Estimands in clinical trials

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ICH-E9(R1) Addendum

E9 Statistical Principles for Clinical Trials

- **E9**
  - **Statistical Principles for Clinical Trials**

- **E9(R1)**
  - **Addendum: Statistical Principles for Clinical Trials**

  **Acting Rapporteur**: Dr. Frank Petavy (EC, Europe)
  **Regulatory Chair**: Dr. Yuki Ando (MHLW/PMDA, Japan)
  **Description**: This topic was endorsed by the ICH Steering Committee in October 2014. An Addendum was proposed to 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. This Addendum is proposed to focus on statistical principles related to estimands and sensitivity analysis, not on the use or acceptability of specific statistical procedures or methods. While a variety of mid-stage and late-stage clinical trials may be in scope, the primary focus of the Addendum will be on confirmatory clinical trials. It will promote harmonised standards on the choice of estimand in clinical trials and describe an agreed framework for planning, conducting and interpreting sensitivity analyses of clinical trial data.

  **Status**: Step 3

- **ANVISA, Brazil** - Deadline for comments by 5 February 2018
- **CFDA, China** - Deadline for comments by 28 February 2018
- **EC, Europe** - Deadline for comments by 28 February 2018
- **FDA, United States** - Deadline for comments by 30 April 2018
- **Health Canada, Canada** - Deadline for comments by 3 January 2018
Historical perspective

2010

• EMA - Guideline on missing data in confirmatory clinical trials
• FDA request to the National Research Council - The prevention and treatment of missing data in clinical trials

2014

• ICH-E9 (R1) Addendum to Statistical Principles in Clinical trials

2019-20

• Final ICH-E9 (R1)

Choosing appropriate estimands and defining sensitivity analysis in clinical trials

Moving away from LOCF to MMRM and MI and extensive sensitivity analyses

FDA request to preserve the ITT principle

Keep subjects in trial even if discontinuation of drug
Historical perspective: Dapagliflozin - 2013

- Primary variable: Change in HbA1c from baseline to 24 weeks
- Analysis population: modified intention to treat
- Data after initiation of rescue medication was considered as missing
- Primary analysis: ANCOVA using LOCF
- Sensitivity analysis: Mixed Model Repeated Measures
- FDA statistical reviewer assessment:

“While FDA has implicitly endorsed LOCF imputation for diabetes trials in the past, there is now more awareness in the statistical community of the limitations of this approach. [...] My preferred analysis simply uses the observed values of patients who were rescued.”
Historical perspective: Dapagliflozin - 2013

The results in the previous paragraph are based on the planned primary analysis, which used last-observation-carried-forward (LOCF) imputation, disregarding observations recorded after any rescue treatment. While FDA has implicitly endorsed LOCF imputation for diabetes trials in the past, there is now more awareness in the statistical community of the limitations of this approach. In particular, the argument has been made that LOCF can be anti-conservative (i.e., it sometimes favors the alternative hypothesis more than other approaches) and the findings from the placebo-controlled studies that I reviewed bear this out.

My preferred analysis simply uses the observed values of patients who were rescued. This approach may seem counterintuitive if one believes that rescue treatment makes the subsequent outcomes less relevant to evaluation of the test agent. It has the virtue, however, of respecting the intent-to-treat principle, in the sense that the analysis is based on the randomized treatment rather than the treatment actually received (i.e., planned treatment plus rescue). I conducted this

I do not believe that sensitivity analysis 3) is appropriate. It is not actually possible to adjust for use of rescue medication in the way that the Applicant desires. The problem is that subjects who received rescue differed from the other subjects in at least two ways. First of all, they experienced the effect of rescue treatment, and this is the effect that one would want adjust for if it were possible. Secondly, they also met glycemic criteria in order to be eligible for rescue. This
Historical perspective: Dapagliflozin - 2013

SPONSOR

• Disregard observations recorded following rescue medication

• Treatment effect of the initially randomized treatments had no patient received rescue medication

FDA

• Include glycemic data post rescue medication

• Compare treatment policies: ‘dapagliflozin plus rescue’ versus ‘control plus rescue’

Source: Statistical review and evaluation. Application number: 202293Orig1s000
Historical perspective: Sarilumab - 2017

- Reviewers agreed that sarilumab had demonstrated efficacy, they disagreed over the statistical method

- How they treated data for patients who started in the placebo arm but switched over to active drug during trial

- The extent of disagreement internally within the statistical and clinical review teams at FDA, and between the agency and the sponsor, that the issue landed on the desk of Center for Drug Evaluation and Research Director

- Results to be included in the label under discussion
Historical perspective: Sarilumab - 2017

SPONSOR:

• Primary variable: change from baseline to week 52 in the van der Heijde modified Total Sharp Score (radiographic progression)

• Placebo data after switching considered as missing
  
  – 55% [of] patients from the placebo treatment arm had crossed over to the sarilumab treatment arm

• Missing data imputed by linear extrapolation
  
  – previously used in RA programs
  – pre-specified in the study protocol and agreed upon method with the agency at end-of-Phase II meeting and in the statistical analysis plan
Historical perspective: Sarilumab - 2017

FDA stats:

• All available observed data, where data from patients in the placebo arm who crossed over to sarilumab would be counted toward the placebo arm

  – results based on linear extrapolation rely on strong and unverifiable scientific assumptions and the use of inappropriate statistical methodology, and more appropriate alternative statistical approaches are available

