Implementation of the estimand framework: statistical perspectives

Presented by Dr Khadija Rantell
Accredited Statistical Assessor Licencing Division, MHRA
Disclaimer

The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the MHRA.
Regulatory requirements

- For regulatory approval a medicinal product should have therapeutic efficacy and a positive risk-benefit.

- In addition to statistically compelling evidence of efficacy, the magnitude of the benefit should outweigh the harmful treatment effects.
Examples of issues in CT in CNS

- Large drop-out rates
- Non-compliance: treatment discontinuation or switch, changing dosage
- High variable placebo response
- Large amount of missing data
- Heterogenous population
Choice of estimand: key players

- Scientific question of interest
- ESTIMAND
- Consider the need of the stakeholder
Choice of estimand: key players

- Sponsor
- Regulator
- Payers
- Patients/Prescribers

ESTIMAND
Guideline – Alzheimer's disease

Intercurrent events
“events that occur after randomisation and that would affect the interpretation of an outcome variable or preclude its observation” e.g.

- Discontinue treatment
- Initiation of new medication
- Death
- Vascular or cardiac or metabolic events

Strategies

- Treatment policy (e.g. adherence to treatment)
- Hypothetical (e.g. medication changes)
- Composite (e.g. additional symptomatic treatment)
- Principal stratum (e.g. patients who can tolerate treatment for long time)
### Intercurrent events: Strategies

<table>
<thead>
<tr>
<th>Treatment Policy</th>
<th>Hypothetical</th>
<th>Composite</th>
<th>While on treatment</th>
<th>Principal Stratum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment policy for handling treatment adherence is acceptable.</td>
<td>OK to use if ICE not related to treatment, e.g. COVID-19, use of rescue medication for ethical reasons</td>
<td>Dichotomisation of numerical outcome can lead to loss of information.</td>
<td>Not appropriate when ICE is indicative that treatment was no longer going to be of benefit.</td>
<td>Methodologically challenging. But can be considered valuable if defined a priori (e.g. effect in the population who would tolerate treatment).</td>
</tr>
</tbody>
</table>
Common statistical issues

- Role of different analyses
  - Main analysis
  - Sensitivity analyses
  - Supplementary analyses

- Distinguishing missing data from intercurrent events

- Misalignment between analysis method and target estimand

- Misalignment between the analysis method and outcome scale type
Example 1

The Company proposes to provide estimates of the effect of therapy WOW in the absence of rescue medications (hypothetical estimand), using an MMRM model under the missing at random assumption (MAR) applied to the modified intention-to-treat (mITT) population (all randomised subjects who receive at least one dose of study treatment) and with all data subsequent to use of rescue medication deleted.

Analysis ignores the fact that use of rescue medication could be a consequence of lack of efficacy and hence MAR may be challenges.
Example 2

Estimate the effect of treatment **WOW** assuming all patients had continued on randomised treatment until week 26.

Estimand ignores the fact that some patients may not be able to tolerate treatment or need rescue therapy.
Trial objectives : Need more details

Study XX is designed to assess the effect of experimental treatment WOW over control in patients suffering from DD

Study XX is designed to assess the effect of experimental treatment WOW over control in patients suffering from DD on variable V defined/measured/assessed ….after time T from randomisation based on summary measure S, regardless of whether the patient is still on treatment.
Conclusion

- Regulators require robust, unbiased, and unambiguously defined estimates of treatment effect for decision making.

- Reliable and validated outcomes that are relevant to patients must be considered in decision making.

- We all need to improve how we communicate results to all stakeholders, in particular patients and prescribers.

- We need to learn from each other by sharing real examples of estimands from case studies across all therapeutic areas and stages of development for better implementation of the framework.
Let’s discuss together!

We can offer

• Scientific advice
• Regulatory advice
• Broader scope meetings
• Innovation office meetings - innovationoffice@mhra.gov.uk
• Email advice – clintrialhelpline@mhra.gov.uk
• Telephone assistance – 020 3080 6456
Acknowledgement

Ines Reis (MHRA)
James Bell (EIWG)
Thank You
Regulatory aspects of the estimand framework - a medic’s perspective

Dr Joel Raffel, Medical Assessor, MHRA
Speaker Introduction

- Medical Assessor, MHRA, 2018
- PhD – Imperial College London, 2014-2018
  - Outcome measures in multiple sclerosis
- Neurology Registrar, 2013

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Presentation outline

A medic’s perspective…

- General thoughts on the estimand framework

- Examples from neurological disease
General thoughts

Survey of five medical assessors:

1. “I tried to read the guideline, but found the vocabulary confusing. I will probably rely on a statistician when I need it!”

2. “I don’t really fully understand where it fits in… Is it an alternative to PICO?”

3. “I haven’t used it in my assessments yet – some of it seems unnecessarily complicated, and describes what we have been doing for decades.”

4. “I’ve seen an estimand-based analysis and didn’t really trust it - I think it is often safer to just use ITT analysis.”

5. “Once you understand it, it’s very useful….. it can improve the relevance of clinical trial data to real-world efficacy/safety, and can help standardise how we assess.”
1. “I tried to read the guideline, but found the vocabulary confusing. I will probably rely on a statistician when I need it!”

ICH E9 (R1) Glossary:

“A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.”

“A method of analysis to compute an estimate of the estimand using clinical trial data.”

“A numerical value computed by an estimator.”

“What we want to measure”

“Method of analysis”

“Result”

“Intercurrent events” “Principal stratification strategy” “While on treatment strategy” “Population-level summary” “Target of estimation”
2. “I don’t fully understand where it fits in… is it an alternative to PICO?”
3. “I haven’t used it in my assessments yet – some of it seems unnecessarily complicated, and describes what we have been doing for decades.”

