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Methods for adjusting survival estimates in the presence of treatment switching in cancer trials

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Contents

Background

What is treatment switching and why does it occur?
What problems are created by treatment switching?
What types of switching should we adjust for?

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Treatment switching

- In RCTs often patients are allowed to switch from the control treatment to the new intervention after a certain timepoint (eg disease progression)

➔ PFS (progression free survival) estimates are ok

➔ But OS (overall survival) estimates will be confounded

- Several recent NICE TAs have been affected by treatment switching (sunitinib (GIST, RCC), lenalidomide (MM), pazopanib (RCC), everolimus (RCC), crizotinib (NSCLC), ipilimumab (melanoma), gefitinib (NSCLC), vemurafenib (melanoma), dabrafenib (melanoma))

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Treatment switching

- **Implications:**
  - *If* patients who switch benefit from the new treatment, an ITT analysis is likely to underestimate the treatment benefit

➔Particularly important for reimbursement agencies – OS is critical

➔Cost effectiveness results could be inaccurate

➔**Inconsistent and inappropriate treatment recommendations could be made**

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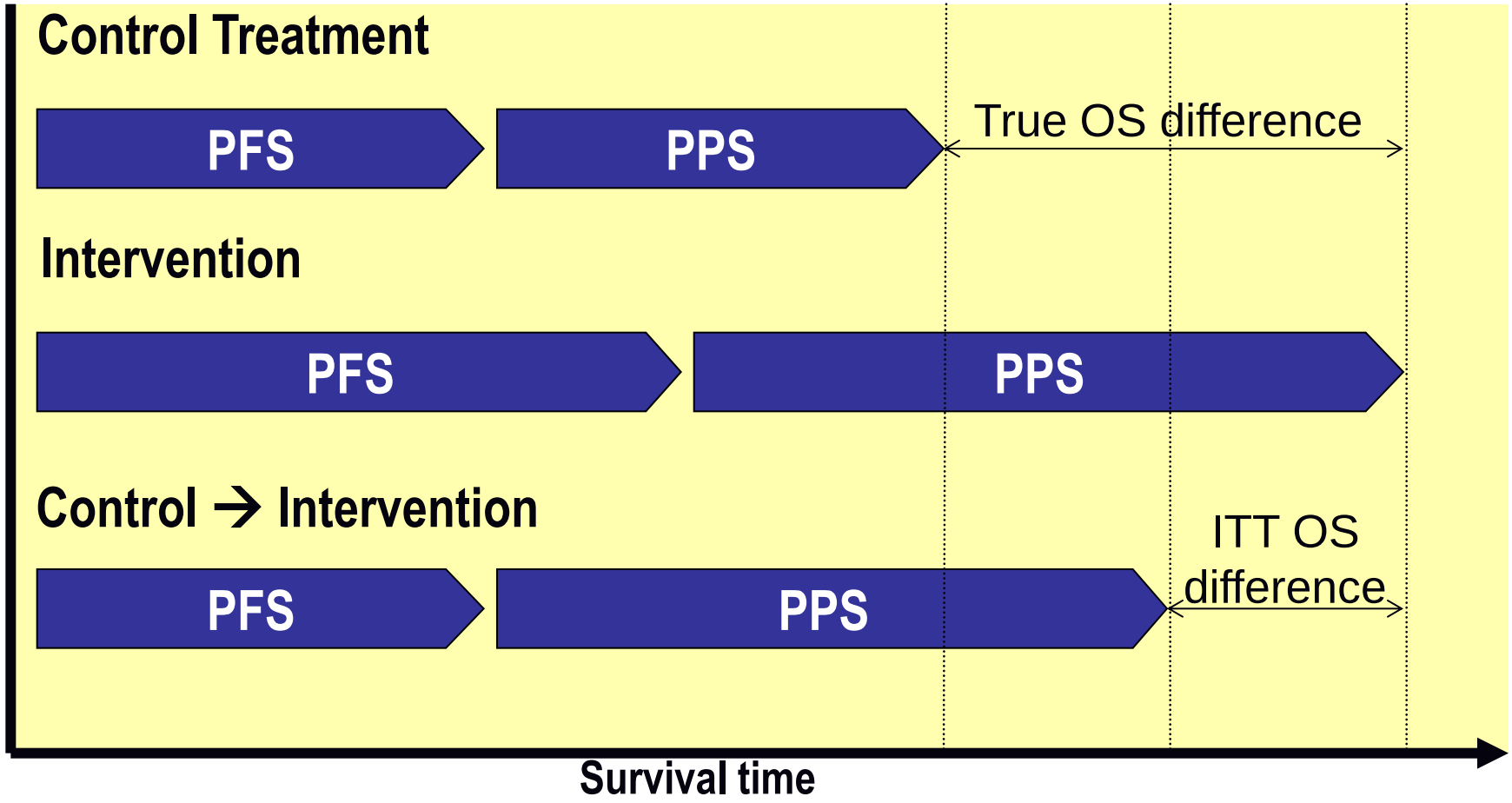
Illustrating treatment switching



