What decision makers need to understand about treatment switching

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My comments are my own, and do not necessarily reflect those of
Cambridge University Hospitals or NICE

What do you need to make a decision when presented with methods to deal with treatment switching?

- 'I'd like to see all the possible methods presented.'
- 'I want to be reminded of the assumptions behind each method'
- 'Adjusting for treatment switching is awful. It's awful because it's clearly necessary, but you have completely confounded data and it's very difficult to make a sensible decision.'
- 'We need to know that the company knows what is actually happening, and has dealt with this thoughtfully'
- 'I want to see survival curves'
- 'Randomisation is a means to get rid of bias. I think the data we get are not fit for purpose and this treatment switching is a step too far. It complicates things!'
- 'What do I need to make a decision? I need to call Nick Latimer'

Decision makers need to understand problem

1. Patients take cancer treatments until disease progression
2. Pharma do trials with 1∘ endpoint of disease progression
   - Because they can; also smaller, shorter, cheaper
3. Patients randomised to old treatment – at progression - then get new treatment
4. NICE wants to know how much longer new drug makes people live
5. Although trial is 'finished', patients followed (a while) to death
6. Pharma analyses patients by treatment to which they are randomised; if new drug lengthens life, this analysis lessens apparent benefit
7. Trial does not answer question: How much longer do people live **on** new treatment compared with people **not** on new treatment? Rather, answers question: How much longer do people live who get new drug **earlier** compared with **later**?
8. Techniques discussed today disentangle the treatment effect

Metaphors can help understanding
Barca vs. Cambridge United 'friendly'

Score at half-time: 5-1

At half-time: Messi and 5 others swap with Cambridge United players

Score at full-time: 5-4

What would the score have been had the players not 'crossed over'?
How much more effective is Barcelona, really?

Metaphor courtesy of Nick Latimer

Need to understand that techniques can apply to 'follow-on' treatments

Follow-on drug 'indirect switching'

New drug

Not only 'cross over', but drugs post progression which both extend life and are not available in the NHS

Need to understand jargon: 'Censoring'
Outcome of interest didn't happen; different kinds of censoring

Need to understand jargon: 'Counterfactual'
What would have happened if…?

*Sliding Doors, 1998. '..*based on the two paths the central character's life could take depending on whether she catches a train, and causing different outcomes in her life.'

https://en.wikipedia.org/wiki/Sliding_Doors

Need to understand that these techniques well established in field of epidemiology

- 'Randomized trials .. with their potential for substantial deviations from the protocol…are subject to many of the biases that we have learned to associate exclusively with observational studies.'
- 'Other than baseline randomization, there are no other necessary differences between analysis of observational data…and randomized trials. That is, a randomized trial can be viewed as a follow-up study with baseline randomization and the analyses of observational longitudinal data as a follow-up study without baseline randomization.'
- '…one would expect that randomized trials and observational studies would be analysed similarly (apart from the need to adjust for baseline confounders in observational studies)'

Miguel A Hernan and James M Robins

Ref: Methods in Comparative Effectiveness Research. Gatsonis and Morton, eds. 2017

Inverse Probability of Censoring Weighting
Basics and key assumptions

Basics:
- Problem with censoring switchers among people randomised to old drug who progress is that they probably have a fundamentally different life-expectancy than non-switchers
- IPCW includes, but adjusts for, censoring switchers
- It figure out how switchers differ from non-switchers
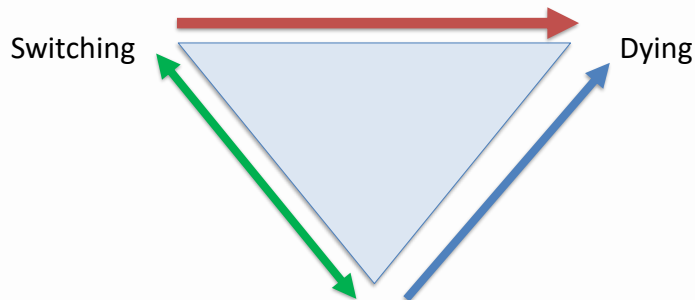- 'Weights' non-switchers to reflect the switchers

Assumptions:
- No unmeasured confounders
- Too few people not switching messes up weighting

Assumption 'no unmeasured confounding' for IPCW and 2-stage

What factors, if taken into account, would change the size of the association between switching and death?

