ESTIMAND

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OUTLINE

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  1. The scientific problem
  2. Structured framework

Part II  Estimands
  1. Description of estimands
  2. Construction of estimands

Part III  Case Study
Scope

The ICH E9(R1) Addendum builds on ICH E9:

- i.e. its primary focus is confirmatory clinical trials;
- clarity on treatment effects of interest for regulatory decision making is demanded.

However, the framework is applicable whenever treatment effects are to be estimated and tested:

- in other phases of clinical development, including post-authorisation;
- in clinical trials and in observational studies;
- regardless of therapeutic area or experimental design.
Aims

The addendum aims to improve the planning, design, analysis and interpretation of clinical trials.

• The addendum aims to facilitate dialogue regarding the treatment effects that a clinical trial should address:
  • between disciplines (medics, statisticians etc).
  • between sponsor and regulator.

• Having clarity in the trial objectives when describing the treatment effect of interest at the planning stage should inform better choices about trial design, data collection and statistical analysis.
Aims

The addendum aims to improve the planning, design, analysis and interpretation of clinical trials.

- Without a precise understanding of the treatment effect that is being tested and estimated there is a risk that:
  - trial objectives will lack clarity;
  - statistical analyses will be misaligned to trial objectives
  - the treatment effect reported will be misunderstood.
- Clear trial objectives should be translated into key scientific questions of interest by defining suitable estimands.
- An estimand defines the target of estimation for a particular trial objective (i.e. “what is to be estimated”).
The challenge

• Today’s practice doesn’t address treatment-policy, and perhaps that is ok, but it hasn’t been clear which treatment effect is then being estimated, and estimators violate principles related to randomisation.

• ‘Treatment discontinuation’ has been conflated with ‘Trial discontinuation’. Multiple problems have been labelled as ‘Missing data’.

• Can we answer questions other than treatment-policy whilst maintaining the benefits of randomisation.

• **What attributes need to be specified to define an estimand?**

• **What other questions might be posed?**
Opportunities

Aligning drug developers and regulatory bodies’ expectations for the target treatment effect in advance has the potential to give:

• More meaningful descriptions of treatment effects for licensing and prescribing decisions

• Clinical trials with designs that are aligned to agreed objectives

• Fewer problems with data analysis and inference

• More predictable regulatory assessment procedures
ICH E9(R1)

Addendum presents a **structured framework** to address the problems described:

- How to introduce the estimand into clinical trial planning?
- What attributes are needed to describe an estimand?
- Which strategies are available to frame a scientific question to address intercurrent events?
- How to construct an estimand for a given trial objective?
- Communication through examples.
Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

- The main estimator will be underpinned by certain assumptions.
- To explore the robustness of inferences from the main estimator to deviations from its underlying assumptions, a sensitivity analysis should be conducted, in form of one or more analyses, targeting the same estimand.
Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

- **Trial Objective**
- **Estimand**
- **Main Estimator**
- **Main Estimate**

**Target of estimation = WHAT**

- **Method of estimation = HOW**
- **Sensitivity Estimator 1**
  - **Sensitivity Estimate 1**
- **Sensitivity Estimator 2**
  - **Sensitivity Estimate 2**

**Sensitivity analysis**
A new framework: Basics

Trial Objective

Design

Conduct

Data analysis and interpretation

Clinical Trial

Appropriate estimand will be the main determinant for aspects of trial design, conduct and analysis.

This framework aligns clinical trial planning, design, conduct, and data analysis and interpretation.

