine a large number of subgroups because of small sample size in subgroups and chance. Thus the best estimate of the treatment effect on total mortality for any subgroup is the estimate of the hazard ratio for the overall trial.
Common Issues between MRCTs and the need for diversity in Clinical Trials:

- What is adequate representation?
- How do you design for multiple regions/diversity?
- How do you analyze for diversity?

Analogous for issues with consistency of subgroups?
Common Issues between MRCTs and the need for diversity in Clinical Trials:

- What is adequate representation?
- How do you design for multiple regions/diversity?
- How do you analyze for diversity? Analogous for issues with consistency of subgroups?
- It all needs to be addressed at the design stage
Multi-Regional Clinical Trials

• What is adequate representation?
• How do you design for multiple regions/diversity?
• How do you analyze for diversity? Analogous for issues with consistency of subgroups?
• Trial Design, for example:
  ➢ I/E criteria
  ➢ Target recruitment, not just choosing sites because of ease of recruitment


Due in print in March 2016, the book “Multi-Regional Clinical Trials for Simultaneous Global New Drug Development”, with many of the MRCT Consistency Expert Group as chapter authors.
Thank you for your attention!