How to Construct Estimands

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Outline

• When....

• Who....

• How....

• How estimands were constructed for a trial in opiate detoxification – FORWARDS-2
When...

- Clear trial objective
- Estimand
- Study design
- Study conduct
- Statistical analysis = main estimator
- Numerical result = main estimate
Requires understanding trial objective

- Who will use the results and what decision they will make, for example:
  - Policy makers
  - Payers
  - Prescribers
  - Patients
  - Regulators

- Define the general question of interest to the decision maker

- The estimand must align with the decision-maker(s) needs

- Trial may need to address the needs of multiple different stakeholder – leading to multiple objectives and estimands
Who...

- A multi-disciplinary undertaking involving all those normally involved in protocol development:
  - clinicians
  - statisticians
  - other stakeholders
How....

• An *iterative thinking process* where - *in line with objective* - need to:

1. Consider what is clinically relevant for the therapeutic setting
2. Identify plausible intercurrent events
3. Discuss strategies to address intercurrent events
4. Complete specification of all 5 estimand attributes
5. Can derive a reliable estimate for decision making?

*ICH training slides, Ratich et al 2020*
Determine relevant intercurrent events

- List all the **intercurrent events** that are plausible

- Events occurring after randomisation that affect either the interpretation or the existence of patient outcomes, e.g.:
  - use of alternative treatment (rescue/prohibited/subsequent line of therapy ..etc )
  - discontinuation of treatment
  - treatment switching
  - dose alterations
  - terminal events such as death

- Discuss anticipated rates of occurrence
Handling of Intercurrent events

• Specify how to handle intercurrent events:
  
  - treatment policy
  - hypothetical
  - composite
  - while-on-treatment
  - principal stratification

• How to properly handle an event may depend on the underlying reason
  - e.g. different strategies for treatment discontinuation due to AE versus lack of efficacy
Specify 5 attributes

• Clear understanding of the treatment conditions under evaluation

• Where relevant include;
  - doses/dose ranges for the initially randomized treatments
  - background therapies
  - allowable rescue medications
  - prohibited medications

• Clear specification might reflect multiple relevant intercurrent events
Specify 5 attributes

- Complete specification of population/variable

- If relevant some intercurrent events may be reflected in population (principal stratification) or variable (e.g. composite/while-on-treatment)

- Intercurrent events not included in treatment/population/variable clarified under handling of intercurrent event
Specify 5 attributes

- Different **population level summary measure** can give quite different impressions. E.g., HR versus difference in proportions

Kahan et al, 2020, Treatment estimands in clinical trials of patients hospitalised for COVID-19
Specify 5 attributes

- Different **population level summary measure** can give quite different impressions. E.g., HR versus difference in proportions

\[ \text{Difference in proportion of deaths @ 28 days} = 0\% \]

\[ \text{HR} = 0.9 \]

Kahan et al, 2020, *Treatment estimands in clinical trials of patients hospitalised for COVID-19*
Specify 5 attributes

- For **odds ratios/hazard ratios** conditioning on a covariate in the analysis changes the very nature of the treatment effect being estimated (the estimand)

- Due to non-collapsability, see:
  - Morris et al 2022, *Planning a method for covariate adjustment in individually randomised trials*
  - Daniel et al 2021, *Making apples from oranges: comparing no collapsible effect estimators*

- Clarify whether marginal/conditional estimand is of interest first so appropriate analysis can be performed
Reliable for decision making?

- Should be agreed that reliable estimation is possible before estimand is finalised
- If not an alternative estimand would need to be considered
• Opiate addiction (e.g. morphine, heroin, etc...) is a major challenge worldwide

• Treatment: Opiate detoxification therapy entails switching from an uncontrolled to a substitute controlled by a doctor – commonly methadone – gradually reduced
Case study - FORWARDS-2

- Opiate addiction (e.g. morphine, heroin, etc...) is a major challenge worldwide

- Treatment: Opiate detoxification therapy entails switching from an uncontrolled to a substitute controlled by a doctor – commonly methadone – gradually reduced
Case study - FORWARDS-2

