Estimands: Are we estimating what we intend to estimate?

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Outline

- Background on estimand framework
- Choice of estimands in clinical trials
- Recent regulatory experience
- Conclusions

Background – 1

- Randomization is cornerstone of clinical drug development
- ICH E9 recommends that statistical analyses of randomized clinical trials ought to include all randomized patients to ensure inference is free from baseline confounding
- However, this may not protect from confounding due to events that occur after randomization, e.g.
  - discontinuation of treatment due to adverse events or lack of efficacy, use of rescue medication, treatment switching, death etc.
- Such events complicate the definition of relevant treatment effects
  - treatment impacts the clinical measurements of interest as well as these post-randomization events

Background – 2

- At present these post-randomization events are dealt with by choices made about data collection and statistical analysis
- Importantly, these choices implicitly define the measure of treatment benefit that will be addressed through the estimation
- There is an increasing awareness that this practice needs to be reversed
  - First, the relevant treatment effect to be estimated, i.e. the **estimand**, should be clearly defined
  - Subsequently, trial design, data collection and statistical analysis approaches that are aligned with the estimand should be selected

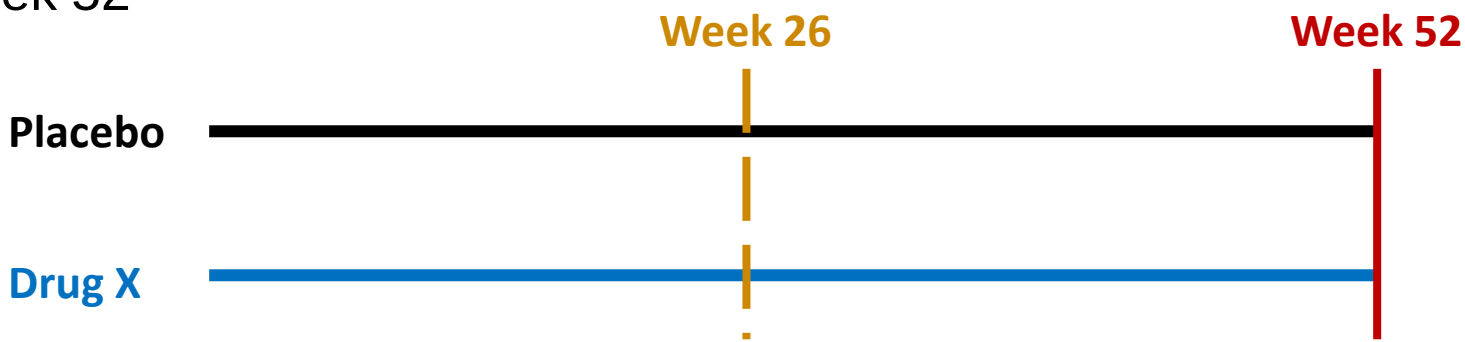
Choice of estimands

- Which estimands are currently of regulatory interest?
- ICH E9 states that the effect of a treatment can be best assessed on the basis of the 'intention to treat a subject' = 'treatment-policy effect'
- An analysis that targets this effect does not require adjustments for post-randomization events, e.g. intake of rescue medication or treatment switching

- Two questions remain:
  - Is the effect of the treatment-policy really always of clinical interest?
  - If not the treatment-policy effect, then what?

Case study for illustration

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



- **Patients are allowed to switch to biologic escape therapy (including Drug X) after week 26 if symptoms are not controlled**
- **Many Placebo patients are expected to switch to Drug X after week 26**
- **No deterministic rule for treatment switching**
- **Patients are followed up beyond treatment switching**

What choice of estimands do we have?

1. Difference in outcomes in all randomized patients regardless of treatment switching

   - Many Placebo patients are expected to switch to Drug X
   - If treatment switching is not taken into account one may end up comparing ‘immediate start of Drug X versus delayed start of Drug X’ $\rightarrow$ deemed to be not clinically meaningful

What choice of estimands do we have?

