Choosing Estimands in a Clinical trial

Introduction

Rosa Lamarca

38th Annual Conference International Society for Clinical Biostatistics

13th of July 2017
Disclosure statement

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<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>9:30 – 13:00</td>
<td><strong>Session 1: New scientific and regulatory environment</strong></td>
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<td></td>
<td>ICH E9 Addendum</td>
<td>Chair R. Lamarca</td>
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<tr>
<td>9:30 – 9:45</td>
<td>Introduction</td>
<td>R. Lamarca</td>
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<td>9:45 – 12:30</td>
<td>ICH E9 addendum on 'Estimands and Sensitivity Analysis'</td>
<td>R. Hemmings / M. Akacha</td>
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<td>(break 11:00)</td>
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<tr>
<td>12:30 – 13:00</td>
<td>Clinical perspective</td>
<td>E. García</td>
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<td>13:00 – 13:30</td>
<td>Panel discussion</td>
<td>Moderator F. Bretz</td>
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<td>R. Hemmings / M. Akacha/ E. García</td>
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<td>13:30 – 14:30</td>
<td><strong>Lunch</strong></td>
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<td>14:30 – 15:30</td>
<td><strong>Session 2:</strong> Methodological perspectives on the estimand framework</td>
<td>Chair R. Lamarca</td>
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<tr>
<td>14:30 – 15:00</td>
<td>Statistical perspective</td>
<td>J. Roger</td>
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<td>15:00 – 15:30</td>
<td>Causal inference perspective</td>
<td>R. Daniel</td>
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<td>15:30 – 16:00</td>
<td><strong>Session 3:</strong> The new era in clinical research</td>
<td>Moderator F. Bretz</td>
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<tr>
<td>15:30 – 16:00</td>
<td>Panel discussion and Q&amp;A</td>
<td>M. Akacha, F. Bretz, R. Daniel, E. García,</td>
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<tr>
<td></td>
<td>R. Hemmings and J. Roger</td>
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Around 2008, it was further discussed the impact of MISSING DATA on clinical trials research.

**Background**

- **Minimise the percentage of missing data**
  - Robustness
  - Adherence to treatment
  - Less assessments

- **WHO ARE THEY?**
  - Collect post-treatment discontinuation data
  - Time to withdrawal
  - Missing at random

- **Underlying mechanism causing missing data**
  - Study design
  - LOCF

- **Imputation**
  - Patterns of discontinuation
  - Designs with less burden to the patients

- **Sensitivity analysis**

- **Missing completely at random**
  - Causes of discontinuation

- **Missing not at random**
  - Adherence to treatment

- **Missing at random**

- **Minimise the percentage of missing data**

- **Designs with less burden to the patients**
A review of the handling of missing data in clinical trials

Å Powney et al. Trials 2014, 15:237

- Database: MEDLINE (Ovid interface)

- Keywords: longitudinal randomised controlled trial$ or repeated measure$ randomised controlled trial$ or longitudinal RCT$ or the same searches with ‘controlled’ replaced by ‘control’

- published between 2005 to 2012

- written in English

- Exclusion: papers with only binary outcomes and nonhuman participants

Å 100 papers were selected at random due to time constraints
A review of the handling of missing data in clinical trials

<table>
<thead>
<tr>
<th>Primary approach to analysis</th>
<th>Papers</th>
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<tr>
<td>Complete case analysis</td>
<td>32</td>
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<tr>
<td>Mixed models</td>
<td>18</td>
</tr>
<tr>
<td>Simple imputation</td>
<td>14</td>
</tr>
<tr>
<td>LOCF/FOCF/BOCF</td>
<td>9</td>
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<tr>
<td>Average value either side imputed</td>
<td>1</td>
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<tr>
<td>Simple algorithmic-based imputation</td>
<td>1</td>
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<tr>
<td>Mean of other patients values imputed</td>
<td>1</td>
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<tr>
<td>Median values imputed</td>
<td>1</td>
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<tr>
<td>Multiple imputation methods</td>
<td>4</td>
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<tr>
<td>Other non-imputation-based methods(^1)</td>
<td>14</td>
</tr>
<tr>
<td>Exclusion based on amounts/reason of missingness</td>
<td>7</td>
</tr>
<tr>
<td>No missing data</td>
<td>9</td>
</tr>
<tr>
<td>Unclear</td>
<td>3</td>
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32% of papers failed to provide any reasons for patients dropping out

\(^1\) One paper which used a complete case analysis also used simple imputation as a secondary analysis

\(^2\) Comparison of means, for example, t-test, RMANOVA.
Guideline on missing data reviewed

Guideline on missing data in confirmatory clinical trials

The Prevention and Treatment of Missing Data in Clinical Trials
Panel on Handling Missing Data in Clinical Trials; National Research Council
This free PDF was downloaded from: http://www.nap.edu/catalog/12955.html

Panel of experts:
RJA Little, R D'Agostino, K Dickersin, SS Emerson, JT Farrar, C Frangakis, JW Hogan, G Molenberghs, SA Murphy, JD Neaton A Rotnitzky, D Scharfstein, W Shih, JP Siegel, H Stern, M Cohen, and A Gaskin (assistant)
Regulatory actions - 2010

Â Proportion and timing of withdrawals

Â Causes of discontinuation (non-compliance, AE, lack of efficacy, etc.)

