Estimands in Clinical Trials – An Illustration based on NASH

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Outline

1. Background on estimands and why they are important
2. Illustrative example
3. Estimand framework
4. Estimands in NASH
5. Impact on our work
6. Discussion
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‘Guiding star’ of pharmaceutical statistics

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9

Current Step 4 version

dated 5 February 1998
Draft ICH E9 (R1) – the addendum

ICH E9(R1)

臨床試験のための統計的原則 補遺
臨床試験における estimand と感度分析
（案）

European Medicines Agency
Science Medicines Health

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EMA/CHMP/ICH/436221/2017
Committee for Human Medicinal Products

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials
So what is an estimand?

• An *estimand* precisely defines the treatment effect of interest in a clinical trial

• Some may ask: have we not always done that?

• Our answer is: YES and NO...

• YES: In the context of clinical trials we define the population, endpoint and treatment comparison of interest

• NO: We often do not sufficiently account for the diversity in patient journeys and how they affect the assessment of clinical benefit of the investigational treatment
Diversity in patient journeys

- Some patients may **discontinue the prescribed treatment** due to an adverse reaction
- Some patients may **start alternative treatments** before observing the clinical outcome of interest
- Some patients may **die due to a disease-related cause** before observing the clinical outcome of interest
- Some patients may **die due to causes unrelated to the underlying disease** before observing the clinical outcome of interest

These are all **events** that may themselves be related to the disease or the effects of the treatment...
What is the information inherent to such events?

• Some may reflect a positive or negative effect of the treatment
  – This may not be directly captured through the clinical outcome

• Some may impact the interpretation of the clinical outcome: what caused or contributed to the outcome?
  – E.g. measurements after intake of concomitant medication

• Some may prevent the observation of the outcome
  – E.g. when patients die

All these events happen in clinical practice!
What does that mean for clinical trials?

• In a clinical trial setting, we call such events intercurrent events

• The draft ICH E9/R1 defines intercurrent events as ‘Events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation’

• Intercurrent events raise a critical question:

How to define the treatment effect of interest (‘estimand’) in the study population, for the relevant primary endpoint in the presence of varied intercurrent events?
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Example for illustration

- Randomized, double-blind, placebo-controlled Phase III study
- Compare a biologic Drug X versus Placebo in the treatment of an inflammatory disease
- Clinical measurement of interest: continuous symptom score at Week 52

- Patients are allowed to switch to rescue therapy (essentially Drug X itself) after Week 16 if symptoms do not improve
- Many Placebo patients are expected to switch to Drug X after Week 16
- No fixed rule for switching to rescue therapy
- Patients are followed up beyond switching to Week 52
Trial objectives

Objective according to the protocol:

“To demonstrate that the efficacy of Drug X at Week 52 is superior to Placebo based on the change from baseline in the continuous symptom score.”
Is this objective precise enough?

These events are not captured in the objectives!
Objective leaves room for **ambiguity on the estimand** (the WHAT)

Drug X is superior to Placebo in the situation...

- where we **assign the treatments to patients**, regardless of whether they actually take their assigned treatment or not?
- where all patients remained on the **randomized treatment throughout 52 weeks**?
- where the patients that **switch to rescue therapy are considered treatment failures**?
- where we compare the effect **only in patients that would not switch to rescue therapy** regardless which treatment they are randomized to?
This is more than just a topic to be discussed among statisticians

• In current practice the choice of study design and/or statistical methods often drives (implicitly and unknowingly) which estimand is assessed

• Intercurrent events are often treated as a nuisance which are ‘mislabeled’ as missing data and handled through some statistical approach (the 'HOW')
  – E.g. multiple imputation, last-observation carried forward etc.

