Federal Institute
for Drugs
and Medical Devices

Disentangling Estimands and the Intention-to-Treat Principle

Ann-Kristin Leuchs

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Disclaimer

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Introduction

- Intention-to-treat (ITT) principle is considered gold standard when analyzing randomized controlled trials (RCT).
- **But:**
  - much ambiguity in definition of ITT in practice
  - ITT often inadequately described or applied
  - ICH E9 is imprecise in defining ITT
- Updated CONSORT statement even recommends to refrain from using the term ITT in favour of precisely stating what has been done

- Draft Addendum to ICH E9 (R1) open for consultation:
  - Ideal time point to solve the ambiguity in ITT definition!?
  - ITT might remain gold standard!?
  - How does the ITT principle fit within the estimand framework?

Contents

1. The intention-to-treat (ITT) principle
   - Ambiguity in ITT definitions and aspects constituting potential ITT definitions
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The intention-to-treat (ITT) principle

Different definitions of ITT

- "Analyzing **all randomized patients** according to their **assigned treatment group**."
  - Excluding patients that did not take study treatment
  - Excluding patients that don't have post baseline values
  - Excluding patients that do not fulfill inclusion/exclusion criteria
  - Specific missing data handling required
  - Analyzing patients according to their treatment received
  - …
- "Analyzing **all randomized patients** according to their **assigned treatment group** and including **complete follow-up data** from all patients."

Aspects that may constitute ITT

(1) Allocation

- Treatment groups are defined by the randomized allocations

(2) Population

- All randomized patients are included

(3) Follow-up and data used for analysis

- Complete follow up of all patients irrespective of any intercurrent events
- All data are included into the analysis

- General agreement that (1) and (2) are part of ITT
- Disagreement exists on whether complete follow up (3) or specific missing data handling is part ITT

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ITT = (1) + (2)

↓

"all patients as allocated"

ITT = (1) + (2) + (3)

↓

- Treatment policy
- ITT conform analysis impossible in case of missing data

Review of methodological articles on ITT (Alshurafa et al., 2012)

- With regard to missing data handling, three different ITT definitions were identified
  - "complete follow-up needed"
    → ITT defined as (1) to (3)
  - "Must or may use specific strategy for missing outcome data"
    → (1) + (2) + specific missing data handling
  - "ITT and missing outcome data are separate issues"
    → (1) + (2)
- Almost 50% of the articles addressing the missing data problem approved of more than one ITT definition

Bradford Hill, 1961

One has to keep *„(…) all patients in the comparison and thus measure the intent to treat a subject in a given way rather than the actual treatmen*t“

→ Assessment of treatment policy (assignment)?!

Bradford Hill, 1961

One has to keep *„(…) all patients in the comparison and thus measure the intent to treat a subject in a given way rather than the actual treatmen*t“

→ Assessment of treatment policy (assignment)?!

Hill’ s example: treatment of lung cancer

- RCT to compare pneumonectomy with radiation
- Radiation possible for every patient randomized to it, surgery only for some
- Endpoint could have been survival: likely to be observed for every patient irrespective of treatment actually received

All randomized patients should be included in the comparison, since by excluding patients from the pneumonectomy arm who have not received surgery, one can no *“(…) longer be sure that one has comparable groups differentiated only by treatment*”.

→Assessing treatment assignment/policy is not the purpose of analyzing ‚*all patients as randomized*‘ but a consequence of having complete data

Reasoning behind ITT

- Randomization to attain comparability of groups
    - Obtain groups that are on average identical with regard to baseline characteristics and potential confounders
      (over all possible randomizations)

- If all subjects are included according to their randomized group, observed differences can be accredited to treatment and causality can be concluded in case of significant differences

- If subjects are excluded form the analysis, observed differences might either be a result of treatment or differences in patient characteristics

Why is there ambiguity in defining ITT?

- ITT introduced long before the extensive discussion of missing data
  - i.e. missing data may not have been considered an issue when ITT was originally defined

- Missing data handling long discussed before handling of intercurrent events (estimands) was widely discussion
  - i.e. precise target of estimation (estimand) was not considered explicitly when choosing missing data handling and analysis

- How to include all patients (i.e. apply ITT) if data of some patients are missing (e.g. due to intercurrent events)?
- How should data collected under treatment deviating behavior be considered when applying ITT?

Why is there ambiguity in defining ITT?