  – For the latter part of the study, when some placebo-treated patients have crossed over to sarilumab, the comparison is between the same treatments, sarilumab to sarilumab
Historical perspective

ICH-E9 (R1) addendum: motivation

- Insufficient clarity with respect to study objectives and the associated treatment effect parameters
- Not clear connectivity between study objectives, design, conduct, analysis and interpretation
- Misalignment between missing data approaches and estimands of interest: intercurrent events were often approached as a missing data problematic

ICH-E9 (R1) aims to provide a structured framework to align planning, design, conduct, analysis and interpretation of a clinical trial
ICH-E9 (R1) addendum

Objective

Estimand

Main estimator

WHAT to estimate

HOW to estimate

Main estimate

Sensitivity estimator 1

Sensitivity estimator n

Sensitivity estimate 1

Sensitivity estimate n

Source: ICH E9(R1) Technical Document
Estimand: attributes

- Population of interest
- Variable
- How to account for intercurrent events
- Measure of intervention effect, taking into account the potential impact of intercurrent events
- Population level summary for the variable
Intercurrent events: events after randomisation

Patient 1
- ...
  death
- ...
Patient 2
- ...
  Treatment discontinuation
  †
- ...
Patient 3
- ...
- ...
Withdrawal from the study
Patient 4
- ...
  Rescue medication /Treatment switching
  ...
Patient 5
- ...
  Kee replacement
Patient 6
- ...
Randomisation
- ...
1-year
Primary endpoint

Time on study
## Strategies of dealing with intercurrent events (IE)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment policy</td>
<td>- The IE is irrelevant&lt;br&gt;- The value of the variable is used regardless IE</td>
</tr>
<tr>
<td>Composite</td>
<td>- The IE is an individual component of the variable</td>
</tr>
<tr>
<td>Hypothetical</td>
<td>- What would have happened if the IE did not occur</td>
</tr>
<tr>
<td>Principal stratum</td>
<td>- The population of interest is the stratum in which an IE would not occur</td>
</tr>
<tr>
<td>While on treatment</td>
<td>- The response to treatment prior to ICE is of interest&lt;br&gt;- No need to collect data after treatment discontinuation</td>
</tr>
</tbody>
</table>
Treatment policy estimand
The Intercurrent event is irrelevant

Patient 1

Patient 2

Patient 3

Patient 4

Patient 5

Patient 6

death
Treatment discontinuation
Withdrawal from the study
Rescue medication /Treatment switching
Kee replacement
Randomisation

Time on study

Primary endpoint

1-year
Treatment policy estimand
The Intercurrent event is irrelevant

- IE: treatment non-compliance – all assessments are used regardless of not the subject is adherent to the treatment

- Includes the effect of the IE in the treatment effect estimation

- Captures the effect attributable to assignment to the treatment group

  A. All exposed subjects.

  B. Change from baseline to week 52 in HbA1c.

  C. Use of rescue medication is ignored.

  D. Difference in means between the treatment conditions.
Composite estimand
The intercurrent event is a component of the variable

- IE: treatment discontinuation due to lack of efficacy

A. All exposed subjects.
B. A binary response variable indicating a successful response if the change from baseline to week 52 in HbA1c is below 0, and use of rescue medication did not occur.
C. Use of rescue medication is captured through the definition of the endpoint of interest.
D. Odds ratio of a successful response between the treatment conditions.
Composite estimand
The intercurrent event is a component of the variable

• IE: adding asthma medication
• Combined effect of the assigned treatment and the additional medication

• Well-controlled asthma week:

a. **Two or more of the following criteria are fulfilled:**
   • No more than 2 days with a daily asthma symptom score >1
   • No more than 2 days of ‘as needed’ medication use, up to a maximum of 4 occasions per week
   • Morning PEF ≥80% predicted every day

b. **Both of the following criteria are fulfilled:**
   • No night-time awakenings due to asthma
   • No additional inhaled and/or systemic steroid treatment due to asthma
Hypothetical estimand
What would have happened if the intercurrent event did not occur

• Treatment effect when taken as intended in the protocol

• IE: treatment discontinuation - the profile is the same as their counterparts in the same treatment group who had not discontinue

• All the assessment after IE should be considered as missing

• No need to keep patients in the study after the IE
Hypothetical estimand
What would have happened if the intercurrent event did not occur

• It is important that only a minor proportion of the subjects is expected to experience the IE to avoid a large proportion of missing data.

• The impact of the intercurrent event on the endpoint of interest is not important when using this strategy.

• The reason is that the hypothetical strategy leaves out the effect of the intercurrent event.

• is relevant
• because knowing what to expect when patients adhere is important
Hypothetical estimand
What would have happened if the intercurrent event did not occur

• Treatment effect when taken as intended in the protocol

A. All exposed subjects.
B. Change from baseline to week 52 in HbA1c.
C. If use of rescue medication would not occur.
D. Difference in means between the treatment conditions.
FROM “MISSING DATA” TO CAUSAL ESTIMAND

Estimands, Sensitivity Analysis and Missing Data

Ilya Lipkovich, PhD
Eli Lilly and Company

Clinical Biostatistics Symposium
Kyoto, 14 December, 2018
References

• Estimands and Sensitivity Analysis in Clinical Trials ICH E9/R1. Step 2 version dated 16 June 2017
It is coming…
Jornada de Primavera de la Societat Catalana d’Estadística

• 5 de juny a les 9:30 a l’ETSAB

• Inscripcions gratuïtes: https://forms.gle/zdA6h2xtBxwYEgvk8
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