- Trial objective \(\rightarrow\) scientific question of interest \(\rightarrow\) estimand.
  - Defines target of estimation (estimand = what is to be estimated).
  - Choice of estimand may impact study design and conduct.
A new framework: Basics

- Description of estimand \(\rightarrow\) selection of method of estimation.
  - Main estimator \(\rightarrow\) estimate of treatment effect.
- Assumptions underpin main estimator
  - Deviations from assumptions \(\rightarrow\) sensitivity analyses;
  - Sensitivity estimators still relate to the same estimand.
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A. Population

Patients targeted by the scientific question

B. Variable (or endpoint)

that is required to address the scientific question (to be obtained for each patient)

C. Intercurrent event

The specification of how to account for intercurrent events to reflect the scientific question of interest

D. Population-level summary for the variable

which provides, as required, a basis for a comparison between treatment conditions
Together these attributes describe the **Estimand** defining the target of estimation.

- **A. Population**
  - Patients targeted by the scientific question

- **B. Variable (or endpoint)**
  - Variable that is required to address the scientific question (to be obtained for each patient)

- **C. Intercurrent event**
  - The specification of how to account for intercurrent events to reflect the scientific question of interest

- **D. Population-level summary for the variable**
  - Population-level summary for the variable which provides, as required, a basis for a comparison between treatment conditions
Description of an estimand

A. Population

Patients targeted by the scientific question

- The population is typically characterised through inclusion/exclusion criteria in the protocol.
- In some cases, a stratum of those patients may be of interest, defined in terms of a potential intercurrent event;
  - for example, the stratum of subjects who would adhere to treatment.
Description of an estimand

B. Variable (or endpoint) that is required to address the scientific question (to be obtained for each patient)

- The variable typically consists of
  - measurements taken: e.g. blood pressure;
  - functions thereof: e.g. change from baseline to one year in HbA1c;
  - quantities related to observed events: e.g. time of death, number of relapses.

- The variable may also include intercurrent events such as discontinuation of intervention.
  - using measurements taken prior to discontinuation (e.g., AUC of HbA1c until discontinuation);
  - Or using composites (e.g., treatment failure defined as non-response or treatment discontinuation).
C. Intercurrent event

The specification of how to account for intercurrent events to reflect the scientific question of interest

- Specify how to account for potential intercurrent events in a way that reflects the scientific question of interest.
- Intercurrent events can present in multiple forms and can affect the interpretation of the variable.
- Clinical trials are often faced with more than one type of intercurrent event.
- The set of intercurrent events for consideration will depend on the specific therapeutic setting and trial objective.
Description of an estimand

D. Population-level summary for the variable

which provides, as required, a basis for a comparison between treatment conditions

• It could be, for example, a mean, a hazard rate or a proportion.

• In case of treatment comparisons, examples are:
  • the difference in mean change from baseline to one year in HbA1c, or
  • the difference or ratio in the proportion of subjects meeting specified criteria, under two different treatment conditions, or
  • hazard ratio or t-year event-rate difference or restricted mean survival time difference
The estimand attributes A through D are inter-related and should not be considered independently (Section A.3.1).
The description of an estimand will not be complete without reflecting how potential intercurrent events are reflected in the scientific question of interest.
Intercurrent events

The description of an estimand will not be complete without specifying how potential intercurrent events are reflected in the scientific question of interest.

- Randomised trials are free from baseline confounding but certain events that occur after randomisation complicate the description and estimation of treatment effects.
- Events may occur that make the relevance, the definition, or even the existence of the primary variable questionable.
- Such events may include: death, treatment discontinuation due to adverse events or lack of efficacy, use of other medicines affecting the outcome, whether specified or prohibited by the protocol.
Strategies for addressing intercurrent events

At least...

5 Strategies

• ... to consider when addressing one or multiple intercurrent events, which can be used alone or in combination

• Several intercurrent events per trial means multiple strategies per estimand

• The relevance of each strategy will depend on the therapeutic and experimental context
How are potential intercurrent events reflected in the scientific question of interest?

