Federal Institute
for Drugs
and Medical Devices

Estimands in clinical trials and how they influence trial planning: a regulatory view

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Disclaimer

Views expressed in this presentation are the author's personal views and not necessarily the views of BfArM.

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Estimands and their influence on trial planning: a process chart

Introduction

- Pots-randomization events (e.g. non-adherence, death, …) raise the need to precisely define trial objectives
  → estimands
- Lack of common understanding/agreement of how to handle estimands during drug development
  → ICH Concept Paper on estimands and sensitivity analyses

ICH
harmonisation for better health

Final Concept Paper
E9(R1): Addendum to Statistical Principles for Clinical Trials
on
Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials
dated 22 October 2014
Endorsed by the ICH Steering Committee on 23 October 2014

Estimands and there influence on trial planning

Biostatistics: Analytical Report

DIA DEVELOP INNOVATE ADVANCE

Therapeutic Innovation
& Regulatory Science
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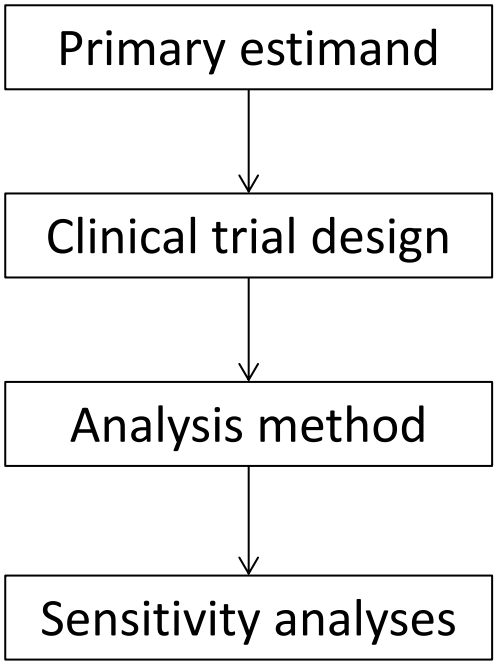
Choosing Appropriate Estimands in Clinical Trials

Ann-Kristin Leuchs, MSc[1], Jörg Zinserling, PhD[1], Andreas Brandt, PhD[1], Dorothee Wirtz, MSc[1], and Norbert Benda, PhD[1]

Abstract

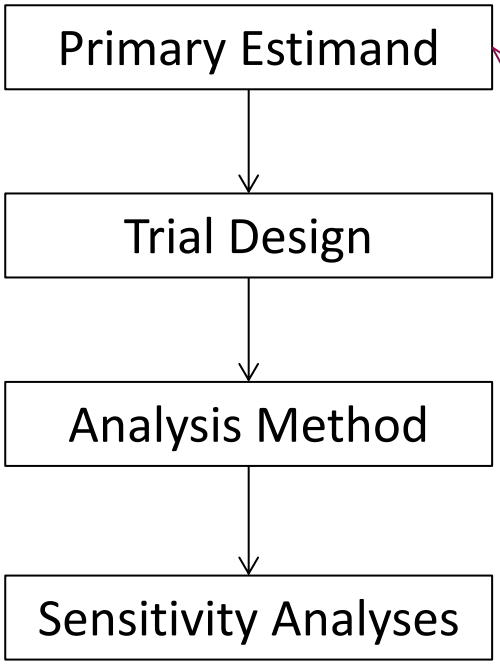
Lack of adherence to study protocol and missing data are often unavoidable in clinical trials, and both increase the need to differentiate between the ideal treatment effect if the medication is taken as directed and the treatment effect in presence of the actual adherence pattern. In this regard, estimands have become the focus of attention. An estimand is simply that which is being estimated. In the context of treatment benefit, an estimand may address either efficacy or effectiveness aspects. Defining the estimand of interest is an essential step to take before deciding on trial design and primary analysis. The choice of estimand has consequences for various other factors to be considered during any clinical trial's planning phase. This study presents a process chart including all aspects to consider during planning. After deciding on the primary

A process chart



Be clear about the trial‘s objective (i.e. primary estimand) before deciding trial design and analysis!

