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# Adjusting for treatment switching in randomised controlled trials

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Thanks to Ian White, who I run a course with on this.
Some of my slides have borrowed from his

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# Health economic evaluation and HTA

- Economic evaluation plays an important role in HTA. Aim to ensure limited health care budget is allocated efficiently
- This means that the benefits of programmes that are implemented must exceed their opportunity costs
- Need to compare the new treatment to all relevant comparators
- Usually involves a comparison of the costs and effects of the new treatment and the standard treatment
  - Decision problem: compare state of the world where the new treatment exists, to state of the world where new treatment does not exist
- Usually information to make these comparisons is taken from randomised controlled trials using an intention to treat analysis

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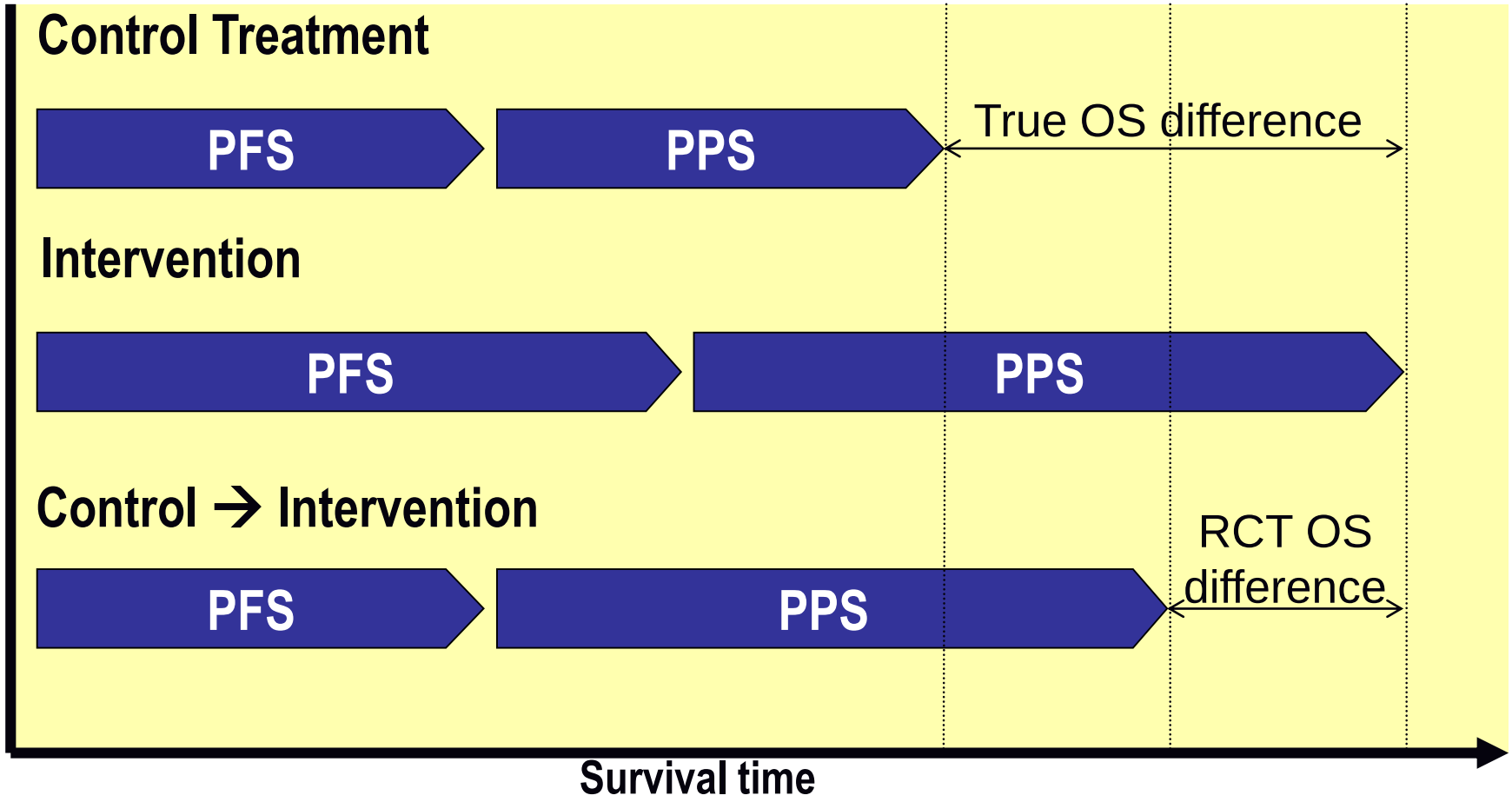
# Treatment switching