Let’s take an example:

Drug X → chronic, non-life-threatening disease

- Response to treatment: monitored monthly (continuous measurement).
- Main scientific question: comparison of Drug X to placebo at month 6 best addressed by a randomised clinical trial.
- Intercurrent events:
  - Use of placebo in the clinical trial is considered ethical but only if provision is made for subjects to discontinue their treatment and switch to rescue medication due to lack of efficacy (after which it is still possible to collect the variable measurements).
  - This is also the case after other intercurrent events such as discontinuation of treatment due to an adverse event, but not for intercurrent events such as death (considered very unlikely in this setting).
1. Treatment policy strategy

- Actual values of the variable regardless of whether the intercurrent event has occurred.
  - May be relevant if a value for the variable is meaningful notwithstanding an intercurrent event.
  - Inference can be complemented by defining an additional estimand and analysis pertaining to the intercurrent event itself.
  - No estimand based on actual values can be properly defined when the actual values do not all exist;
    - In particular, a treatment-policy strategy is meaningless with respect to values of a variable not obtained due to death.
Treatment policy strategy - example

**Estimand:** Difference in means between treatment conditions in the change from baseline to month 6 in the targeted patient population, regardless of whether or not switching to rescue medication had occurred.

*If switch to rescue medication ‘intercurrent event’ occurs...*

**Applying the treatment policy strategy**

Legend:
- End point value has been collected
- Part of patient time course considered
- Intercurrent event ignored
2. Composite strategy

- Modified definition of the variable or the summary measure such that an intercurrent event becomes a component of the outcome.

- Particularly relevant if the intercurrent event is itself the most meaningful outcome that can be observed, e.g.
  - The fact that a patient has died may be much more meaningful than observations before death, and observations after death will not exist;
  - Discontinuations of treatment for lack of efficacy or for AEs may provide meaningful information on the drug effect, even though they do not yield a numerical value for the intended variable.
Composite strategy - example

**Estimand:** The estimand assesses the treatment effect based on a composite variable which combines a clinically meaningful dichotomous change in the designated measurement with the intercurrent event of switching to rescue medication.

**If switch to rescue medication ‘intercurrent event’ occurs...**

**Applying the composite strategy**

Legend:
- End point value has been collected
- Part of patient time course considered
- Part of patient time course not considered
- Intercurrent event as part of the composite variable. Time of intercurrent event marks end of data collection.
3. Hypothetical strategy

- A scenario is envisaged in which the intercurrent event would not occur.
- The value to reflect that scientific question of interest is that which the variable would have taken in the hypothetical scenario defined.
  - For example, when rescue medication must be made available for ethical reasons, a treatment effect of interest might concern the outcomes if rescue medication had not been available.
  - Care is required to precisely describe the hypothetical conditions reflecting the scientific question of interest in the context of the specific trial. For example, the hypothetical condition might usefully address both the use of a rescue medication and adherence to treatment as intercurrent events in order for an estimand to be precisely described.
Hypothetical strategy - example

**Estimand:** The estimand assesses the treatment effect in an alternative, hypothetical setting where rescue medication was not available to subjects.

If switch to rescue medication ‘intercurrent event’ occurs...

- **Applying the hypothetical strategy**

Legend:
- End point value has been collected
- Part of patient time course considered
- No need to collect end point value
- Intercurrent event hypothetically not present

No need to collect an end point value
4. **Principal stratum strategy**

- The target population might be taken to be the principal stratum in which an *intercurrent event would not occur*.

- **Principal stratum**: subset of the broader population who would not experience the intercurrent event.

- The scientific question of interest relates to the treatment effect only within that stratum.
  
  - Effects in principal strata should be clearly distinguished from any type of subgroup or per-protocol analyses where membership is based on the trial data.
Principal stratum strategy - example

**Estimand:** The estimand assesses the treatment effect of the initially randomised treatments in the stratum of the population who would not require rescue medication over a period of 6 months regardless of which treatment arm they were randomised to.

**If switch to rescue medication ‘intercurrent event’ occurs...**

- Patient 1: Switch to rescue medication in the stratum.
- Patient 2: Switch to rescue medication not in the stratum.