- In the rare case of complete data
  - Easiest way to apply ITT is inclusion of all data of all patients irrespective of any deviations (e.g. intercurrent events)
  - This approach estimates treatment policy estimand

- Due to not distinguishing between intercurrent events, missing data and different conditions under which data are obtained

ITT evolved

from

being a principle to avoid bias and preserve causal assessment

to the idea of

ITT as a principle to address treatment policy!

Proposed ITT definition

ITT	Analyzing **all randomized patients** (population) according to their **randomized treatment allocation**.

- ITT **is** a way to handle selection bias an maintain comparable groups and **guarantees** that like is compared with like
- ITT **is not** intended to provide specific missing data handling and **cannot** handle bias introduced by loss to follow up
- ITT **is not** intended to provide specific handling of intercurrent events and **does not** define a specific estimand

Distinction between ITT, estimands, missing data

Separating estimands, missing data and ITT

Intercurrent events
→ Estimands

Missing data
→ Analysis

Intention-to-treat principle

Separating estimands, missing data and ITT

Intercurrent events
→ Estimands

Prior to planning the study design, analysis …!

- How should intercurrent events be handled?
- What is the **estimand** of interest?
- Definition of estimand independent of availability of data to estimate it

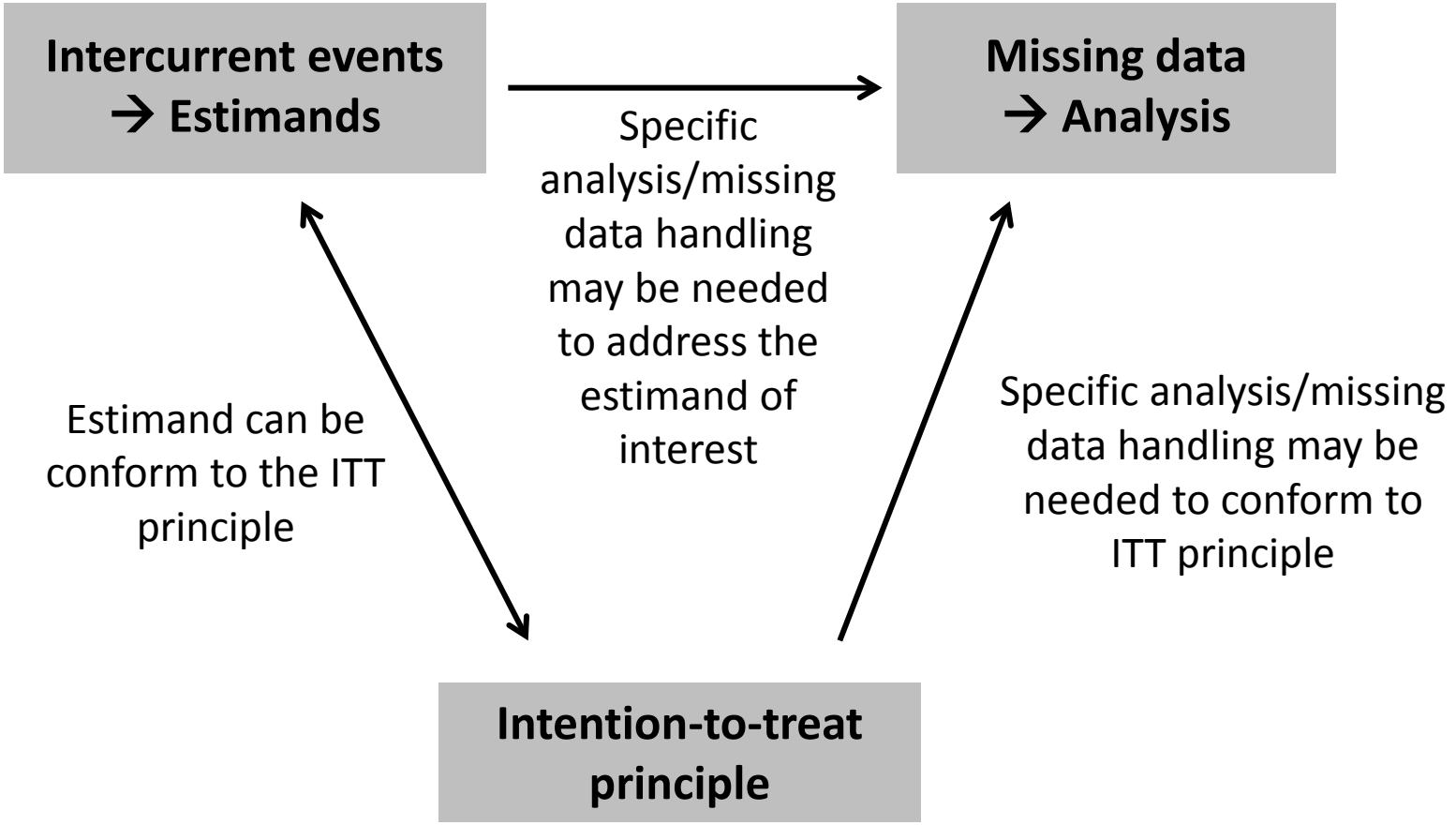
Separating estimands, missing data and ITT