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

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When do we need to adjust?

- HTA decision problem typically = comparison two "states of the world":
  a) State of the world in which the new intervention exists (State A)
  b) State of the world in which the new intervention does not exist (State B)
- State B should not be contaminated by the new intervention

➔ We need to adjust if control group patients receive the new treatment

- The situation is less clear if patients (in either group) receive *other* post-study treatments
- If these are available in the real world, they may represent realistic treatment pathways → unnecessary/undesirable to adjust

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Adjustment methods

What are the potential solutions?

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What is usually done to adjust?

- No clear consensus
- Numerous 'naive' approaches have been taken in [illegible]:
  - Take no action at all
  - Exclude or censor all patients who switch

Very prone to selection bias – switching isn't random

- Occasionally more complex statistical methods have been used, eg:
  - Rank Preserving Structural Failure Time Models (RPSFTM)
  - Inverse Probability of Censoring Weights (IPCW)
  - Two-stage methods

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What are the consequences?

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

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

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Potential solutions (RPSFTM)

RPSFTM / IPE algorithm

$$U_i = T_{off} + e^{\psi 0} T_{on}$$

- Developed for use on RCT datasets, makes use of randomisation to estimate counterfactual survival times

Key assumptions: Common treatment effect and non-active comparator

Practicalities: Require data on switching times, duration of treatment, event times

Relatively straightforward to apply

Testing of assumptions difficult / not possible

Robins JM, Tsiatis AA. Correcting for Noncompliance in Randomized Trials Using Rank Preserving Structural Failure Time Models. Commun Stat Theory Methods. 1991; 20(8):2609-2631.

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Potential solutions (IPCW)

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. Does *not* assume "common treatment effect"

Practicalities: Require data on switching times, event times & time-dependent cov.
Complex to apply
Testing of assumptions difficult / not possible

Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the joint causal effect of nonrandomized treatments. J Am Statist Assoc. 2001; 96(454):440-448.