A process chart



Be clear about the trial‘s objective (i.e. primary estimand) before deciding trial design and analysis!

Primary estimand

Choose one specific estimand from a set of different possible de jure and de facto estimands

Primary estimand

- Clinical meaning/relevance
- Scientific question
- Stage of development
- Regulatory aspects
- Different interest of different stakeholders
- …

Primary estimand

- Stage of development (see Mallinckrodt (2013))
    - Early phases: de jure to establish “proof of concept”
    - Later phases: de facto to increase external validity

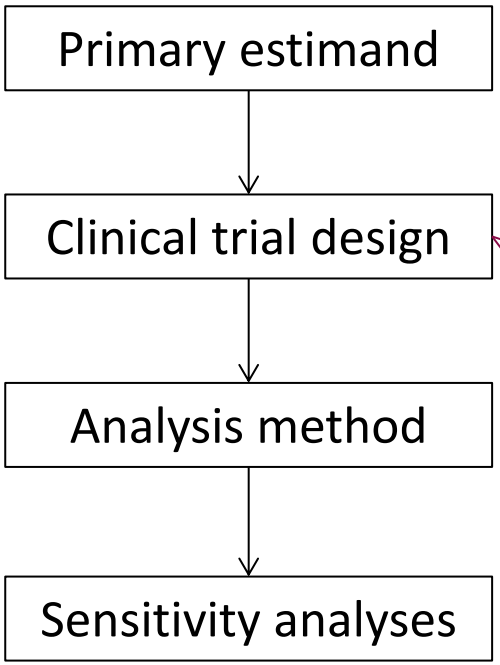
- Different interest of different stakeholders
    - Patients
    - Sponsors
    - Regulators
    - Scientist
    - …

Primary estimand

Regulatory aspects

- Conservatism: not favor the active treatment (see Kenward (2013))
    - Choosing a conservative method to estimate effect
    - Choosing a conservative estimand
- Null hypothesis
  (non-inferiority, equivalence, superiority)
    - e.g. de jure estimand may be preferred in equivalence trials

A process chart



Be clear about the trial‘s objective (i.e. primary estimand) before deciding trial design and analysis!

Clinical trial design

Customize the design considering the choice of primary estimand

Trial design

Examples

- **Data retrieval:** Collecting observations while non-adhering to treatment
  - De jure estimands → Retrieval of data may not be necessary
  - De facto estimands → Usefulness of retrieval depends on estimand
    - Useful for "*difference in all rand. patients*"
    - Useful for "*difference in all rand. patients attributable to initially rand. treatment*" **only if** retrieved patients without any treatment exist
- **Measures to ameliorate adherence** → suitable for de jure

Trial design

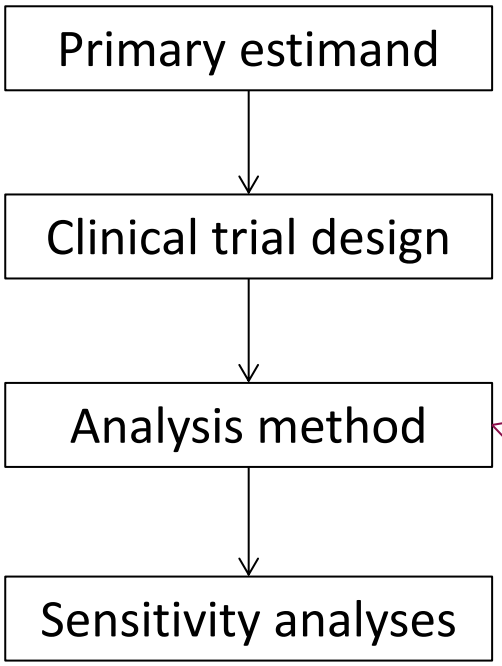
Additional Remarks

→ Retrieval of data can be reasonable irrespective of the estimand to allow assessment of a variety of different estimands

→ Trial designs can limit the choice of estimands

→ Secondary and additional estimands should also influence the trial design

A process chart



Be clear about the trial‘s objective (i.e. primary estimand) before deciding trial design and analysis!