Missing data
→ Analysis

When planning the analysis!

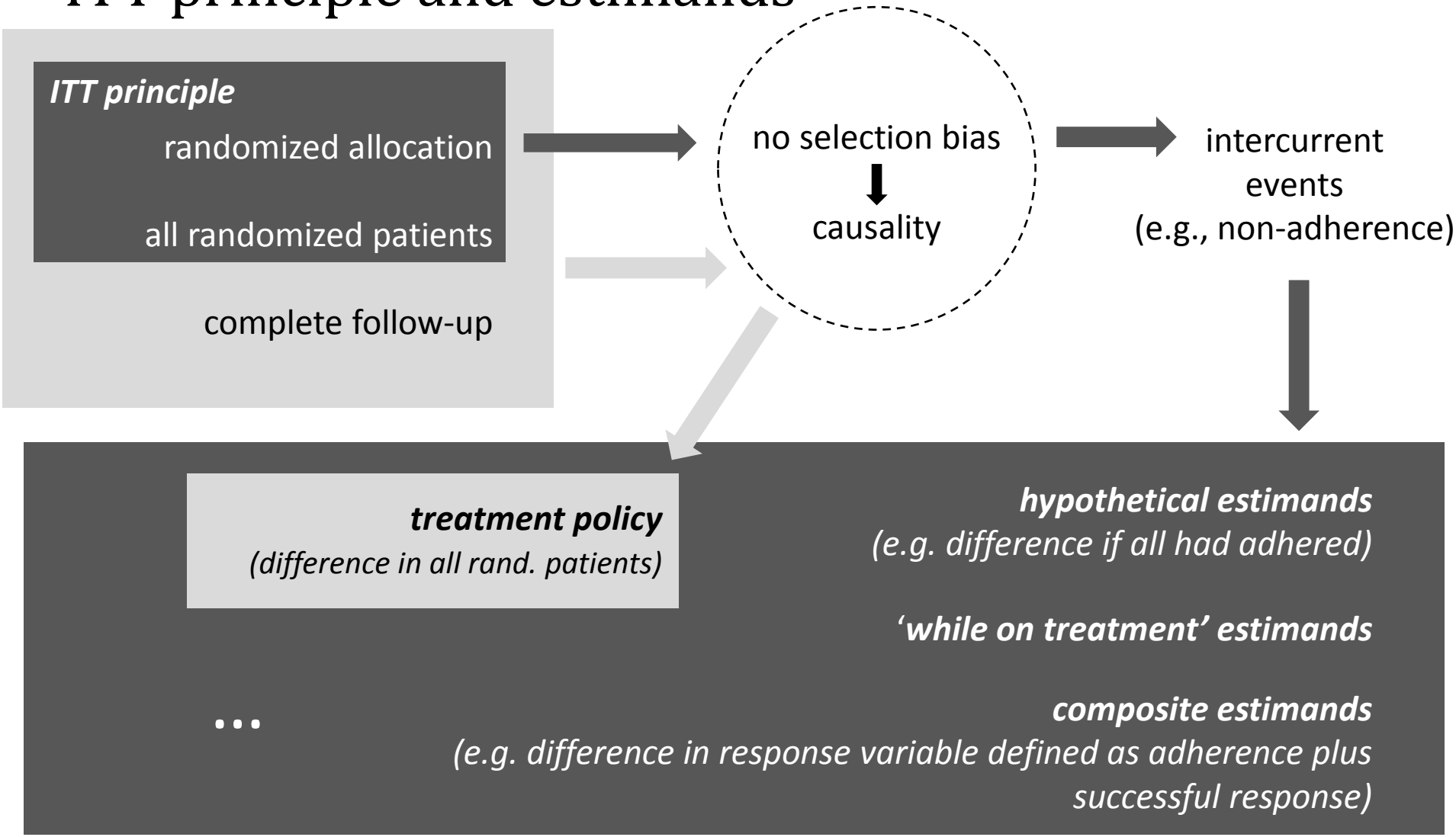
- What data are missing for the chosen estimand?
- How can I still estimate it?
- What assumptions are needed?
- Is the estimation robust with regard to deviations of these assumptions?
- What sensitivity analyses can/should be planned?