**Legend:**
- Green dot: End point value has been collected
- Blue line: Part of patient time course considered
- Orange plus: Intercurrent event expected to occur
- Gray dash: Part of patient time course not considered

**Applying the principal stratum strategy**

- In the stratum: Patient 1
- Not in the stratum: Patient 2
5. While on treatment strategy

- Response to treatment prior to the occurrence of the intercurrent event is of interest.
  - If a variable is measured repeatedly, its values up to the time of the intercurrent event may be considered to account for the intercurrent event, rather than the value at the same fixed timepoint for all subjects.
  - For example, subjects with a terminal illness may discontinue a purely symptomatic treatment because they die, yet the success of the treatment can be measured based on the effect on symptoms before death.
  - Alternatively, subjects might discontinue treatment, and in some circumstances it will be of interest to assess the risk of an adverse drug reaction during the period of adherence.
While on treatment strategy - example

**Estimand:** The estimand assesses the treatment effect of the initially randomised treatments in the stratum of the population who would not require rescue medication over a period of 6 months regardless of which treatment arm they were randomised to.

**If switch to rescue medication ‘intercurrent event’ occurs...**

- **Patient 1**
  - Switch to rescue medication
  - No intercurrent event
  - Treatment complete
  - End point value collected

- **Patient 2**
  - Switch to rescue medication
  - Intercurrent event

**Applying the while on treatment strategy**

- **Patient 1**
  - Switch to rescue medication
  - No intercurrent event
  - Treatment complete

- **Patient 2**
  - Switch to rescue medication
  - End point value collected at the moment when the intercurrent event occurs

**Legend:**
- End point value has been collected
- Part of patient time course considered
- Part of patient time course not considered
- Time of intercurrent event marks end of data collection [merged with green dot]
Different types of intercurrent events within a trial

- In practice, clinical trials will often be faced with more than one type of intercurrent events.
  - These events may be informative about efficacy and safety of a drug, and should not be treated as one homogenous problem;
  - A decision is required which events need to be considered explicitly in the construction of the estimand in order to give a clear understanding of the treatment effect to be estimated.
<table>
<thead>
<tr>
<th>Treatment policy</th>
<th>Composite</th>
<th>Hypothetical</th>
<th>Principal stratum</th>
<th>While on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Population</td>
<td>Defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval</td>
<td></td>
<td>Subjects who would not require rescue medication over a period of 6 months regardless of treatment assignment, within the targeted population defined by inclusion/exclusion criteria</td>
<td>Defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval</td>
</tr>
<tr>
<td>B. Variable</td>
<td>Change from baseline to month 6 in the designated measurement</td>
<td>Binary response variable indicating a successful response at month 6 if the change from baseline to month 6 in the designated measurement is above a pre-specified threshold, and no switching to rescue medication occurred;</td>
<td>Change from baseline to month 6 in the designated measurement</td>
<td>Average of the designated measurements while on randomised treatment</td>
</tr>
<tr>
<td>C. Intercurrent events</td>
<td>Regardless of whether or not switching to rescue medication had occurred</td>
<td>The intercurrent event is captured through the variable definition</td>
<td>Had rescue medication not been made available to subjects prior to month 6</td>
<td>The intercurrent event is captured through the variable definition</td>
</tr>
<tr>
<td>D. Population-level</td>
<td>Difference in variable means between treatment conditions</td>
<td>Difference in response proportions between treatment conditions</td>
<td>Difference in variable means between treatment conditions</td>
<td></td>
</tr>
</tbody>
</table>
The construction of an estimand should be...

- **consequent to the trial objectives** and should precede choices relating to data collection and analytic approaches.

- **clinically interpretable**, in terms of the population and endpoint, but also in terms of the intercurrent events of interest and, finally, the summary measure.

- duly justified **considering the therapeutic setting** and the treatment goals of the intervention, from which the key scientific questions of interest can be derived.