• Revision of the ICH E9 was triggered by concerns that we often focus on the HOW rather than on the WHAT (the 'estimand')
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Proposed estimand framework

• New framework ensures alignment between trial objectives, design, protocol language, trial conduct and statistical analyses
  – Health authorities are already adopting the estimand framework

• Need to engage clinical teams, regulators and other stakeholders in estimand discussions during the planning phase of the study

• Estimand choice impacts trial design and conduct
  – E.g. data collection after change of randomized treatment (strategy)
Framework presented in the ICH E9 (R1)

Objective

Estimand

Study design

Statistical analysis

Sensitivity analyses

- Population
- Variable/Endpoint
- Intercurrent events
- Summary measure
Suggested thinking process according to ICH E9 (draft) addendum

A thinking process...

1. Therapeutic setting and intent of treatment determining a trial objective
2. Identify intercurrent events
3. Discuss strategies to address intercurrent events
4. Construct the estimand(s)
5. Align choices on trial design, data collection and method of estimation
6. Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions
7. Document the chosen estimands
Some strategies to address a given intercurrent event

• Treatment policy:
  – Treatment effect regardless of intercurrent event; comes close to the traditional “ITT principle”

• Composite:
  – Treatment effect based on a composite endpoint where the intercurrent event is part of the endpoint, e.g. patients with early discontinuation of treatment are non-responders

• Hypothetical:
  – Treatment effect if the intercurrent event had not occurred

• Principal stratum:
  – Treatment effect in subgroup of patients that would not experience the intercurrent event

• While on treatment:
  – Treatment effect while the intercurrent event did not occur, e.g. while patients do not take any rescue medication
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Estimands and NASH

• Not yet discussed in the scientific community
• No established standards
• Discussions can benefit from applying the structured estimand framework

• In the following, we will focus on a F2-F3 NASH population as an example, and
  – assume that outcome of treatment will be primarily determined by taking a liver biopsy after one year
  – highlight some potential intercurrent events
  – illustrate the impact in a clinical trial setting
  – discuss possible strategies to address intercurrent events
  – ignore the type of summary measure for now
Reminder: Process according to ICH E9 (draft) addendum

A thinking process...

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Exemplary patient journeys

Patient 1: Treatment discontinuation due to lack of effect on surrogates

Patient 2

Patient 3: Patient did not show up anymore

Patient 4: Treatment discontinuation due to adverse events

Patient 5

Patient 6: Treatment discontinuation: patient goes to other doctor because of rumors about better treatment option there

Patient 7: Change of diabetes medication (medical need)

Patient 8: Considerable weight loss (exercise)

TIMELINE

Start of treatment

Outcome (one year)
Example 1: Diabetic medication

- Patient is on stable anti-diabetic medication for several months at start of a NASH treatment (Drug X) but there is a need to change the diabetes medication while being on Drug X due to worsening of diabetes

- Points to consider:
  - Change in anti-diabetic medication is an intercurrent event
  - Anti-diabetic medication may have an effect on liver histology
  - In a clinical trial setting, this can confound the assessment of the effect of an investigational treatment (Drug X) compared to a control treatment: what is the estimand of interest?
Example 1: Potential strategies

• **Treatment policy:**
  – Treatment effect regardless of change in anti-diabetic medication
  – Resulting comparison focuses on the effects of ‘investigational trt + potential change in anti-diabetic meds over one year’ versus ‘control trt + potential change in anti-diabetic meds over one year’
  – If change of anti-diabetic medication has an effect on liver histology the treatment policy effect will be different to a ‘pure/biological’ effect of ‘investigational trt over one year’ versus ‘control trt over one year’

• **Hypothetical:**
  – Treatment effect in the hypothetical scenario where no patient would change anti-diabetic medication over one year
  – May be of little practical interest if anti-diabetic therapy is indeed changed in clinical practice

• **While on original treatment only:**
  – Treatment effect while patients are on stable anti-diabetic medication
  – Using this strategy stands in conflict with the aim of assessing the outcome of treatment by taking a liver biopsy after one year
Example 2: Treatment discontinuation due to medical event

- Patient discontinues NASH treatment because of an adverse event that might be related to treatment

- Points to consider:
  - Treatment discontinuation due to a medical event is an intercurrent event
  - Treatment discontinuation results in a shorter exposure to the treatments of interest which may impact the expected treatment effects on liver histology
  - In a clinical trial setting, this can confound the assessment of the effect of an investigational treatment (Drug X) compared to a control treatment: what is the estimand of interest?
Example 2: Potential strategies