Separating estimands, missing data and ITT

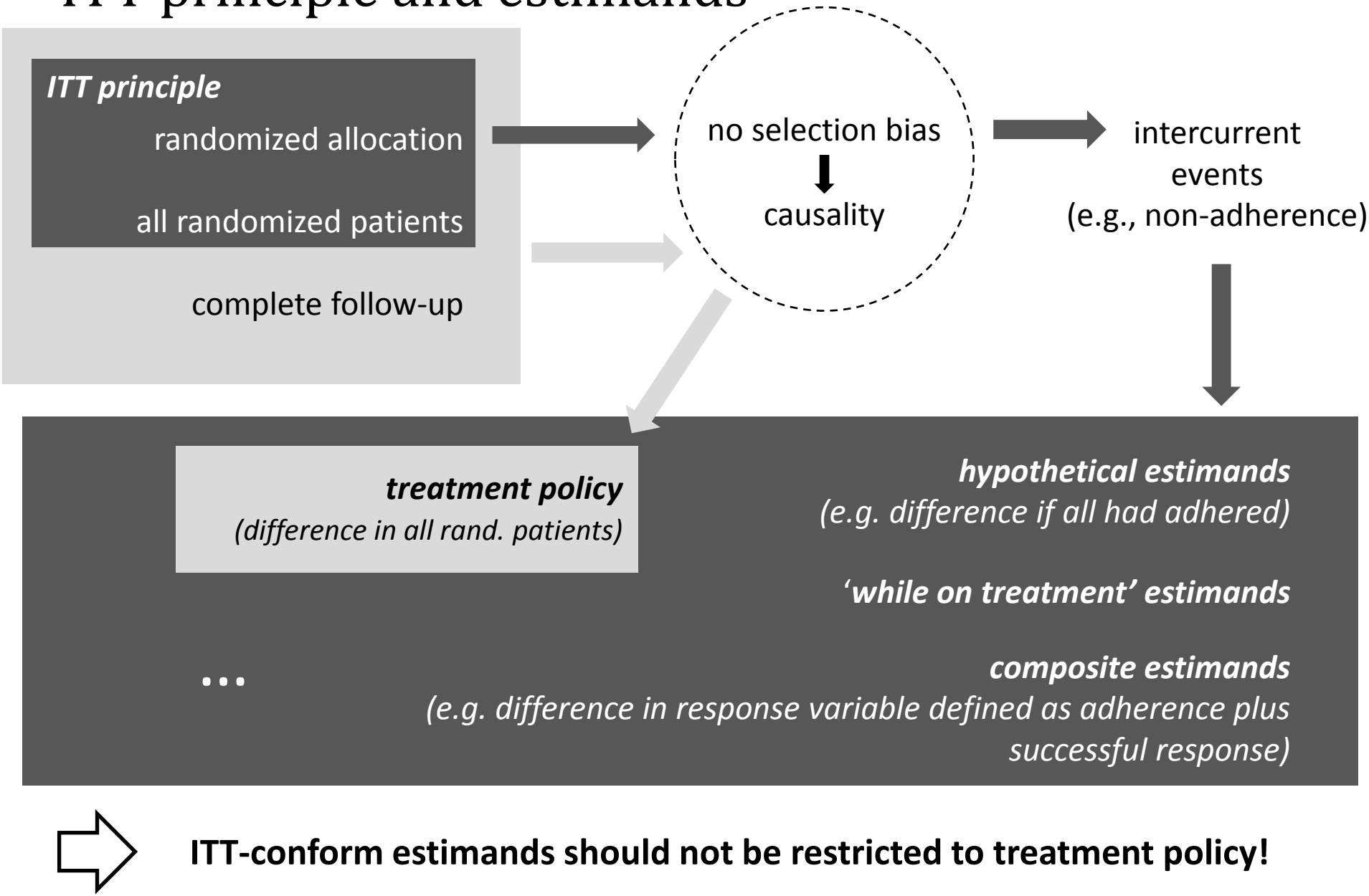


Arguments supporting proposed ITT definition

ITT principle and estimands