Analysis method

Choose a primary analysis method applicable for the chosen design and explicitly addressing the primary estimand

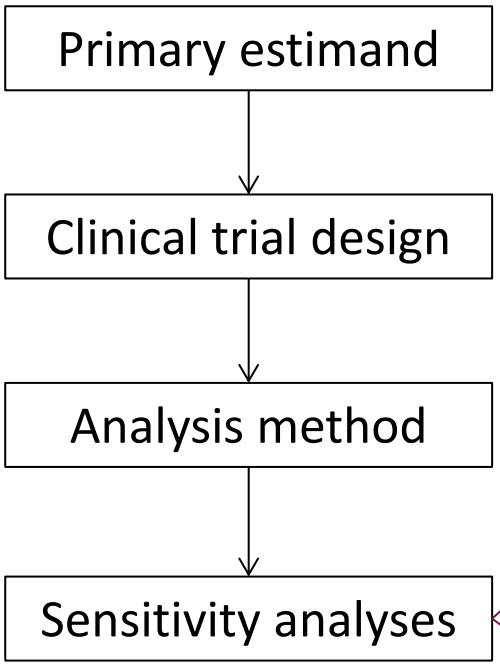
Analysis method

- **Primary analysis** should …
  - … address the primary estimand
  - … preferably be unbiased/consistent
  - … be based on reasonable assumptions

- Depending on the estimand, for example:

  → MAR-based methods (e.g. MMRM)
  → Multiple imputation methods
  → …

A process chart



Be clear about the trial‘s objective (i.e. primary estimand) before deciding trial design and analysis!

Sensitivity analyses

Select a number of different sensitivity analyses

Sensitivity analyses

… to assess the robustness of trial results!

Robustness of the analysis method

Robustness of the primary estimand
→ Robustness with regard to general-izability of trial results

Internal validity

External validity

Sensitivity analyses: internal validity

- Robustness of the estimation
- Analyses addressing the primary estimand but using different sets of assumptions
- A broad spectrum of relevant assumptions should be covered
- Consistent sensitivity analyses increase the trust in the results

Sensitivity analyses: external validity

- Robustness with regard to generalizability of trial results
- Address alternative estimands
- Provide a more complete picture of the treatment under investigation
- Deviating results are expected, since different estimands are addressed
- Could instead be considered as analyses for secondary or exploratory endpoints

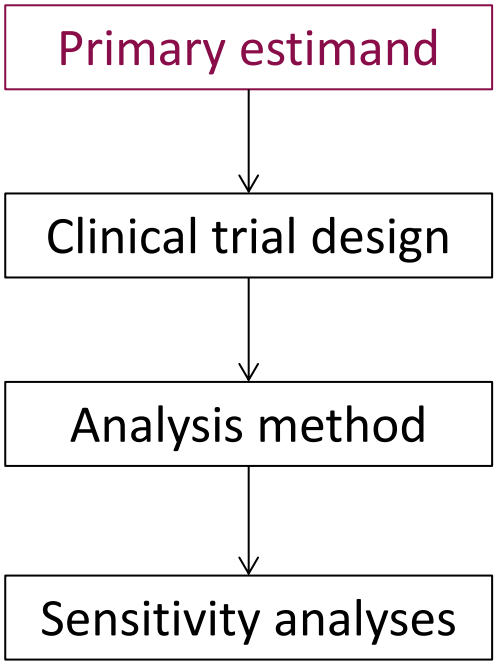
→ Classification not always straightforward!

Summary

- It is essential to differentiate between de jure and de facto objectives/estimands
- Choice of primary estimand should be chosen before deciding on trials design and analysis methods
- Choice of primary estimand and trials design and analysis should be discussed, justified and pre-defined in the protocol