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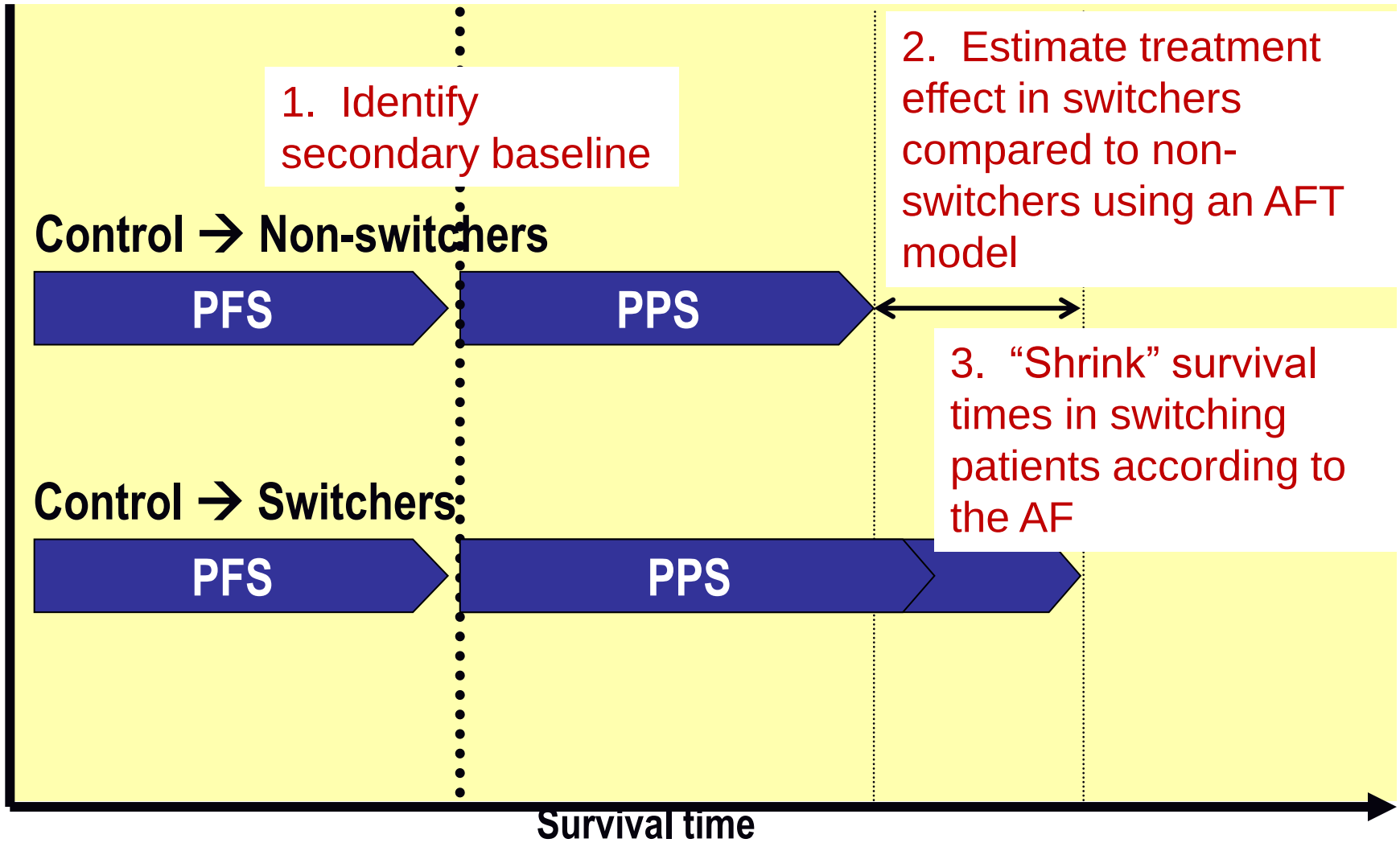
Potential solutions (2-stage)

Two-stage approach

- Use disease progression as secondary baseline, estimate treatment effect in switchers compared to non-switchers and derive counterfactual dataset

Latimer N, Abrams KR, Lambert PC, Crowther MJ, Wailoo AJ, Morden JP, Akehurst RL, Campbell MJ. Adjusting survival time estimates to account for treatment switching in randomised controlled trials – an economic evaluation context: Methods, limitations and recommendations. Medical Decision Making, online first Jan 2014

Potential solutions (2-stage)



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Potential solutions (2-stage)

Two-stage approach

- Use disease progression as secondary baseline, estimate treatment effect in switchers compared to non-switchers and derive counterfactual dataset

Key assumptions: "No unmeasured confounders" at secondary baseline time-point; switching only after progression, no time dependent confounding between time of progression and time of switch

Practicalities: Require data on switching times, event times & prognostic cov. at secondary baseline
Relatively straightforward to apply
Testing of assumptions difficult / not possible

Latimer N, Abrams KR, Lambert PC, Crowther MJ, Wailoo AJ, Morden JP, Akehurst RL, Campbell MJ. Adjusting survival time estimates to account for treatment switching in randomised controlled trials – an economic evaluation context: Methods, limitations and recommendations. Medical Decision Making, online first Jan 2014

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How can we identify an appropriate adjustment method?

Evidence on performance of methods

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Performance of methods

- None of these methods are perfect
- But we need to know which are likely to produce least bias in different scenarios

➔**Simulation studies**

- Simulate survival data for two treatment groups, applying switching that is linked to patient characteristics/prognosis
- In some scenarios simulate a treatment effect that changes over time
- In some scenarios simulate a treatment effect that remains constant over time
- Test different switch %s, treatment effects, sample sizes, simulation mechanisms

[Note: simulation studies are limited by scenarios investigated, and because results may be influenced by simulation process. But we need to know the "truth"]