- Proof-of-concept double-blind randomised placebo-controlled trial

- Objective: To determine if baclofen is effective in reducing methadone detoxification therapy in comparison to placebo

- Patients randomised to Baclofen or Placebo

- Primary outcome: Reduction methadone dose at 12 weeks
FORWARDS-2 – constructing estimands

• When:
  - At initial planning stages to inform protocol development

• Who was involved:
  - Statisticians + PI + Lead Clinical researchers met to discuss exactly what we want to find out
Relevant Intercurrent events established:

1. Stopping randomised treatment (baclofen/placebo) – for any reason
FORWARDS-2 – intercurrent events

- Relevant Intercurrent events established:

  1. Stopping randomised treatment (baclofen/placebo) – for any reason
  2. Changing dose of randomised treatment (baclofen/placebo)

- Death [worst outcome]
FORWARDS-2 – intercurrent events

• Relevant Intercurrent events established:

1. Stopping randomised treatment (baclofen/placebo) – for any reason
2. Changing dose of randomised treatment (baclofen/placebo)
3. Discontinuing detoxification pathway prior to 12 weeks; still on methadone (i.e., no longer desiring abstinence)

5. Relapse/use on top e.g. of heroin [considered worse than baseline – but unclear how often will occur/be reported]
6. Death [worst outcome]
4. Use of other medications: e.g. any depression/anxiety medication/sleeping tablets/gut health.... etc
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FORWARDS-2 – intercurrent events

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6. Death
FORWARDS-2 – intercurrent events

• Handling Intercurrent events:

1. Stopping randomised treatment
2. Discontinuing detoxification pathway prior to 12 weeks
FORWARDS-2 – intercurrent events

• Handling Intercurrent events:

1. Stopping randomised treatment Treatment policy
2. Discontinuing detoxification pathway prior to 12 weeks Treatment policy
FORWARDS-2 – intercurrent events

• Handling Intercurrent events:

1. Stopping randomised treatment Treatment policy
2. Discontinuing detoxification pathway prior to 12 weeks Treatment policy
3. Changing dose of randomised treatment Treatment policy
4. Use of other medications: e.g. any depression/anxiety Treatment policy
5. Relapse/use on top e.g. heroin Treatment policy
Handling Intercurrent events:

1. Stopping randomised treatment *Treatment policy*
2. Discontinuing detoxification pathway prior to 12 weeks *Treatment policy*
3. Changing dose of randomised treatment *Treatment policy*
4. Use of other medications: e.g. any depression/anxiety *Treatment policy*
5. Relapse/use on top e.g. heroin *Treatment policy*
6. Death *While-alive*
FORWARDS-2 – treatment conditions

12 weeks of Baclofen compared to Placebo, regardless of any randomised treatment discontinuation for any reason or detoxification treatment discontinuation prior to stopping methadone
The population of eligible trial participants; those initially engaging in detoxification treatment as defined by the trial exclusion/inclusion criteria
FORWARDS-2 – outcome

• What outcome variable do we want to know?

> The reduction in the methadone dose at 12 weeks
FORWARDS-2 – outcome & summary measure

- What outcome variable do we want to know?
  > The reduction in the methadone dose at 12 weeks

- What population-level summary measure do we want to know?
  > The mean difference in methadone dose between treatment conditions at 12 weeks
Case study – FORWARDS-2

• Handling Intercurrent events:

1. Stopping randomised treatment
2. Discontinuing detoxification pathway prior to 12 weeks
3. Changing dose of randomised treatment Treatment policy
4. Use of other medications: e.g. any depression/anxiety Treatment policy
5. Relapse/use on top e.g. heroin (i) Treatment policy, (ii) Composite
6. Death (i) While-alive, (ii) Composite
Case study – FORWARDS-2

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Case study – FORWARDS-2

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6. Death (i) While-alive, (ii) composite
Reflections

• Took time to properly think through plausible intercurrent events and how to handle

• Defining estimands was an ‘iterative thinking process’ requiring multi-disciplinary input

• Will ensure FORWARDS 2 answers questions of interest
  – in past deaths/relapse after thought