How to Construct Estimands

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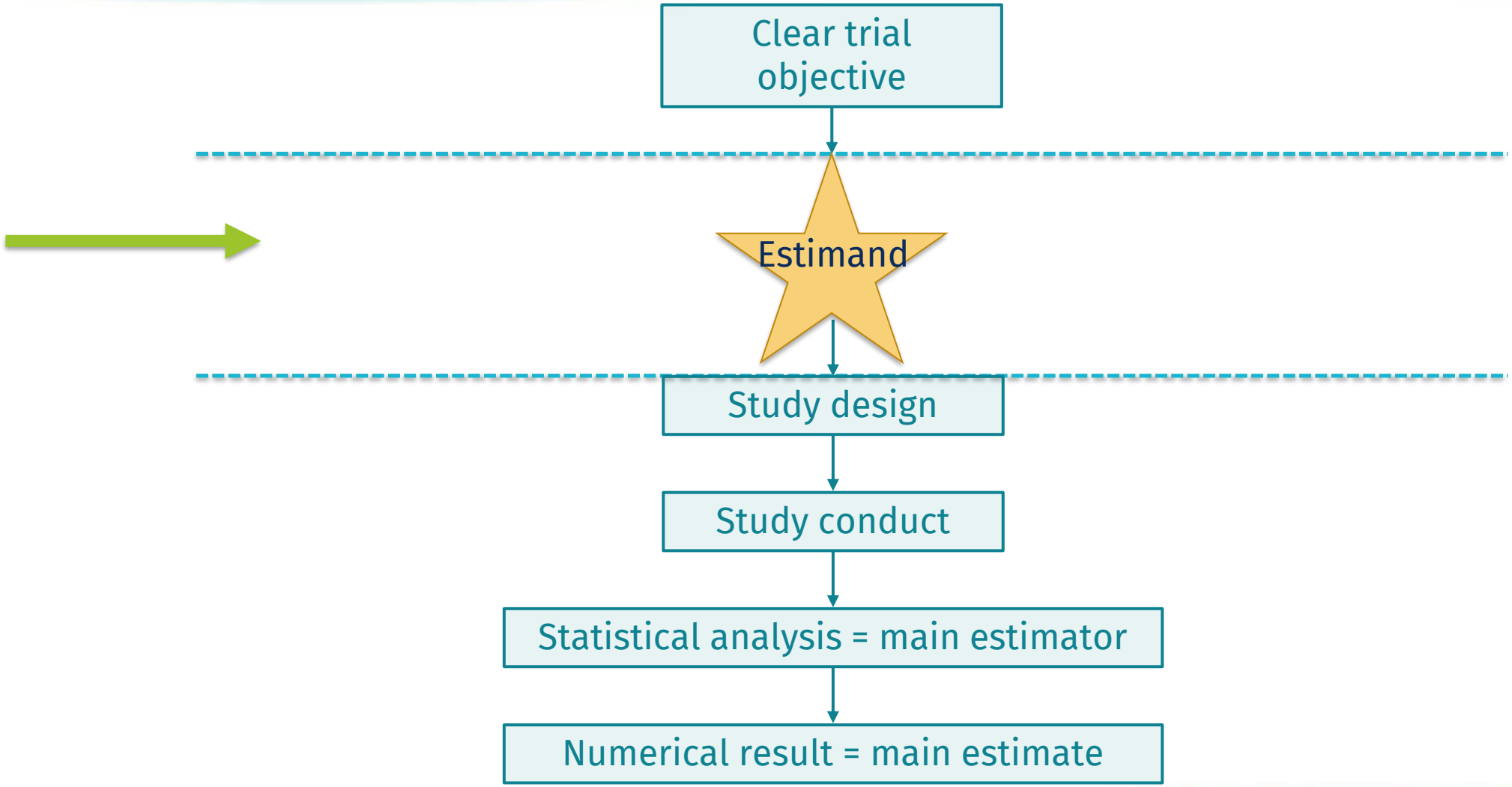
Outline