➔***How does the bias and coverage associated with each method compare?***

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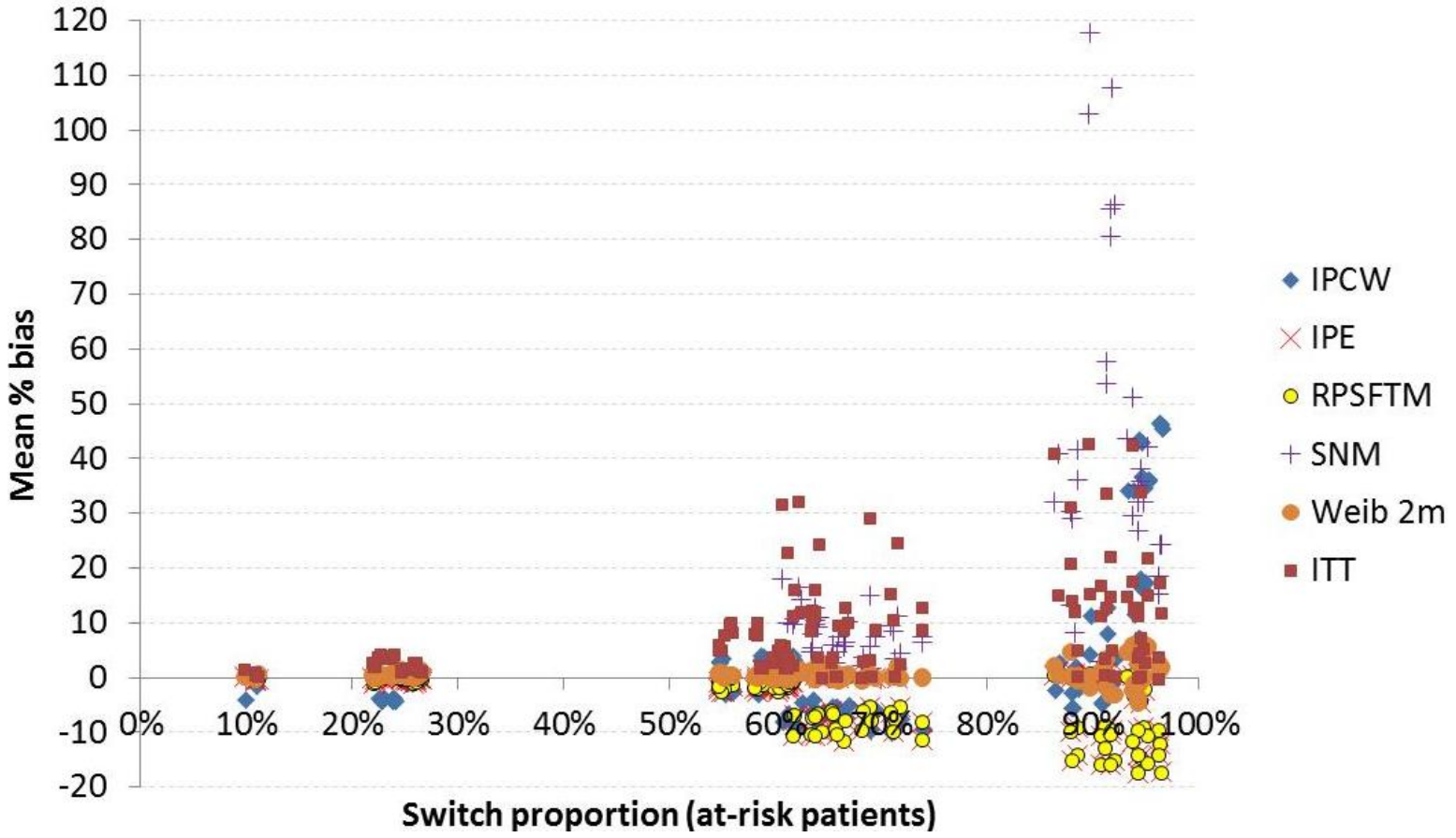
Performance of methods

Study 1 and Study 2: Relationship between bias and treatment switch %



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What is recommended?

What does NICE say?

Methods Guide

- Previous Guide said nothing. The 2013 does address switching:

"In RCTs, participants randomised to the control group are sometimes allowed to switch treatment group and receive the active intervention. In these circumstances, when intention-to-treat analysis is considered inappropriate, statistical methods that adjust for treatment switching can also be presented..."

