Treatment switching (1)

- In RCTs often patients are allowed to switch from the control treatment to the new intervention after a certain timepoint (e.g., disease progression)
  - PFS (progression free survival) estimates are ok
  - But OS (overall survival) estimates will be confounded

- What are the implications of this?
  - For clinical analysis
  - For economic analysis
    - There are different drivers for these two analyses
Treatment switching (2)

- **Clinical analysis**
  - Drug regulatory bodies such as FDA and EMA accept that PFS is sufficient for licensing
  - There are reduced incentives for companies to collect longer term survival data
  - There are reduced incentives to maintain randomisation post-progression
    - Practical reason why treatment switching occurs
    - Combined with ethical reasons, strong incentives to allow switching

- **Economic analysis**
  - For interventions that impact upon survival OS is a key input in the economic model
  - Need accurate estimates of the treatment effect on PFS and OS

Treatment switching (3)

- Treatment switching is *not* just an issue for economic evaluation
- But it can appear that way because it becomes more of an issue at the “fourth hurdle”

- **Implications:**
  - Cost effectiveness results will be inaccurate → an ITT analysis is likely to underestimate the treatment benefit
  - Inconsistent and inappropriate treatment recommendations could be made

- **Note:** the treatment pathway observed may no longer be relevant for the NICE decision problem – but it could still be important…
Treatment switching (4)

Switching is likely to result in an underestimate of the treatment effect.

What is usually done to adjust?

- No clear consensus
- Numerous ‘naive’ approaches have been taken in NICE appraisals:
  - Take no action at all
  - Exclude or censor all patients who switch
- Occasionally more complex statistical methods have been used, eg:
  - Rank Preserving Structural Failure Time Models (RPSFTM)
  - Inverse Probability of Censoring Weights (IPCW)
- And others are available from the literature, eg:
  - Structural Nested Models (SNM)
What are the consequences?

NICE TA 215, Pazopanib for RCC [51% of control switched]

- **ITT:** OS HR (vs IFN) = 1.26 \( \rightarrow \) ICER = Dominated
- Censor patients: HR = 0.80 \( \rightarrow \) ICER = £71,648
- Exclude patients: HR = 0.48 \( \rightarrow \) ICER = £26,293
- IPCW: HR = 0.80 \( \rightarrow \) ICER = £72,274
- RPSFTM: HR = 0.63 \( \rightarrow \) ICER = £38,925

Potential solutions (1)

**RPSFTM**

\[ U_i = T_{off} + e^{\psi_0 T_{on}} \]

- Developed for use on RCT datasets, makes use of randomisation to estimate counterfactual survival times
- **Key assumption:** common treatment effect

**IPCW**

- Developed for use on observational datasets, censors xo patients, weights remaining patients, runs weighted Cox model
- **Key assumptions:** “no unmeasured confounders”; must model OS and crossover using covariate data

**SNM**

- Observational version of RPSFTM
- **Key assumptions:** “no unmeasured confounders”; must model OS and crossover
Potential solutions (2)

Another option…

- Consider the treatment switching typically seen in oncology trials…
- Data on PFS is required for licensing, thus only allow switching post-progression
- If switching only happens after progression, and happens soon after progression, we may consider a simple “two-stage” approach:
  - Use disease progression as a secondary baseline for control group patients and consider control group data after this time-point as an observational dataset
  - Apply an accelerated failure time model to this dataset including covariates for crossover and other prognostic covariates measured at the secondary baseline
  - Use the AF derived for crossover to “shrink” survival times of switchers
  - Counterfactual dataset

Key assumptions: “no unmeasured confounders” at secondary baseline time-point; switching only after progression, and soon after progression

Potential solutions (3)

1. Identify secondary baseline

Control → Non-switchers

- PFS
- PPS

Control → Switchers:

- PFS
- PPS

2. Estimate treatment effect in switchers compared to non-switchers using an AFT model

3. “Shrink” survival times in switching patients according to the AF
Implications for study design

- All methods have key methodological limitations and are likely to only approximate the “truth”
- But certain steps can be taken during study design to aid future adjustment attempts:

1. Small sample sizes reduce the likelihood that adjustment will result in accurate results
   a) This is particularly the case for observational methods, but also relevant for RPSFTM/IPE
   b) 2:1 randomisation is likely to exacerbate this

2. Observational methods require “no unmeasured confounders”
   a) Unlikely to be perfectly true
   b) But can take steps to ensure data are collected on known relevant confounders
   c) Require that data are collected at regular intervals throughout the study
   d) Do not stop collecting data after disease progression – this is needed
   e) Need to be able to model the probability of switching – collect data to allow this. This may include data on patient choice, clinician, country, centre as well as prognostic covariates
Implications for study design

- All methods have key methodological limitations and are likely to only approximate the "truth"
- But certain steps can be taken during study design to aid future adjustment attempts

3. Two-stage methods
   a) Require "no unmeasured confounders" at the "secondary baseline"
   b) Should be covered by data collection that covers requirements of IPCW – but ensure that data are collected at the secondary baseline
   c) But also require that patients who switch are followed up for survival
   d) And require that a secondary baseline exists (can this be dictated by the protocol?)

Conclusions

- Treatment switching has become common for ethical and practical reasons
- It is a problem for clinical and economic assessment
- Adjustment methods are imperfect but the likelihood that they will perform well can be enhanced by careful study planning

► If treatment switching is likely to be permitted in a proposed clinical trial, take steps to increase the likelihood that robust adjustment analyses can be run in the future
References