Switching → Dying

Potential confounders at beginning (baseline')
AND
that change during trial ('time dependent')

Rank Preserving Structural Failure Time Models
Basics and key assumptions

Basics:
- Daunting name
- Failure time models differ from proportional hazards models - have acceleration factors - switching decelerates time to death
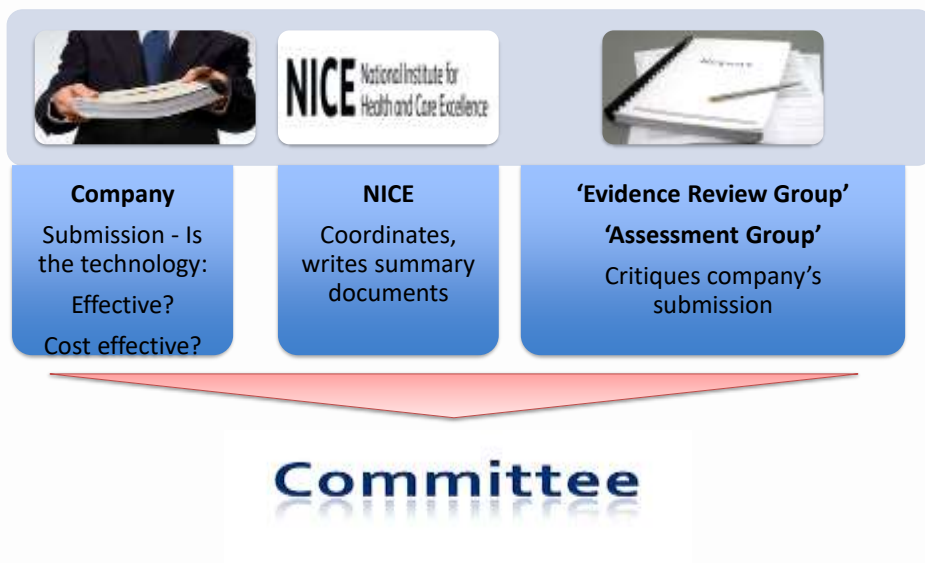
Assumptions:
1. Perfect randomisation
2. 'Common treatment' effect
   Treatment works as well at switching as it did at randomisation
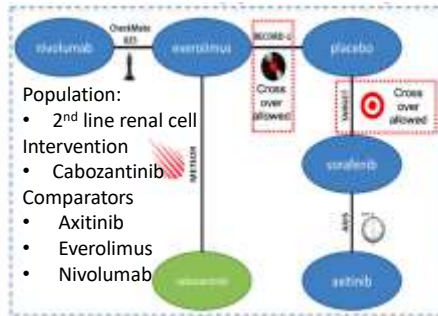
It's in the title
- R randomisation
- P perfect,
- S same
- F functionality (fruitfulness?) of
- T treatment at
- M midpoint

Challenges for Committee

Company	NICE	'Evidence Review Group'
Submission - Is the technology:	Coordinates, writes summary documents	'Assessment Group'
Effective?		Critiques company's submission
Cost effective?		

Committee

When key trial OK, but network meta-analysis not

Population:
- 2nd line renal cell

Intervention
- Cabozantinib

Comparators
- Axitinib
- Everolimus
- Nivolumab

Appraisal consultation document Cabozantinib for previously treated advanced renal cell carcinoma. 2017

"The trials included in the network differed substantially in whether or not the trial permitted patients to switch between treatment arms …TARGET allowed patients to switch treatment after the disease progressed, but the data that the company used from this trial 'censored' those patients who switched treatment. …. The committee concluded that it would take into account any potential biases within the network when making decisions."

When committee not provided with information

"The company was unable to explain the method* it had used to adjust for treatment switching and it could not comment on whether using an alternative method would have affected the estimates of cost effectiveness. The Committee concluded that it was appropriate to adjust for treatment switching in the economic analyses of sipuleucel-T, but it had not been provided with enough information to determine whether the company's method of adjustment was appropriate"

*iterative parameter estimation analysis

Ref: NICE. Appraisal consultation document Sipuleucel T for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer. October 2014.

When company does not prove assumptions, and justifies method because others use it, so it must be OK

- Company's defended: 'A common treatment effect, a recognised limitation of the (RPSFTM) model, is untestable … (company) reiterated that RPSFTM is a widely accepted method …and has been used in a number of oncology clinical trials across different agents and indications.'

Evidence Review Group's Report Crizotinib for untreated anaplastic lymphoma kinase-positive non-small-cell lung cancer
CRD and CHE Technology Assessment Group, University of York

When companies disagree with review group and each other

- Company A defended choice of IPCW
  - All methods have 'limitations'
  - Explored uncertainty - results for RPSFTM and 2-stage
- Company B defended choice of RPSFTM
  - Argued that if none of observed variables predict switching, then the variables that predict switching are unobserved, and IPCW will be biased
  - Argued that if it were to implement the recensoring (2-stage) method … it would result in "such a significant loss of information as to render the method unhelpful"
- Assessment Group
  - Supported use of 2-stage

IPCW, inverse probability of censoring weighted; RPSFTM, rank preserving structural failure time model

Watch this excellent, educational, entertaining piece
'nick latimer' + 'treatment switching' + 'youtube'