Example:
Applying the process chart

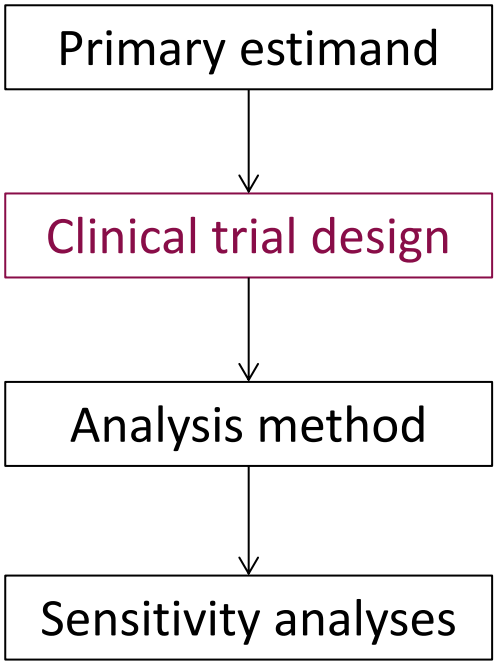
Example



- Acute treatment of depression (6 weeks)
- Longitudinal data (weekly study visits)
- Treatment vs placebo
- Endpoint $HAMD_{17}$
- Some patients will discontinue treatment prematurely

- De jure estimand "difference if all patients adhered"
  - → difference in mean $HAMD_{17}$ change from baseline between treatment and placebo at week 6 if all patients had actually adhered to their treatment

Example

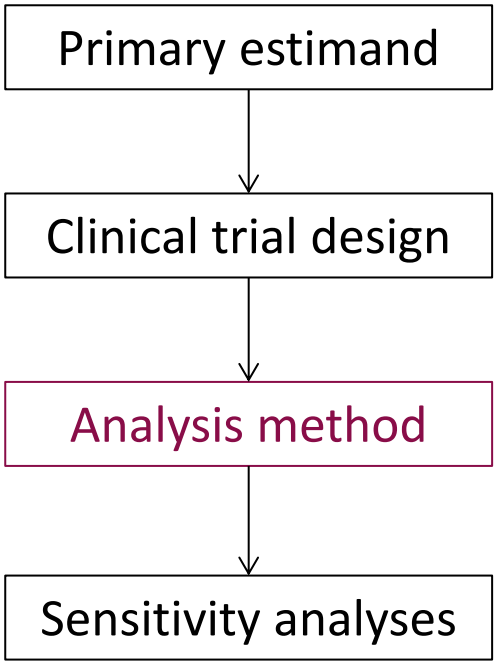


- Acute treatment of depression (6 weeks)
- Longitudinal data (weekly study visits)
- Treatment vs placebo
- Endpoint $HAMD_{17}$
- Some patients discontinued treatment prematurely

- Parallel group trial with measure to maximize adherence to treatment
- Retrieval of data not necessarily needed

- BUT: assessment of de facto estimands is limited

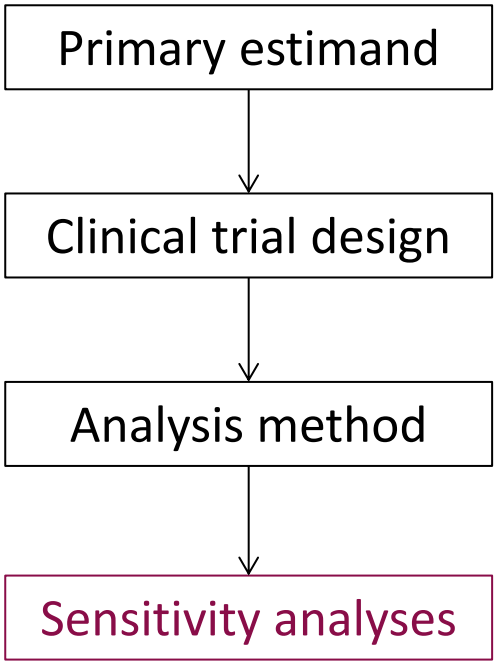
Example



- Acute treatment of depression (6 weeks)
- Longitudinal data (weekly study visits)
- Treatment vs placebo
- Endpoint $HAMD_{17}$
- Some patients discontinued treatment prematurely

- Assuming all data after treatment discontinuation to be missing and to be missing at random, MMRM can be used to estimate the de jure estimand

Example



- Acute treatment of depression (6 weeks)
- Longitudinal data (weekly study visits)
- Treatment vs placebo
- Endpoint $HAMD_{17}$
- Some patients discontinued treatment prematurely