- 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

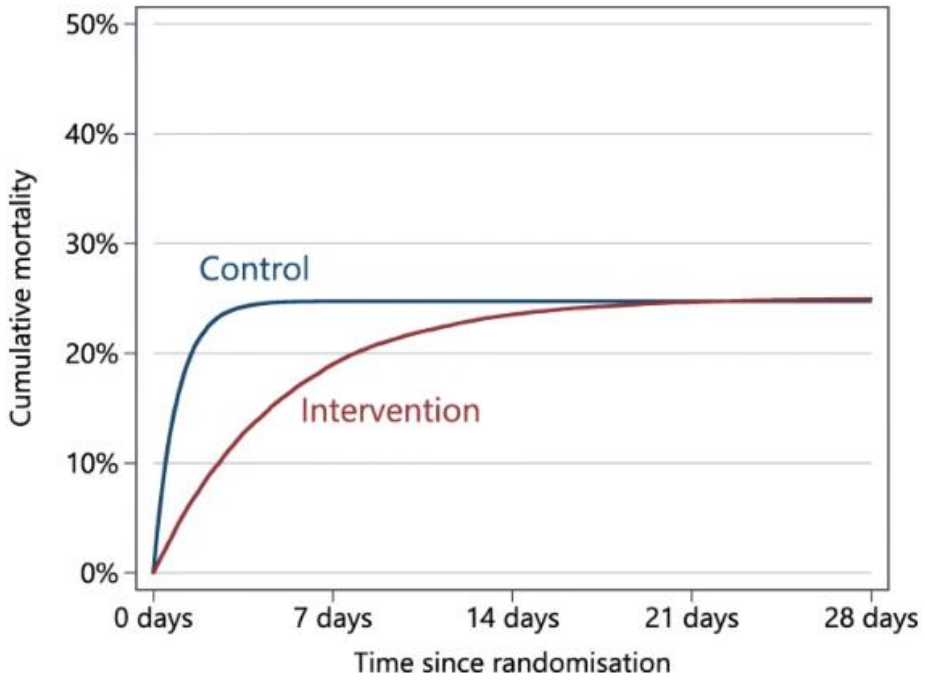
- Complete specification of **population**/**variable**

- 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

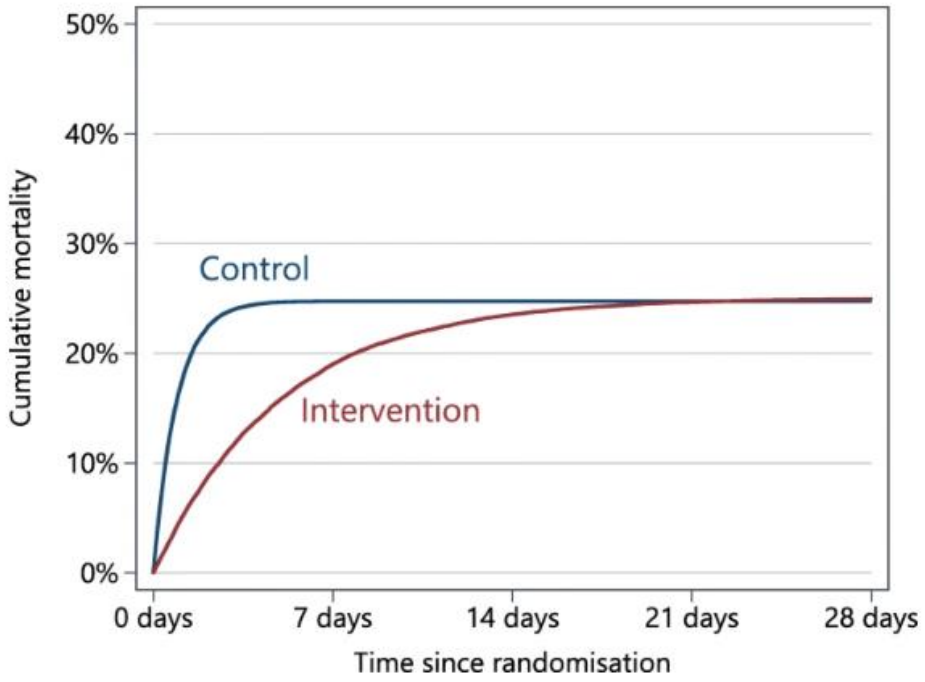


Kahan et al, 2020, Treatment estimands in clinical trials of patients hospitalised for COVID-19

