Exercise 1: Constructing Estimands

Introduction

An estimand is a clear and unambiguous description of exactly **what** treatment effect is to be estimated in a clinical trial. It consists of the following five inter-related attributes:

- The **treatment** condition(s)**,** which are the treatment strategies you want compare.
- The wider **population** of patients who you want to know the treatment effect for (*not* just the study participants or analysis population).
- The outcome **variable** or endpoint to be collected for each patient.
- The specification of how to account for **intercurrent events** (post-randomisation events that affect interpretation of the outcome).
- How outcomes between different treatment conditions will be compared; the population-level **summary measure**, e.g., difference in means/risk ratio, odds ratio etc

Potential strategies for handling intercurrent events include:

- **Treatment policy**; target the treatment effect **regardless** of the occurrence of intercurrent event (Intercurrent event considered as part of the treatment). Patient outcomes after intercurrent event of interest.
- **Composite**; the intercurrent event is **included in the outcome** variable by defining a composite outcome e.g. by assigning it to a particular value of the outcome variable.
- **Hypothetical**; the treatment effect in a hypothetical scenario is targeted, for example the treatment effect **if** the intercurrent event **did not happen**.
- **Principal stratification**; the treatment effect only in the subset of the **population whose intercurrent event status would be identical**, irrespective of treatment group is targeted.
- **While-on-treatment (or while-alive)**; assess the treatment effect **prior to** the intercurrent event (or prior to death); outcomes after the intercurrent events are not relevant.

An example estimand for the FORWARDS-2 trial is shown in the following table:

| Estimand attribute | Description |
|---|---|
| Population | Patients engaging in methadone detoxification treatment meeting FORWARDS2 eligibility criteria (as defined in the trial protocol) |
| Treatment condition(s) | 12 weeks of treatment with baclofen compared to placebo (dose established in FORWARDS 1), **regardless** of any treatment discontinuation or detoxification treatment discontinuation prior to stopping methadone |
| Variable (outcome) | Reduction in methadone dose at week 12 following treatment initiation |
| Handling Intercurrent events | 1.Stopping randomised treatment (baclofen/placebo) – for any reason: **treatment policy** (as part of treatment)<br>2.Discontinuing opiate substitution detoxification pathway prior to 12 weeks but still on methadone (i.e., no longer desiring abstinence) – **treatment policy** (as part of treatment)<br>3. Changing dose of randomised treatment (baclofen/placebo) – **treatment policy**<br>4. Use of other medications – **treatment policy**<br>5. Relapse/use on top e.g. heroin – **treatment policy**<br>6. Death – **while-alive** |
| Summary measure | Mean difference in outcome variable between the treatment conditions |

Scenario

Dr Hesketh has received a grant to run a phase 3 placebo-controlled randomised trial to test a new biological treatment compound, TD23, in children with uncontrolled severe therapy resistant asthma (STRA). Although most asthma cases are mild to moderate and can be controlled with low and safe doses of maintenance inhaled corticosteroids (ICS), a group remain who have problematic severe asthma which cannot be controlled despite maximum prescribed maintenance therapies. She has told you that:

- The trial results will primarily be used by policy makers who will decide whether TD23 should become part of routine care.
- The primary objective of the trial is to compare the superiority of TD23 against placebo in routine practice for children with STRA over a 52-week treatment period.
- A dose of 50mg of TD23 is prescribed to be taken every 2 weeks for 52 weeks for the children allocated to the TD23 group. A matching dose of placebo is prescribed to be taken every 2 weeks for 52 weeks for the children allocated to the placebo group.
- The primary outcome is the change in Asthma Control Questionnaire (ACQ) score at week 52. The ACQ result in a numerical score ranging from 0 to 6 where 0 represents excellent asthma control and 6 represents extremely poor control. The ACQ will also be recorded at weeks 12, 24.