Â Collection of data after discontinuation

Â Carry-out different analytical models assuming different withdrawal mechanisms, dissertation about the plausibility of each model

Â Differential pattern as per cause of discontinuation, including a discussion about the hypothesised treatment effect by cause

Â 18 recommendations on missing data from the National Academy of Science
Regulatory actions - 2010
stopped patient follow-up at the time they discontinued the study drug. Thus, any outcome information after the patients were withdrawn, but before the planned end of study follow-up, was not collected. As such, the fundamental intent-to-treat analysis for such trials was not possible, since the data were truncated at the time of drug discontinuation.

patients who prematurely stop a study medication should not be
considered “drop-outs” unless they absolutely refuse permission for the study
to continue to follow them. Ideally, these patients should be retained in the
study for its duration and any subsequent COPD exacerbations should be
attributed to their randomised group.

Aaron SD, Fergusson D, Marks GB, et al. Counting, analysing and reporting exacerbations of COPD in randomised
Inherent in the discussion

- **Missing data**
  - bias, power
  - Retain patients on-treatment

- **ITT principle**
  - preservation of randomisation to secure the statistical inference
  - to keep all randomised subjects in the trial regardless of intercurrent events
  - (i.e discontinuation of IP, rescue medication intake, treatment switching, non compliance)
A new era for clinical trials

A joint global effort

- all regions
- all parties involved (regulators, academia, pharmaceutical industry, etc.)

Aiming to:

- come back to the scientific question of interest
- re-think about the clinical trial framework to reflect clinical practice and behavior of target population
### E9 Statistical Principles for Clinical Trials

**Description:**
The harmonised tripartite Guideline was finalised under Step 4 in February 1998. This biostatistical Guideline describes essential considerations on the design and analysis of clinical trials, especially the "confirmatory" (hypothesis-testing) trials that are the basis for demonstrating effectiveness.

**Finalised Guideline:**
February 1998

**Implementation:**
- **EC, Europe** - Adopted by CPMP, March 1996, issued as CPMP/ICH/363/96
- **MHLW/PMDA, Japan** - Adopted November 1998, PMBS/ELD Notification No. 1047
- **Health Canada, Canada** - Implemented 10 February 2003, File nr. 03-102451-780
- **Swissmedic, Switzerland** - Refer to the press release on Swissmedic, Switzerland's website
Addendum to ICH-E9 (R) Statistical principles for Clinical trials

- Endorsed by the ICH Steering Committee in October 2014

- Provide clarification on E9 and an update on the choice of estimand in clinical trials to describe an agreed framework for planning, conducting and interpreting sensitivity analyses of clinical trial data.

- Focus on statistical principles related to estimands and sensitivity analysis, not on the use or acceptability of specific statistical procedures or methods.

- Primary focus on confirmatory clinical trials.
Addendum to ICH-E9 (R) Statistical principles for Clinical trials

- Step 1 to be moved to Step 2 shortly

**Work plan**

<table>
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<th>Completion Date</th>
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| 2017            | *Step 1 and Step 2a* Finalisation of the Technical Document (draft Addendum) and sign-off by all ICH Parties’ members in the EWG and by the Assembly.  
*Step 2b* Draft Addendum and sign-off by the ICH Regulatory Parties. |
| 2017            | *Step 3 phase* Publish draft Addendum. |
| 2018 - 2019     | *Step 3 phase* Discuss comments received during the public consultation period and consolidate the Draft Addendum. |
| 2018 - 2019     | *Step 3 and Step 4* Finalisation of the Addendum and sign-off by topic leaders of the ICH Regulatory Parties and by the ICH Regulatory Parties. |
ICH-E9 Survey

• e-survey conducted in May/June 2015

• Participants: pharmaceutical companies (56%), academia (21%), contract research organisations (11%), regulatory agencies (6%), medical device (1%) companies and others (4%)

• 23 questions:
  - 4 demographic
  - 4 estimands,
  - 9 handling of missing data in clinical trials
  - 5 sensitivity analyses
  - 1 general comments

ICH-E9 Survey

71% collect data on patients after they stop taking study medication but who have not withdrawn from the trial.

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