

## Exercise 2: Aligning analysis with the estimand

### Estimand 1

The primary objective of Dr Hesketh’s trial is to compare the superiority of TD23 against placebo in routine practise for children with STRA over a 52-week treatment period.

The primary outcome is the change in Asthma Control Questionnaire (ACQ) score at week 52. The ACQ results 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 measured at weeks 12, 24.

The primary estimand Dr Hesketh has selected to align with this objective is described by the following 5 attributes:

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, <b>regardless</b> of any <i>treatment discontinuation or use of rescue medication or background ICS maintenance therapy</i>
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	<p>Intercurrent event 1: a <b>treatment policy</b> strategy will be used to estimate the treatment effect, regardless of the early discontinuation of treatment for any reason (as part of treatment).</p> <p>Intercurrent event 2: a <b>treatment policy</b> strategy will be used to estimate the treatment effect, regardless of the use of short-acting <math>\beta_2</math>-adrenergic receptor agonist (either salbutamol or levosalbutamol) as rescue medication (as part of treatment).</p> <p>Intercurrent event 3: a <b>treatment policy</b> strategy will be used to estimate the treatment effect, regardless of the use of background ICS (as part of treatment).</p>
Summary measure	Mean difference in the outcome variable between treatment conditions

For questions 1 and 2 suppose all data are complete (i.e. loss to follow-up is not an issue) in this trial. In questions 3 and 4 we will consider the additional impact of missing data.

Question 1) Your task is to discuss an analysis plan that will provide an estimate of Dr Hesketh's primary estimand.

Which of the following estimators would you suggest?

- a) Censor data from time of treatment discontinuation; apply Inverse probability of censoring weighting and a weighted linear regression at the primary time point.
- b) A likelihood-based repeated measures approach, such as mixed model for repeated measures. Fit to data collected prior to treatment discontinuation from all randomized patients.
- c) Censor data from time of rescue medication initiation or treatment discontinuation; apply Inverse probability of censoring weighting and a weighted linear regression at the primary time point.
- d) Censor data from time of treatment discontinuation or initiation of rescue medication or background ICS. Fit a likelihood-based repeated measures approach, such as mixed model for repeated measures.
- e) Use all available data collected from all randomized patients and fit a likelihood-based repeated measures approach, such as a mixed model for repeated measures, or equivalently as no missing data, a linear regression at the primary time point.

## Estimand 2

A supportive objective is to compare the superiority of TD23 against placebo, if rescue medications (intercurrent event 2) were not available, otherwise as used in routine practise for children with STRA over a 52-week treatment period. The following hypothetical supplementary estimand was selected to align with this objective:

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, <b>regardless</b> of any treatment discontinuation or use background ICS maintenance therapy, <b>if rescue medications were not available</b>
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	<p><i>Intercurrent event 1:</i> a <b>treatment policy</b> strategy will be used to estimate the treatment effect, regardless of the early discontinuation of treatment for any reason (as part of treatment).</p> <p><i>Intercurrent event 2:</i> a <b>hypothetical</b> 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 <math>\beta_2</math>-adrenergic receptor agonist (either salbutamol or levosalbutamol)).</p> <p><i>Intercurrent event 3:</i> a <b>treatment policy</b> strategy will be used to estimate the treatment effect, regardless of the use of background ICS (as part of treatment).</p>
Summary measure	Mean difference in the outcome variable between treatment conditions.

Question 2) Which of the following estimators would you suggest to provide the main estimate for the supplementary estimand?

- Censor data from time of rescue medication initiation or background ICS use. Fit a likelihood-based repeated measures approach, such as mixed model for repeated measures.
- Use a two-stage least squares instrumental variable regression to estimate the complier average causal effect (CACE), where a complier is defined as an individual who would not use rescue medication.
- Censor data from time of rescue medication initiation; apply Inverse probability of censoring weighting and a weighted linear regression at the primary time point.
- Censor data from time of initiation of rescue medication or treatment discontinuation or background ICS use. Fit a likelihood-based repeated measures approach, such as mixed model for repeated measures.
- Censor data from time of initiation of rescue medication or treatment discontinuation; apply Inverse probability of censoring weighting and a weighted linear regression at the primary time point.

*Advanced questions:*

Question 3) We have not yet considered the additional impact of having missing data for the primary estimand. Suppose now *some* data was actually missing from patients in the TD23 group who discontinued their treatment early. Some patients in the TD23 group who discontinued treatment early continued to be observed. If you used multiple imputation to impute this missing data what assumption would this make for the missing data?

Question 4) What alternative methods of estimation could you suggest for the primary estimand to explore the impact of different missing data assumption for patients in the TD23 group who discontinued their treatment early? All missing data (from the patients in the TD23 group who discontinued their treatment early) are monotone.