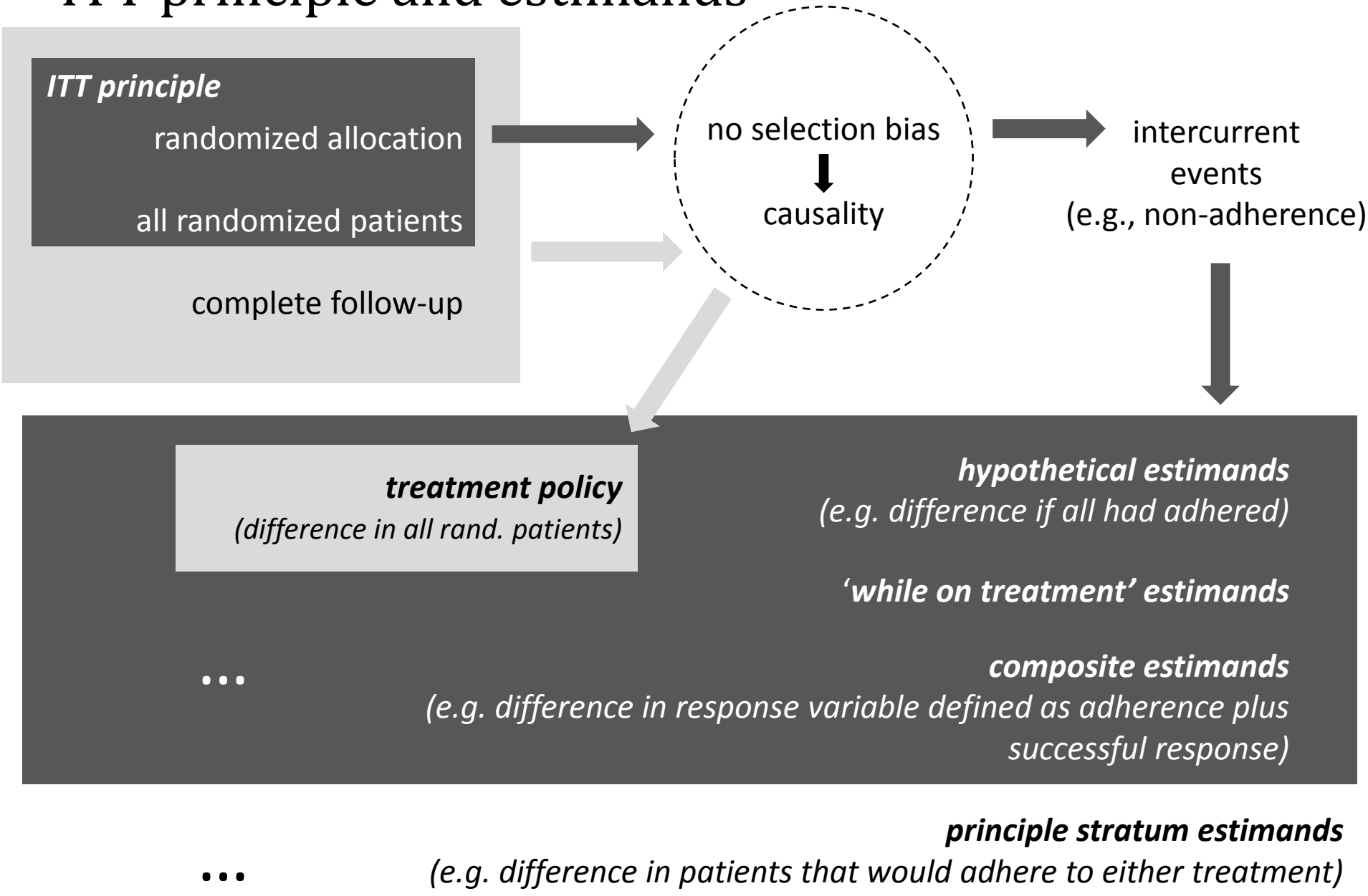


ITT principle and estimands



ITT-conform estimands should not be restricted to treatment policy!