- What if patients randomised to the control group in a clinical trial are permitted to switch onto the experimental treatment at some point during the trial?

# Illustrating treatment switching




PFS: Progression-free survival; PPS: Post-progression survival; OS: Overall survival

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# Treatment switching

- Is an issue in over 50% of oncology technology assessments
  - This is a problem for decision-makers who rely on ITT analyses

  ➔**Need different analytical methods**
  - Adjustment methods can change decisions

**NICE TA321 Dabrafenib for melanoma**

57% switched

| | | |
|---|---|---|
| **ITT analysis:** | OS HR 0.76; | **ICER £95,225** |
| **Adjustment analysis:** | OS HR 0.55; | **ICER £49,019** |

- **Dabrafenib was recommended for use**

… so what's the problem?

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# Treatment switching

…different adjustment methods are available…

…and they might give different results

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

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

(Note, ITT did not include baseline covariates, RPSFTM did…)

As well as IPCW and RPSFTM, two-stage adjustment has been used in HTA to adjust for switching

- ➔ We need an understanding of the methods, so we can decide which one to believe, on a case-by-case basis
- ➔ But first…

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# Types of switching

1. Switching from the control onto the experimental treatment
   - 'Direct' switching

2. Switching from the experimental onto the control
   - 'Direct' switching

3. Switching from control/experimental onto other treatments
   - 'Indirect' switching

- What it is relevant to adjust for depends upon our **decision problem (this is not always straightforward!)**

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# Types of switching

## 'Direct' switching

- 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

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# Types of switching

## 'Direct' switching

- 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

- **BUT**, If control treatment represents a standard therapy (or placebo/BSC), it will be available in State A and State B
- Switching from the new treatment to the control treatment (due to lack of efficacy/toxicity etc.) may represent a realistic treatment pathway in both states of the world

➔ We (usually) do not need to adjust if experimental group patients receive the control treatment

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# Types of switching

**'Indirect' switching**

- Situation 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 within both states of the world
  → unnecessary/undesirable to adjust
- If these include other experimental treatments that are not available in the real world, they may represent unrealistic treatment pathways within both states of the world
  → necessary/desirable to adjust

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# What do we need to adjust for?

1. Switching from the control onto the experimental treatment
   - 'Direct' switching 
2. Switching from the experimental onto the control
   - 'Direct' switching 
3. Switching from control/experimental onto other treatments
   - 'Indirect' switching 

- What it is relevant to adjust for depends upon our **decision problem**

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# Adjustment methods – a summary

- When we want to adjust for treatment switching we have the following options

- Exclude/censor switchers
  - Weak in simple settings
  - But can elaborate it → IPCW
- Model treatment effect after switch → Two-stage
- Model treatment effect → RPSFTM

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# IPCW

Idea is to extend simple per protocol censoring analysis to remove selection bias.

**Four steps:**

1. Censor switchers at point of switch
2. Model probability of switching according to baseline and time-dependent characteristics → No unmeasured confounding
3. Use probabilities to compute weights (e.g. upweight people who have similar characteristics to switchers but *didn't* switch)
4. Use weights in a survival analysis to remove selection bias associated with censoring

Hernan MA, Brumback B, Robins JM *J Am Statist Assoc*. 2001; 96(454):440-448.