- a **multi-disciplinary undertaking** and should be the subject of discussion between sponsors and regulators.
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Case Study: Alzheimer Long-Term Prevention Trial

Objective:

– To determine superiority of drug vs placebo in slowing cognitive decline in asymptomatic subjects at risk for developing Alzheimer’s dementia.
Potential Intercurrent Events

Considered in this example:

• Treatment discontinuation (Trt DC)
• Study discontinuation (Study DC)
• Missed visits and/or cognitive data collection leading to intermediate missing in efficacy measurements (Inter Missing)
• Initiation of Alzheimer disease therapy (Initiation of ADT)

Other potential intercurrent events (not covered):

• Treatment compliance
• Death
Study Design

Screening

1:1 Randomization

Drug

Placebo

Primary time point

4.5 years (54 months)
Double Blind (DB) Phase

Primary efficacy measure:
cognitive scale collected over time in the DB phase
Estimand 1a

**Population:** as defined by the inclusion-exclusion criteria of the study

**Variable:** change from baseline to Month 54 in the cognitive measure

**Intercurrent events and corresponding strategies:**

<table>
<thead>
<tr>
<th>Estimand</th>
<th>Trt DC</th>
<th>Study DC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Treatment Policy</td>
<td>Hypothetical*</td>
</tr>
</tbody>
</table>

*Need to specify the hypothetical scenario

**Summary measure:** mean treatment difference
Treatment Policy Strategy for Trt DC

• The observed value for the variable of interest is used regardless of whether the subject has discontinued treatment
  • In general, regardless of whether the intercurrent event has occurred
  • Captures the effect attributable to assignment to the treatment group
• Important for many types of studies
• Appropriate estimators?
Hypothetical Scenarios for Study DC

What would have happened if subjects who discontinued the study had instead, after discontinuation, similar efficacy:

- **H-MAR**: as the subjects who did not discontinue the study
  - Treatment completers
  - Retrieved dropout subjects (i.e. subjects who discontinued the treatment but NOT the study)

- **H-Control**: as determined by the control group
  - E.g. Similar efficacy relative to control as at the time of dropout – disease modifying setting

- **H-RD**: as the retrieved dropout subjects
Simulation Investigation:
Assumed Off-Treatment Response

Off-treatment response: Retain mean treatment difference at treatment discontinuation but continue with placebo slope
Estimators to be Evaluated

H-MAR:

- **MMRM** – mixed effect model for repeated measures
- **MAR_DC** – Standard Multiple Imputation (MI) Regression
  - With indicator of treatment discontinuation in the imputation model

H-Control:

- **CIR** – Copy Increment from Reference MI

MISTEP SAS macro developed by James Roger and shared through DIA missing data working group site at [http://www.missingdata.org.uk](http://www.missingdata.org.uk); Figure from O’Kelly & Davis short course at the 2015 ASA Biopharmaceutical Workshop
Estimators to be Evaluated (Continued)

H-RD:

• **RD_SUBSET** – Standard Multiple Imputation (MI) Regression on the subset of subjects who did not complete treatment
  – PROC MI, MONOTONE REGRESSION
  – Treatment indicator in the imputation model

• **RD_TRT** – Stepwise MI with different sets of parameters for each pattern: on and off treatment
  – MISTEP SAS macro developed by James Roger and shared through DIA missing data working group site at [http://www.missingdata.org.uk](http://www.missingdata.org.uk)
Summary - Treatment policy strategy for treatment discontinuation

- On- and off-treatment mean trajectories are expected to be different:
  - MAR models lead to bias
  - Bias improved if MMRM replaced by MI that accounts for treatment discontinuation in the imputation model

- Control-based MI or other type of MI could work very well if off-treatment mean trajectory is understood

- Retrieved dropout (RD) MI analyses:
  - Improvement in bias as compared to MAR models but increase in SE
  - Different RD models give similar results for large %retrieved and availability of data within patterns
  - When low %retrieved, the “right” RD model could improve both bias and the variability

Keep subjects in the study!
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