Your task is to construct an estimand to fulfil the primary objective of interest to the policy makers. This should include the following three intercurrent events which Dr Hesketh has identified:

*- Intercurrent event 1: Early discontinuation of treatment with TD23 (for any reason).*

*-Intercurrent event 2: Use of rescue medication in the form of a short-acting $\beta_2$-adrenergic receptor agonist (either salbutamol or -levosalbutamol), which are available in routine practice and permitted as rescue medication for asthma symptoms as needed in the trial*

*-Intercurrent event 3: Use of background maintenance inhaled corticosteroids (ICS) which are available in routine practice.*

Question 1)

a) What should be the strategy for handling each of the three identified intercurrent events?
b) What should the treatment condition be?
c) What should the population be?
d) What should the outcome variable/endpoint be?
e) What should the population level summary measure be?

Question 2)

Although rescue medication will be used by participants as required in the trial, the policy makers would also like to know the treatment effect if rescue medications (intercurrent event 2) were not available, otherwise as used in routine practice.

The objective is to compare the superiority of TD23 against placebo, if rescue medications (intercurrent event 2) were not available, otherwise as used in routine practice for children with STRA over a 52-week treatment period.

Construct a supportive estimand that aligns with this objective. This should include the three intercurrent events which Dr Hesketh has identified:

- *Intercurrent event 1: Early discontinuation of treatment with TD23 (for any reason).*

*-Intercurrent event 2: Use of rescue medication in the form of a short-acting $\beta_2$-adrenergic receptor agonist (either salbutamol or -levosalbutamol), which are available in routine practice and permitted as rescue medication for asthma symptoms as needed in the trial*

*-Intercurrent event 3: Use of background maintenance inhaled corticosteroids (ICS) which are available in routine practice.*

a) What should be the strategy for handling each of the three identified intercurrent events?
b) What should the treatment condition be?
c) What should the population be?
d) What should the variable be?
e) What should the population level summary measure be?

Solutions

Question 1

Based on the provided information a potential estimand that aligns with the presented objective of Dr Hesketh is as follows. The most appropriate estimand will require a conversation with Dr Hesketh to confirm this is exactly what they want to know.

| Estimand attribute | |
|---|---|
| Treatment condition | A 52-week course of TD23 at 50mg every 2 weeks compared to a 52-week course of matching placebo at 50mg every 2 weeks, **regardless** of *any treatment discontinuation* or *use of rescue medication* or *background ICS maintenance therapy* |
| Population | Children with STRA, as defined by the trial inclusion and exclusion criteria. |
| Variable (outcome) | Change from baseline in the ACQ at week 52 |
| Handling intercurrent events | Intercurrent event 1: a **treatment policy** strategy will be used to estimate the treatment effect, regardless of the early discontinuation of treatment for any reason (as part of treatment).<br>Intercurrent event 2: a **treatment policy** strategy will be used to estimate the treatment effect, regardless of the use of short-acting $\beta_2$-adrenergic receptor agonist (either salbutamol or levosalbutamol) as rescue medication (as part of treatment).<br>Intercurrent event 3: a **treatment policy** strategy will be used to estimate the treatment effect, regardless of the use of background ICS (as part of treatment). |
| Summary measure | Mean difference in the outcome variable between treatment conditions |

Question 2

We outline a potential estimand that aligns with the given information and presented objective of Dr Hesketh. The most relevant estimand will require a conversation with Dr Hesketh to establish exactly what they want to know.

| Estimand attribute | |
|---|---|
| Treatment condition | A 52-week course of TD23 at 50mg every 2 weeks compared to a 52-week course of matching placebo at 50mg every 2 weeks, **regardless** of *any treatment discontinuation* or *use background ICS maintenance therapy*, **if** *rescue medications* **were not available** |
| Population | Children with STRA, as defined by the trial inclusion and exclusion criteria |
| Variable (outcome) | Change from baseline in the ACQ at week 52 |
| Handling intercurrent events | *Intercurrent event 1:* a **treatment policy** strategy will be used to estimate the treatment effect, regardless of the early discontinuation of treatment for any reason (as part of treatment).<br>*Intercurrent event 2:* a **hypothetical** strategy will be used to estimate what the treatment effect would have been if all patients did not have rescue medications available (no use of short-acting $\beta_2$-adrenergic receptor agonist (either salbutamol or levosalbutamol)).<br>*Intercurrent event 3:* a **treatment policy** strategy will be used to estimate the treatment effect, regardless of the use of background ICS (as part of treatment). |
| Summary measure | Mean difference in the outcome variable between treatment conditions |