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# Two-stage adjustment

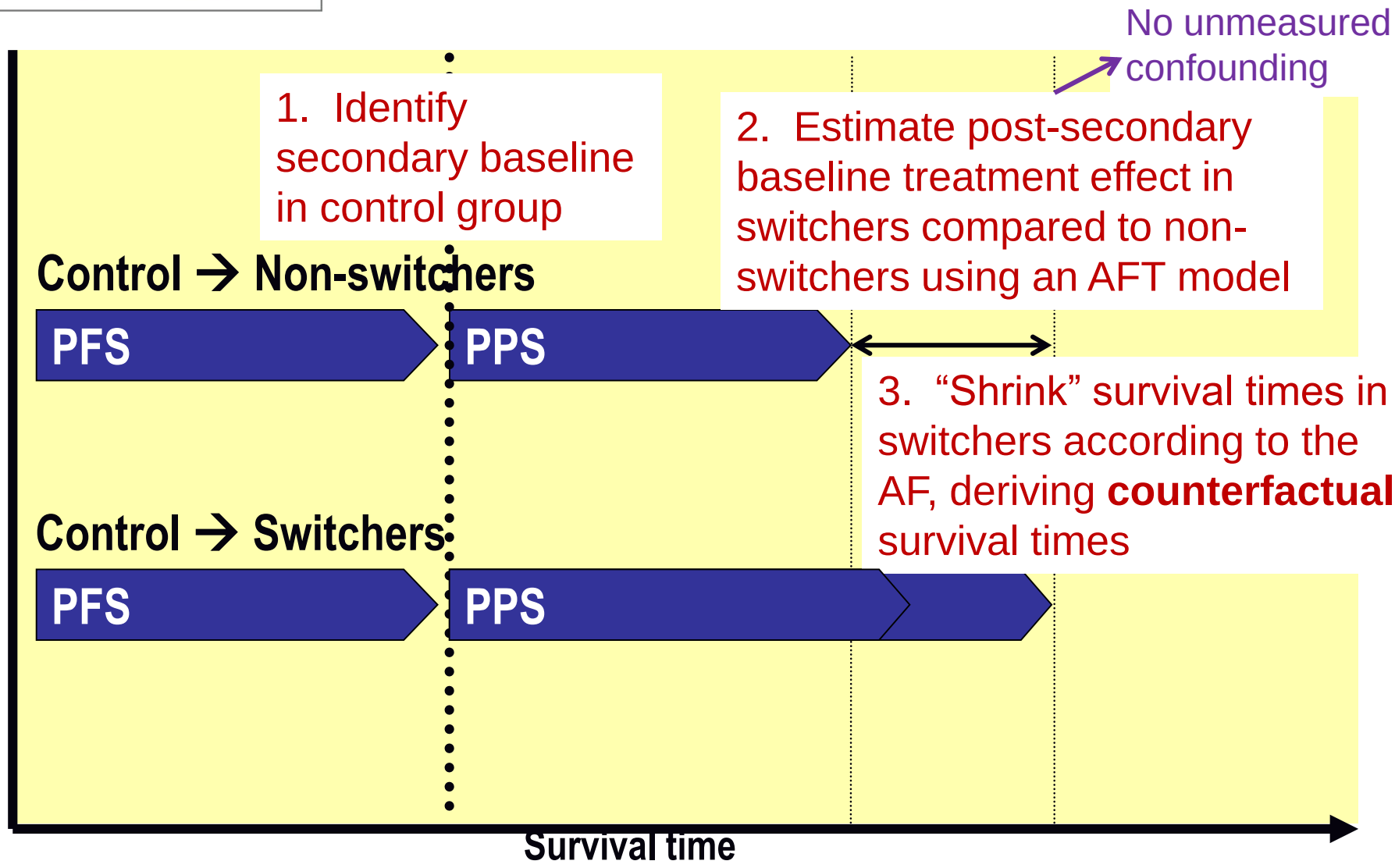
Idea is to estimate the treatment effect associated with switching, allowing us to derive what would have happened in the absence of switching

Applicable when switching happens after a specified disease-related time-point (e.g. disease progression)

**Three steps…**

Latimer N, Abrams KR, Lambert PC *et al. Stat Methods Med Res*. 21 November 2014.