A narrative review of estimands in drug development and regulatory evaluation: old wine in new barrels?

M Mitroiu 1 2, K Oude Rengerink 3 4, S Teerenstra 3 5, F Pétavy 6, K C B Roes 3 5
4. I’ve seen an estimand analysis and didn’t really trust it - I think it is often safer to just use ITT analysis.”

ITT analysis:
- statistically significant difference in outcome at 12 weeks.
- Clinical relevance of difference questionable.
5. “Once you understand it, it’s very useful…… it can improve the relevance of clinical trial data to real-world efficacy/safety, and can help standardise how we assess.”
Examples

1. Huntington’s disease
2. Migraine
3. Neuropathic pain
4. Multiple sclerosis
5. Alzheimer’s disease

MY OWN PERSONAL VIEWS. UNINFORMED. NOT AN ASSESSMENT.
Huntington’s disease

- **Withdraw from Treatment**
  - Due to Treatment and/or Disease Progression Related reasons (TDPR) -> Treatment Policy
    - the actual observed “off-treatment” values will be analyzed.

  ![Diagram 1: Withdraw from Treatment due to lack of efficacy](image1)

- Due to Non-Treatment or Disease Progression Related reasons (NTDPR) hypothetical strategy
  - Discard the actual observed “off-treatment” values and imputed by hypothetical values as if patients had continued receiving the study treatment.

  ![Diagram 2: Withdraw from Treatment due to pregnancy](image2)

ICH E9 R1:
"A very different hypothetical scenario might postulate that intercurrent events would not occur, or that different intercurrent events would occur. For example, for a subject that will suffer an adverse event and discontinue treatment, it might be considered whether the same subject would not have the adverse event or could continue treatment in spite of the adverse event. The clinical and regulatory interest of such hypotheticals is limited and would usually depend on a clear understanding of why and how the intercurrent event or its consequences would be expected to be different in clinical practice than in the clinical trial."
# Proposed estimands for ICE in migraine prevention

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<tr>
<th>Intercurrent event</th>
<th>Estimand strategy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of “rescue” medication (e.g. Triptans)</td>
<td>Composite strategy on assessment level, define “failure” for respective study day, i.e. count a migraine day irrespective of occurrence of a migraine attack</td>
<td>Failure on a study day basis</td>
</tr>
<tr>
<td>Use of prohibited medications for migraine</td>
<td>Composite strategy, i.e. define patient as a treatment failure for responder analysis</td>
<td>Failure on a patient level basis or failure on a study day basis used in counting of migraine days.</td>
</tr>
</tbody>
</table>

**Proposed composite strategy:**

*Estimand: The effect of treatment on the chance of seeing a 50% reduction in days with migraine or use of rescue medication, without use of prohibited preventive migraine medication, while remaining in the study*

Proposal taken from slides presented by Mette Krog Josiassen, Lundbeck, and Peter Quarg, Novartis Pharma AG
Proposed estimands for ICE in chronic neuropathic pain

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<td>Use of short term acute “rescue” medication (e.g. Paracetamol)</td>
<td>Hypothetical strategy by collecting the value prior to intake as representative for that day (what if no rescue would have been taken)</td>
<td>Handling on a study day basis</td>
</tr>
<tr>
<td>Use of prohibited medications for neuropathic pain</td>
<td>Composite strategy, i.e. define patient as a treatment failure for responder analysis</td>
<td>Failure on a patient level basis</td>
</tr>
</tbody>
</table>

**Proposed composite strategy:**
**Estimand:** The effect of treatment on the chance of seeing a 50% improvement in average weekly pain levels without starting prohibited pain medication. Patients are required to enter pain levels prior to intake of short acting pain medication on a study day.

Proposal taken from slides presented by Mette Krog Josiassen, Lundbeck, and Peter Quarg, Novartis Pharma AG
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<td>Treatment withdrawal for lack of efficacy</td>
<td>Composite variable or treatment policy strategy</td>
<td>Impute an event or use future information. Keep patients on study</td>
</tr>
<tr>
<td>Treatment withdrawal, not efficacy related</td>
<td>Treatment policy strategy</td>
<td>Use future information. Keep patients on study</td>
</tr>
<tr>
<td>Start of other DMT therapy due to lack of efficacy</td>
<td>Treatment policy strategy (until highly effective DMT would be available)</td>
<td>Since start of other DMT therapy also means treatment withdrawal</td>
</tr>
<tr>
<td>Start of other DMT therapy, not efficacy related</td>
<td>Treatment policy strategy (until highly effective DMT would be available)</td>
<td>Since start of other DMT therapy also means treatment withdrawal</td>
</tr>
<tr>
<td>Death</td>
<td>Composite variable strategy or ignore</td>
<td>Imputation of event. Since number of deaths usually balanced and low in size, simple censoring likely not changing anything (“ignore”)</td>
</tr>
</tbody>
</table>
| Relapse event                                          | - Hypothetical strategy to estimate effect on progression independent of relapses  
- Principle stratum strategy to estimand treatment effect in non-relapsing patients | Progression defined as a worsening of 1 point or 0.5 points on the EDSS scale, required to be confirmed by a second assessment 3 months later |

Proposal taken from slides presented by Hans Ulrich Burger, Nikos Sfikas and Fabian Model. Roche and Novartis, Basel
Alzheimer’s disease

We might assume:

What was observed:

[Diagram showing time vs. response for ITT/treatment policy strategy and "hypothetical" strategy]

Taken from slides presented by Paul Delmar, Roche
Possible Estimands:

- **Treatment policy**: what is the treatment effect, regardless of whether symptomatic medications are taken

- **Hypothetical policy**: what is the treatment effect in the hypothetical scenario where symptomatic medications are not taken
Let’s discuss together!

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