ITT principle and estimands



ITT principle and ICH E9

- ICH E9 recommends following the ITT principle when analyzing RCTs
- Imprecise description and definition of ITT in ICH E9
- Can be interpreted in different ways

"*The **ITT principle implies that the primary analysis method should include all randomized subjects** (…)*" to preserve the initial randomization and prevent bias.

"*The principle that **asserts that the effect of treatment policy can best be assessed by evaluating on the basis of the intention to treat a subject rather than the actual treatment given***."

"Compliance with this principle would **necessitate complete follow-up of all randomized subjects.**"

⇨

- Focus not restricted to treatment policy
- Requiring complete follow up could be a way to avoid missing data problem rather than a request to address treatment policy

ITT principle and ICH E9

- A distinct asset is the clear recommendation of following the ITT principle when analyzing RCTs

⇩

Maintaining this advantage requires

a unique and consistent definition of ITT!

- ITT conform objectives should not be restricted to treatment policy
- A variety of different ITT-conform trial objectives should be allowed

⇩

ITT= “all randomized as allocated”

Per protocol based analyses

- Per protocol set includes all patients that adhere to study protocol
  → Usually defined by all or some of the following aspects:
    - Sufficient adherence to treatment
    - Availability of primary outcome data
    - Absence of major violations of the inclusion/exclusion criteria

- Per protocol analyses try to address the pure effect of study treatment not blurred by treatment deviations
    - i.e. “when taken as directed” → hypothetical estimand
      “if all had adhered”

- Problem:
    - Selection bias: one does not compare like with like!

ITT/treatment policy and PP analyses

ITT addressing treatment policy
(aspects 1 to 3)

PP analyses
(addressing hypothetical estimand)

- Are similar results supportive of robustness?
- Is there a need for the whole estimand framework, since ITT/treatment policy and PP analyses may cover relevant questions?

ITT/treatment policy and PP analyses

ITT addressing treatment policy
(aspects 1 to 3)

PP analyses
(addressing hypothetical estimand)

Are similar results supportive of robustness?

- Considering one specific estimand, both analyses cannot be considered sensitivity analyses of one another
- They do not allow addressing the robustness of estimating a specific estimand
- Similar results support robustness with regard to different handling intercurrent events
  (i.e. influence of different handling of intercurrent events is small)

ITT/treatment policy and PP analyses

ITT addressing treatment policy (aspects 1 to 3)	**PP analyses** (addressing hypothetical estimand)

Is there a need for the whole estimand framework, when ITT/treatment policy and PP analyses cover relevant questions?

- Is PP analysis an appropriate way to estimate a hypothetical question? → No!
  - Selection bias (→ might be reduced by covariate adjustment)
  - One can never be sure that all relevant confounders are covered!
- There are other relevant estimands not covered by ITT/treatment policy and PP.
- PP analysis and ITT (all as randomized) analysis of hypothetical estimand ("if all had adhered") assuming MAR do not always yield similar results

→ITT/treatment policy and PP analysis not sufficient to cover relevant questions

→Instead, different estimands should be considered for ITT-based analysis

Per protocol analysis

- PP analysis has limited use due to potential selection bias
- There is no „PP estimand“
- Often biased for any meaningful estimand

- PP analysis might be considered as a sensitivity analysis for the hypothetical estimand „if all had adhered“
  - Similar results as for “ITT and MAR based analysis” can strengthen ones beliefs in the robustness of results
  - Deviating results might indicate stronger selection issue, question the robustness and raise the need to further evaluate data and different patterns of intercurrent events and missing data

Summary

Summary

ITT = include all randomized patients according to their randomized allocation

- Allow different ITT-conform estimands as primary target of inference
- Maintain the benefit of having one clear statement on how to analyze RCTs
- Shortcomings of PP-based analyses as a replacement of hypothetical estimands

- Proposed definition satisfies Hill‘s original intent of the ITT principle
- ITT principle can be fully implemented also in settings where complete follow up is not achievable
- Complete follow up should nevertheless be pursued to reliably estimate treatment policy which is still relevant in many settings

Thank you very much for your attention!

Contact

Federal Institute for Drugs and Medical Devices
Research Division
Biostatistics and Special Pharmacokinetics
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn
Germany

Contact person
Ann-Kristin Leuchs
Ann-Kristin.Leuchs(at)bfarm.de
www.bfarm.de

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