• Treatment policy:
  – Treatment effect regardless of treatment discontinuation
  – Resulting comparison focuses on the effects of ‘investigational trt followed by no trt if investigational trt is discontinued due to medical event over one year’ versus ‘control trt followed by no trt if investigational trt is discontinued due to medical event over one year’
  – Could be reflective of treatment effect to be expected in clinical practice (unless alternative NASH trts are available to patients)

• Composite:
  – Treatment effect based on a composite endpoint where patients with early discontinuation of treatment due to medical event are non-responders
  – Changes the clinical outcome of interest from a liver biopsy endpoint at one year to a composite endpoint

• Hypothetical:
  – Treatment effect in the hypothetical scenario where no patient would discontinue treatment due to a medical event and all patients would take their assigned treatment for one year
  – Unrealistic scenario and may thus be of little practical interest
Construct the estimand

• For each of the intercurrent events, which of the strategies results in an effect that we are interested in?

• Different stakeholders may be interested in different estimands:
  – Regulatory agencies: marketing authorization!
  – Payers: reimbursement!
  – Prescribers!
  – Patients!!

• There are no right or wrong estimands, but in submission trials one estimand may have to be defined as «primary» (with justification)
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Impact of estimand choice on trial design and conduct

• Provides the framework to discuss alternative approaches other than the traditional ITT or ‘treatment policy’ approaches with HAs

• Sample size estimation could be affected by the choice of estimands

• Different choices could have impact on data collection
  – Depending on the strategy being adopted, the importance of collecting the data post IcE is different

• Need to consider the potential intercurrent events and make sure the information is collected accurately and if possible collect reason why data is missing as part of study conduct
Impact of estimand choice on statistical analysis

• Allow for more insight into data limitations and the extent of assumptions

• Will aid more targeted sensitivity analyses (of the methodology applied to the estimand) to ensure robustness of the conclusions being made.

• The best approach for the handling of missing data will be situation-dependent
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What is changing

• A multidisciplinary topic – not just a discussion among statisticians

• Change of mindset – considered upfront when designing the protocol
  – the choice of statistical analyses should not drive the estimand choice

• Early discussions with health authorities (HAs) and other key stakeholders critical to harmonize trial objectives

• Intercurrent events are no longer a nuisance that can be ignored
  – their impact to treatment effect estimate needs to be explicitly discussed

• Increasing requests being received from HAs on estimands

• Terminology
  – Sensitivity analyses: same estimand but different assumptions
  – Supplementary analyses: different estimands
  – Analysis set (e.g. Per-protocol set): may be replaced by estimand language
What is the added value of estimands

• Common language to discuss different perspectives among different stakeholders in a more efficient and effective way

• Better interactions with stakeholders
  – Address the needs of regulators, payers, physicians and patients
  – Covering of different perspectives and scientific questions of interest in a transparent way

• More informed internal decision making

• Better protocol and SAP
  – More transparent about the treatment effect of interest and this is up-front in the protocol.
What are challenges?

• It is challenging to precisely lay out the estimands
  – Many potential intercurrent events in NASH need to be taken into account
  – Limited knowledge on natural history of disease
  – Limited information on the association between intermediate and long-term outcomes
  – Identify the population of interest
    o Histology
    o Phenotypic definition
    o Pharmacogenomics, proteomics, metabolomics, etc.
Panel questions for Liver Forum Discussion on Estimands

• What are the potential intercurrent events for the population of
  – NASH patients with advanced fibrosis F2, F3
  – Compensated cirrhosis due to NASH
  – Decompensated cirrhosis due to NASH

• Should the treatment effect from histological endpoints be adjusted due to the intercurrent events that can be measured?

• If the estimate of treatment effect should be adjusted, given that generally there may be only one post-baseline biopsy prior to evaluation of the endpoints, how should the intercurrent events be accounted for?

• Which estimands are possible and meaningful in a case where the treatment outcome is determined by a (single) follow-up biopsy?
Thank you
References