Internal validity

- Assuming data after discontinuation to be missing, evaluate MNAR alternatives using, e.g., delta adjustment

External validity

- pMI to address de facto estimand *"difference in all rand. patients attributable to the initially randomized treatment"*

Comments of the PSI/EFSPI Working Group on Estimands

DIA DEVELOP INNOVATE ADVANCE

Letter to the Editor

Therapeutic Innovation & Regulatory Science
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Choosing Appropriate Estimands in Clinical Trials (Leuchs et al): Letter to the Editor

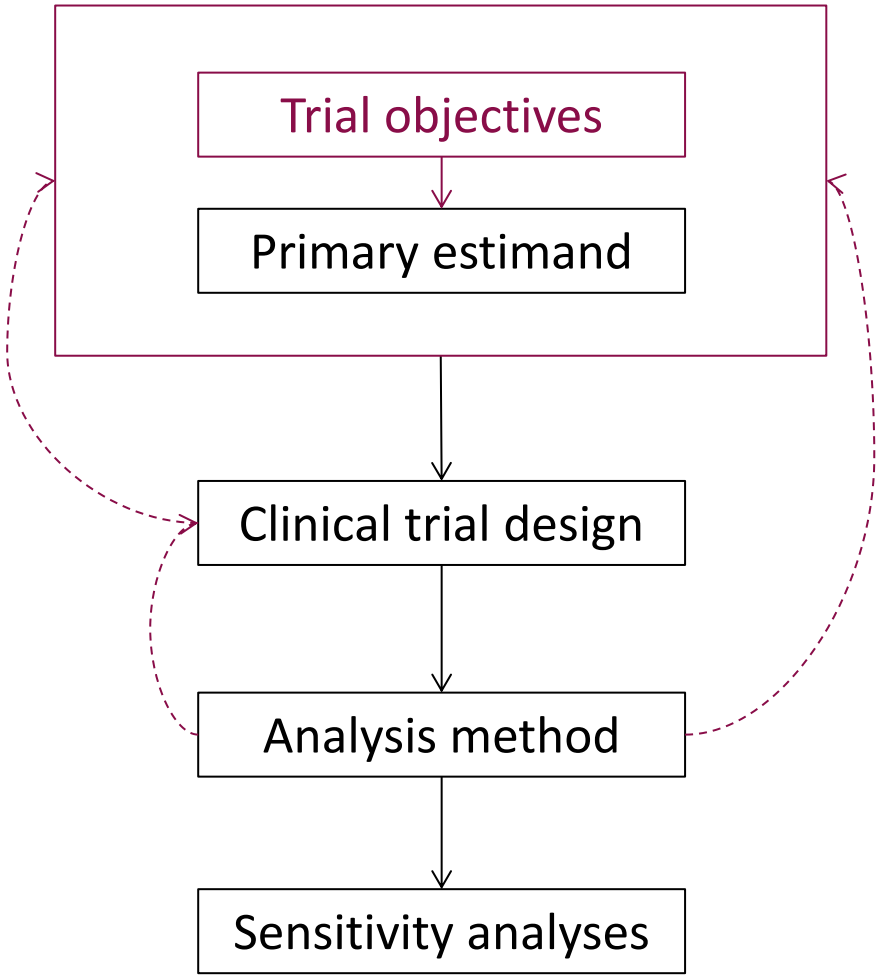
The topic of estimands is an important and relatively new one in clinical development and the paper by Leuchs et al[1] should be commended for its contribution to this subject area. The PSI/EFSPI Working Group (WG) on Estimands finds much to agree with—particularly in the area of sensitivity analyses—and would like to take the opportunity to expand on some areas whilst also highlighting various nuances.

The assessment of the WG is that the trial objectives are a key component in choosing an estimand and that defining these objectives represents an important first step in the process. This augments the Leuchs et al process (Figure 1[1]) to include trial objectives as follows: (1) trial objectives, (2) estimand(s), (3) clinical trial design, (4) method of analysis, and (5) sensitivity analysis. The recent focus on estimands appears to be driven by multiplicity,[4] the WG recommends that clearly defined secondary estimands should also be required to support label claims. More generally, all protocols should include a description as to how each estimand addresses the objectives.