Methods Guide

"Simple adjustment methods such as censoring or excluding data from patients who crossover should be avoided because they are very susceptible to selection bias…"

Methods Guide

"The relative merits and limitations of the methods chosen to explore the impact of switching treatments should be explored and justified with respect to the method chosen and in relation to the specific characteristics of the data set in question…"

Methods Guide

"These characteristics include the mechanism of crossover used in the trial, the availability of data on baseline and time-dependent characteristics, and expectations around the treatment effect if the patients had remained on the treatment to which they were allocated."

- So it's clear that adjustment for switching is acceptable
- But the chosen adjustment method should be appropriately justified, based upon methodological assumptions and trial characteristics

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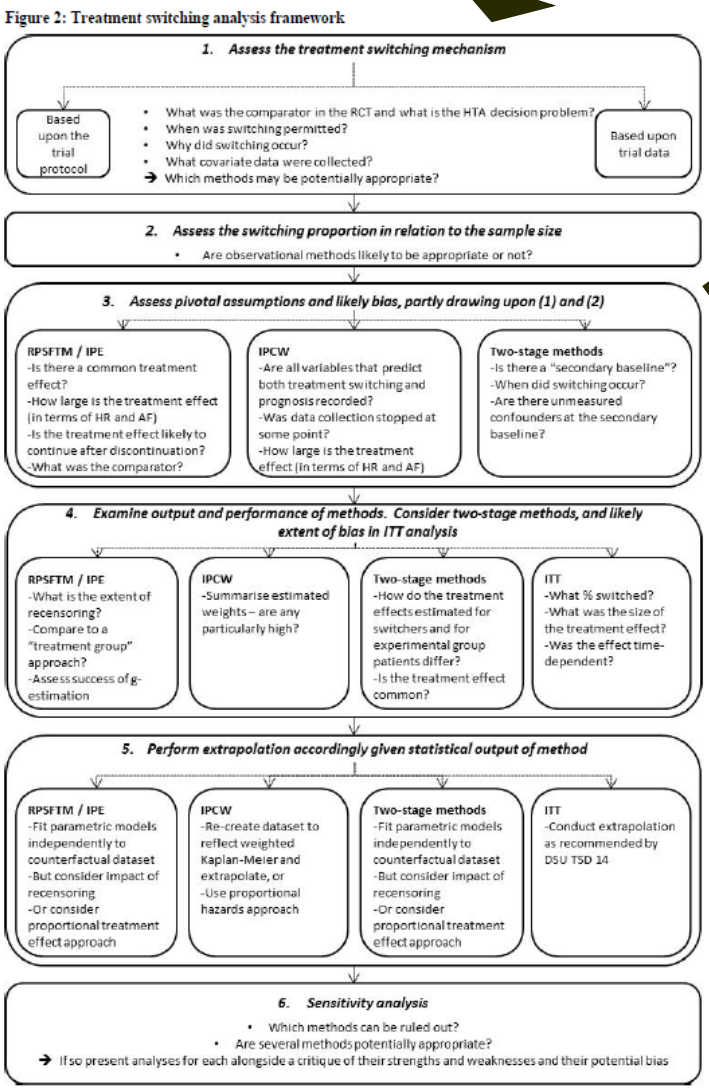
DSU

- DSU Technical Support Document 16 (Latimer and Abrams, 2014)



- Assess the treatment switching mechanism
- Assess the switching proportion and sample size
- Assess pivotal assumptions of adjustment methods in relation to trial characteristics
- Examine output/performance of methods
- Perform extrapolation according to statistical output of adjustment method
- Present sensitivity analysis for potentially appropriate methods

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Conclusions and further research

Conclusions

- Treatment switching is an important issue that has come to the fore in HE arena
- Current methods for dealing with treatment switching are imperfect and have been used uncertainly in TAs
- Naïve methods highly prone to bias. Complex methods will be unsuitable in some cases
- It is acceptable for manufacturers to attempt to adjust for treatment switching
  - **But methods used should be justified in detail**
  - **ERGs should be aware of how to assess appropriateness of methods on a case-by-case basis (precedent is not enough)**

Further research

- Here focus has been on adjustment using statistical models and survival analysis
- There are several other areas that warrant further research:
  - Making adjustment for other trial-based outcomes – utilities, costs
  - Using external data, design of clinical development programme
  - Making adjustments based upon summary data (for indirect comparisons)

A familiar story?