Specify 5 attributes

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

HR=0.9



Difference in proportion of deaths @ 28 days = 0%

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

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

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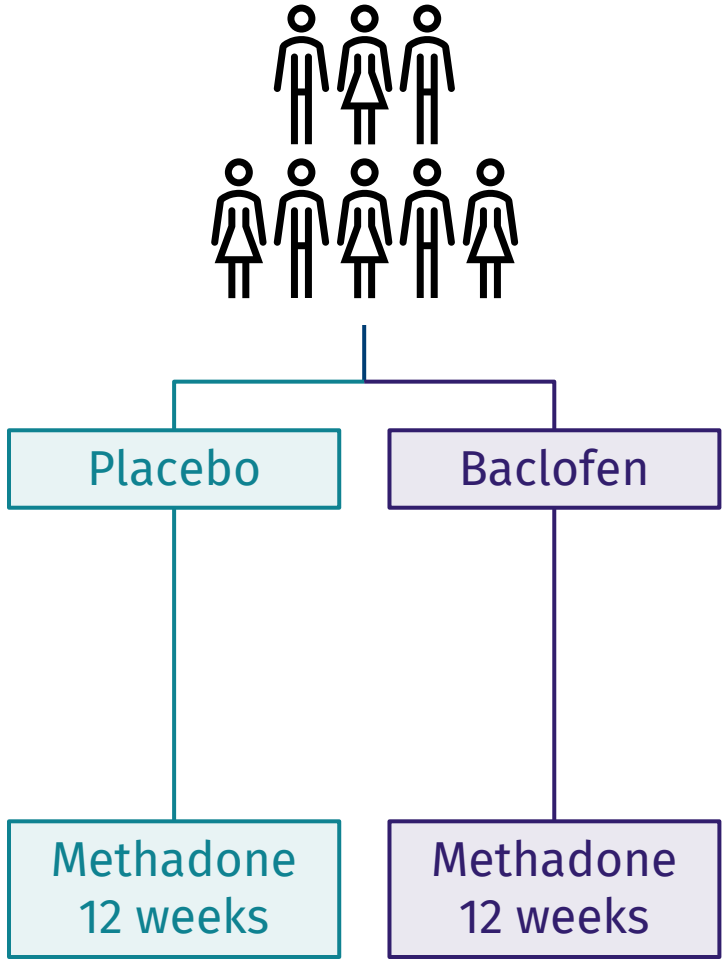
- Treatment: Opiate detoxification therapy entails switching from an uncontrolled to a substitute controlled by a doctor – commonly methadone – gradually reduced

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

FORWARDS-2 – intercurrent events

- Relevant Intercurrent events established:

  1. Stopping randomised treatment (baclofen/placebo) – for any reason

FORWARDS-2 – intercurrent events

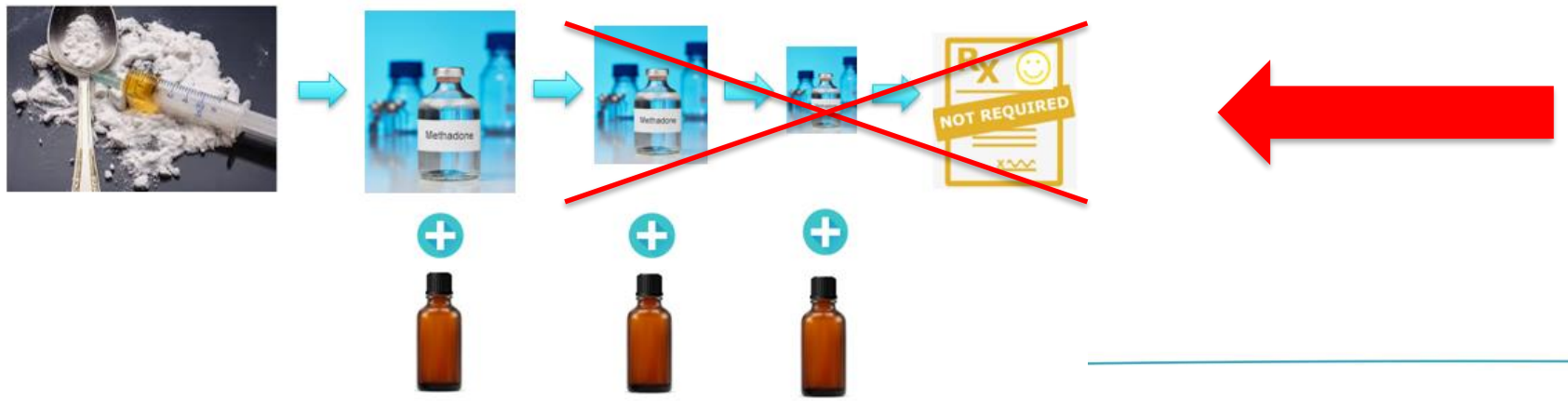
- Relevant Intercurrent events established:

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

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)



FORWARDS-2 – intercurrent events

4. Use of other medications: e.g. any depression/anxiety medication/sleeping tablets/gut health…. etc

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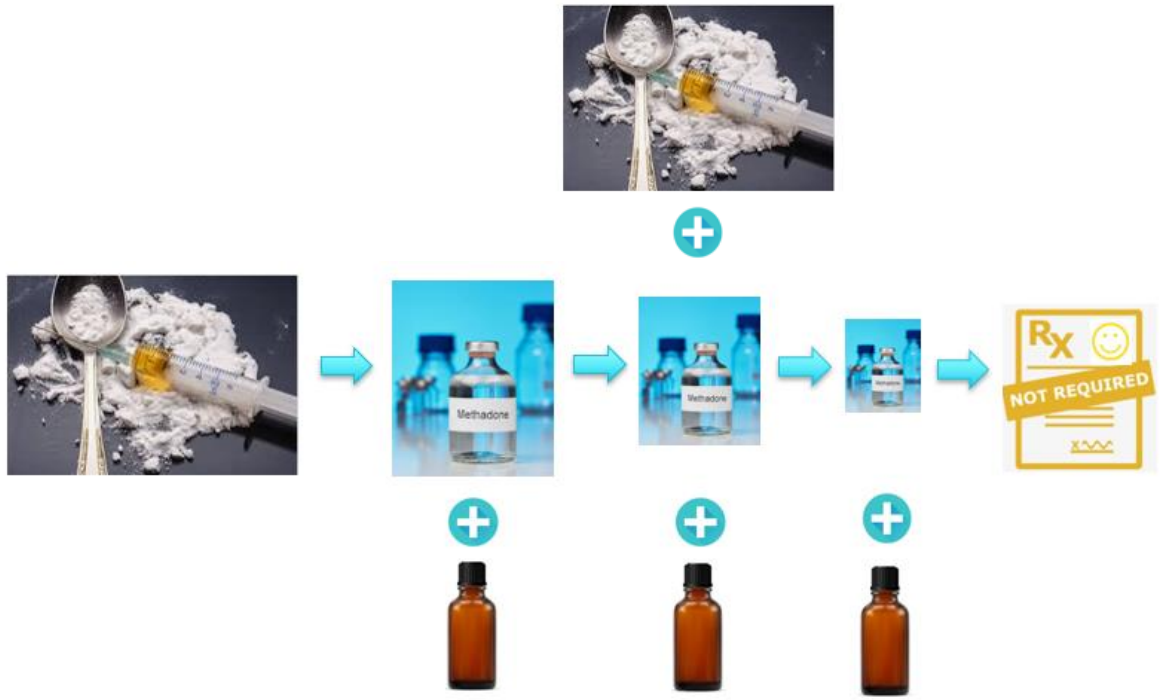
5. Relapse/use on top e.g. use of heroin



FORWARDS-2 – intercurrent events

4. Use of other medications: e.g. any depression/anxiety medication/sleeping tablets/gut health…. etc

5. Relapse/use on top e.g. use of heroin

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
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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
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**

FORWARDS-2 – population

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

- Handling Intercurrent events:

1. Stopping randomised treatment
2. Discontinuing detoxification pathway prior to 12 weeks

} **(iii): 1-2 While-on-treatment**

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

- Handling Intercurrent events:

1. Stopping randomised treatment
2. Discontinuing detoxification pathway prior to 12 weeks

} **iv) : 1-2 Principal Stratum**

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**

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