Treatment switching is common in clinical trials of cancer treatments—often patients randomised to the control group are permitted to switch onto the new intervention upon disease progression. If survival is extended in patients who switch, an intention to treat analysis will underestimate the overall survival (OS) advantage and the cost-effectiveness of the new intervention. The observed OS difference is less than would have been observed in the absence of switching (Figure 1).

Statistical methods to adjust for switching have been used in health technology assessments (HTA). “Naïve” methods (censoring or excluding switchers) are prone to selection bias. More complex methods also have important limitations—their applicability depends on the characteristics of the trial in question.[1]

We consider how trials may be designed to help reduce the treatment switching problem.

### Methods

1. First we provide methodological background on the key assumptions and requirements of the main switching adjustment methods.
2. We then summarise key findings from simulation studies on the performance of these methods across a range of scenarios.
3. We discuss trial design issues and how these correspond with the requirements of the adjustment methods.
4. Finally, based upon the theoretical requirements of the methods, their performance, and practical trial design issues, we list recommendations to be taken into account in the trial design stage to help ensure appropriate methods can subsequently be applied to adjust for switching.

### 1. Adjustment methods and their key requirements

#### RPSFTM

The standard single parameter RPSFTM model splits the observed event time $T_i$ into time spent “on” treatment ($T_{on}$) and time spent “off” treatment ($T_{off}$). Counterfactual event times, $U_i$, are calculated, and are related to observed event times with the following causal model:

$$ U_i = T_{off} + e^{\frac{\mu}{\lambda}} T_{on} $$

where $\lambda$ represents the acceleration factor associated with the intervention—the amount by which an individual’s expected survival time is increased by treatment.

**Key model requirements:**
- Non-active (e.g. placebo) comparator
- Common treatment effect: effect received by switchers is the same (relative to time treatment taken for) as effect received by patients in the experimental group

#### IPCW

The IPCW involves censoring switchers at the time of treatment switch, and weighting remaining patients according to their similarity to switchers, using information on baseline and time-dependent covariates.

A weighted Cox regression model is utilised to estimate and adjusted hazard ratio. A weighted Kaplan-Meier curve can also be obtained.

**Key model requirements:**
- No unmeasured confounders: need data collected at baseline and over time on all variables that are prognostic of switching or survival
- E.g. patient choice as to whether to switch
- Correctly specified models for switching and survival

#### Two-stage methods

Two-stage methods involve using data on post-progression survival in the control group as an observational dataset, and estimating the treatment effect specific to switchers. Then, counterfactual survival times are estimated using:

$$ U_i = T_{A_i} + \frac{T_{B_i}}{\mu_B} $$

Where $T_{A_i}$ represents the time spent on control treatment, $T_{B_i}$ represents the time spent on the new intervention, and $\mu_B$ is the treatment effect (acceleration factor) in switching patients.

**Key model requirements:**
- No unmeasured confounders at the time of new intervention
- Switching only after progression

### 2. Performance issues

- All adjustment methods are prone to increased bias when sample size is small—particularly in the control group.[1]
- All methods work less well with extreme levels of switching (note: this is a function of sample size—e.g. 90% in a sample size of 500 is equivalent to 75% in a sample size of 200).[1]
- The IPCW is more sensitive than other methods to small sample sizes and extreme switching proportions.[1]
- The RPSFTM is prone to bias when the common treatment effect assumption does not hold.[1]

### 3. Discussion

- Control group sample size is important for all methods
- RPSFTM requires data on duration of treatment for all patients (including switchers)
- No unmeasured confounders is important for IPCW and two-stage methods. Data on covariates required at baseline and over time.
- Two-stage method requires the existence of a secondary baseline
- RPSFTM requires non-active comparator—often not practical given need for full incremental analyses in HTA. Can apply with stronger assumptions if treatment pathways (aside from switching) are realistic.

### 4. Recommendations – Study design

- **Sample size**
  - Avoid small sample sizes and 2:1 randomisation
- **Data on switchers**
  - Collect data on treatment start/stop dates for all patients
  - No unmeasured confounders
  - Work with clinicians to ensure all relevant data collected
  - Collect data on confounders regularly over time
  - Often data collection stops at the point of disease progression or treatment discontinuation: Avoid this
  - Record patient preference for switch—this is a confounder
- **Two-stage method**
  - Only permit switching after a defined disease-related time-point, e.g. disease progression
- **Treatment pathways**
  - Aside from the treatment switching, ensure subsequent treatments reflect common practice

If switching is to be permitted, take steps to increase the likelihood that adjustment methods can be successfully applied.

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