# Two-stage adjustment



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# RPSFTM

Like the two-stage method, estimate treatment effect associated with switching, allowing us to derive what would have happened in the absence of switching

But, doesn't distinguish between the treatment effect in switchers and the treatment effect in the experimental group

- Doesn't need the NUC assumption, but…

1. Assume perfect randomisation: no treatment, equal average survival
2. Assume there is a common treatment effect
3. Use g-estimation and a counterfactual survival model to identify a value for the treatment effect that gives equal untreated survival times between randomised groups – hence derive untreated survival times for switchers

Robins JM, Tsiatis AA. *Commun Stat Theory Methods.* 1991; 20(8):2609-2631.

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# Identifying appropriate methods

It is not easy to identify the “best” method. Different methods will be best in different circumstances. We need to consider:

1. Methodological assumptions: Are they plausible?
2. Practical issues: Has the analysis “worked”? How (exactly) has it been applied?
3. Evidence on performance of methods: From simulation studies (Latimer N, Abrams K, Lambert P et al. Stat Methods Med Res 21 November 2014; Latimer N, Abrams K, Lambert P et al. Stat Methods Med Res 25 April 2016)

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# Simulation study findings

RPSFTM / IPE produce low bias when treatment effect is common

→ But are very sensitive to this, especially when the treatment effect is high

IPCW is volatile in (relatively) small trial datasets

→ Especially when switching % is very high (leaving low *n* in control group)

Simple two-stage methods are worthy of consideration

Very important to assess trial data, switching mechanism, treatment effect to determine which method likely to be most appropriate

There is a requirement for clinical opinion, to determine justifiable methods

→ **Don't just pick one!!**

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# Adjustment methods and HTA

- Adjustment analyses are becoming increasingly common in HTA
- Several HTA agencies are ready to adopt them
  - NICE, PBAC and SMC ✓
  - IQWiG ✗

→ NICE and PBAC have published technical guides (e.g. see Latimer N, Abrams K. NICE DSU Tech Support Doc 16, 2014)

***BUT…***

- Adjustment analyses not always accepted – case-by-case basis

➔ Concerns are with assumptions that cannot be perfectly tested

➔ And potential scope for "selective" analyses (within methods, and also around what to adjust for)

Which covariates are used in IPCW? Which AFT model is used in two-stage?
Is re-censoring incorporated in two-stage / RPSFTM? Direct and indirect switching?

➔ Sometimes results seem to lack clinical validity

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# Adjustment methods and regulatory

- Adjustment analyses are rarely a feature in regulatory submissions
- But FDA and EMA  have both been actively involved in international workshops discussing the topic (Adelaide, Baltimore)
- Addendum to ICH E9 seems to make the case that analyses to adjust for switching are justifiable
- Perhaps these will begin to feature more in the future?

Latimer NR, Henshall C, Siebert U, Bell H. *Int J Tech Ass Health Care*. 32(3):160-166 14 Sep 2016
Henshall C, Latimer NR, Sansom L, Ward RL. *Int J Tech Ass Health Care*. 32(3):167-174 01 Jan 2016

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# Conclusions

- Treatment switching is a common issue in HTA
- Standard ITT analyses may not answer the question HTA decision-makers are interested in
- Adjustment methods represent an answer and are being used (in some places, with caution)
- Some decision makers are *not* using these methods and some analyses are poor – there is a need to improve quality
- Adjustment methods must be appropriately justified and described, and precedent is not enough