Leuchs et al[1] presented examples of how estimands can be applied to depression and stroke. The WG agrees that shared examples are required to raise awareness and understanding within the scientific community and recommends that future regulatory therapeutic guidelines provide details of specific estimands for specific objectives and designs.

Andrew Garrett, PhD, on behalf of the
PSI/EFSPI Working Group on Estimands
Quintiles, Reading, UK

Comments of the PSI/EFSPI Working Group on Estimands



Iterative process should not lead to estimands with less relevance!

Regulatory experience in scientific advices

Scientific advice: general comment

- Estimands are increasingly addressed in scientific advices
    - By regulators
    - By those seeking advice

- Examples
    - Quality of life in trials with relevant mortality
    - Trials using rescue medication

Scientific advice: QoL and mortality

- Imagine trial with relevant mortality that compares two treatments
- Secondary endpoint: Quality of Life (QoL)

→ Differentiate between missing QoL data prior to and after premature death

→ Death is post-randomization event possibly influenced by treatment

→ Different estimands incorporating death/survival possible

Scientific advice: QoL and mortality

1. Effect in survivors
   - Selected population (post-randomization) → effect may be biased
   - positive overall effect possible despite worse or equal outcome in each patient / subgroup

   → Estimand questionable / should be considered with caution

2. Effect in those who would have survived under both treatment options
   - "Survivor average causal effect (SACE)"
   - Preserves comparability of groups
   - Causal inference methods needed

Scientific advice: QoL and mortality

3. Effect in an "Immortal cohort"
   - Corresponds to de jure estimand
   - Effect if nobody had died (→ but actually some do)
   - "your QoL would be such if you wouldn't die"
   - Questionable, if QoL and death are highly related

4. ITT-kind effect, treating death as worst QoL
   - "Incorporating death into QoL outcome"
   - Different options:
     - Death: QoL = 0 or -100 → arbitrary choice
     - Non-parametric rank analysis:
       → lowest ranks for death patients
       → rank death patients according to survival time
       → rank survivors according to their QoL

Scientific advice: QoL and mortality

5. Effect while alive
   - Use last observation before death
   - Should be accompanied by time to death analysis

Conclusion:

- "ITT-kind estimand"
- Additionally
  - "Effect while alive"
  - "effect in survivors" keeping selection bias in mind

Thank you very much for your attention!

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Scientific advice: rescue medication

(e.g. common in diabetes or pain trials)

- Non-inferiority trial comparing treatment and control while allowing rescue med.
- Endpoint: e.g. HbA1c or pain score

1. De jure: "difference if all patients adhered and did not take rescue medication"
    - Probably the most sensitive estimand

2. De facto: "difference in all randomized patients"
    - Effect of treatment plus rescue medication (and other possible treatment deviations)
    - Follow up of all patients irrespective of rescue medication
    - Is rescue usage in trial comparable to clinical practice?

→ For non-inferiority testing the de jure estimand is preferred → conservative

Scientific advice: rescue medication

(e.g. common in diabetes or pain trials)

- Non-inferiority trial comparing treat. and control while allowing rescue med.
- Endpoint: e.g. HbA1c or pain score

Additional superiority testing:

- De facto estimand should be preferred over de jure estimand due to equalizing effect of rescue
- **BUT:** "difference in all randomized patients" might not be conservative
  - E.g. rescue highly effective and higher rescue rate in active treatment group overcompensates lesser efficacy

- **Alternative:**
  - De facto estimand "difference in all rand. patients attributable to initially rand. treatment"
    - treatment effect is absent after intake of rescue medication

Scientific advice: QoL and mortality

1. Effect in survivors
   - Selected population (post-randomization) → effect may be biased
   - positive overall effect possible despite worse or equal outcome in each patient / subgroup

Subgroup (Prevalence each = 1/3)	Treatment A		Treatment B		
		Mean QoL		Mean QoL	
S1	All die	---	All die	---	A equal to B
S2	All survive	30	All die	---	A better than B
S3	All survive	60	All survive	50	A better than B
Overall		45		50	**"B better than A"**

→ Estimand questionable / should be considered with caution