1. Difference in outcomes in all randomized patients regardless of treatment switching
2. Difference in outcomes in all randomized patients that would have been observed had no patient switched to biologic escape therapy

- May be deemed ‘hypothetical’, however, out of two patients with the same symptoms one may switch while the other one may not switch
- Provides insight into the magnitude of improvement in efficacy that might be achieved with a low proportion of treatment switchers
- An additional assessment of the proportion of treatment switchers is necessary

What choice of estimands do we have?

1. Difference in outcomes in all randomized patients regardless of treatment switching
2. Difference in outcomes in all randomized patients that would have been observed had no patient switched to biologic escape therapy
3. Difference in outcomes in all patients who do not need to switch to biologic escape therapy

   - Addresses effect in a subset of patients - relevant from a clinical perspective
   - Identification of this subset prior to randomization often not possible
   - Estimation may well require causal inference techniques
   - An additional assessment of the proportion of treatment switchers is necessary

What choice of estimands do we have?

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3. Difference in outcomes in all patients who do not need to switch to biologic escape therapy
4. Define an estimand in which patients who switch are considered to have an unfavorable outcome

- How to define ‘unfavorable’ on a continuous scale?
- Is a transition to a dichotomized/ordinal variable necessary? Are cut-offs established in clinical literature?
- Results in a ‘composite estimand’ which may be clinically meaningful – however, a component assessment is important

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4. Define an estimand in which patients who switch are considered to have an unfavorable outcome
5. Define an estimand based on a different endpoint, e.g. continuous symptom score at week 26

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So where do we stand?

- Choice of estimands from a statisticians perspective may be limited to those involving
  - traditional treatment-policy estimand; or
  - composite estimands that incorporate unfavorable events which occur after randomization in the endpoint definition
- Debatable whether these
  - are clinically meaningful
  - provide transparent and relevant information for the label of a treatment
- Some of these challenges could be mitigated by considering different estimands for testing and estimation

Cautionary tale on ‘composite endpoints’

- In discussing the drug label, a regulatory agency was strict in removing all secondary endpoint results despite significant results and multiplicity adjustment

“These results have been removed because of the **challenges in interpreting results at later time points**, such as Week X. The vast majority of patients assigned to placebo crossed over ... prior to Week X. Therefore, for evaluations of binary endpoints in which patients who cross over or up-titrate are considered to be non-responders, it is **difficult to determine whether observed treatment differences ... are due to difference in treatment effects on the outcome of interest or due to differences in the proportions of patients remaining on the initially assigned treatment**.”

- Agreement was reached and the results for an earlier time point will now be included in the label

Tri-partite Estimands
(Akacha, Bretz, Ruberg, SIM 2016)

- Disentangling aspects of non-adherence due to various reasons from the effect on efficacy and safety endpoints in adherers leads to a more transparent and clinically meaningful assessment of the treatment risks and benefits
- We propose three estimand categories
  - For all randomized patients, what percentage of patients discontinues study treatment due to adverse events?
  - For all randomized patients, what percentage of patients discontinues study treatment due to lack of efficacy?
  - For patients who are able to adhere to study treatment for its intended duration, what is the efficacy and safety profile of the experimental treatment?

Need to go beyond intention-to-treat

"A key obstacle in adoption of these complementary methods is a widespread reluctance to accept that overcoming the limitations of intention-to-treat analyses necessitates untestable assumptions.

Embracing these more sophisticated analyses will require a new framework for both the design and conduct of randomized trials."

(Hernan et al., Annals of Medicine, 2013)

Conclusions

- Are we estimating what we intend to estimate?
  - Since the addendum discussions we know better what we are estimating
  - Framework has helped to have early discussions with clinicians and regulators
- Are we estimating what is most clinically meaningful and relevant to all stakeholders involved?
  - ‘Deviations from the treatment-policy estimand should not be taken lightly, but adherence to the intention-to-treat principle should not be done blindly’
  - Separation of testing and estimation may be useful
  - Tri-partite framework offers a transparent alternative framework
- Estimands should primarily be clinically meaningful – involvement of clinical community is needed

John Tukey (1962)

Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise.