The (mis)use of treatment switching adjustment methods in health technology assessment – busting some myths!

ISPOR Barcelona, 2018

Dr Nicholas Latimer (n.latimer@sheffield.ac.uk)
Reader in Health Economics, School of Health and Related Research, University of Sheffield, UK

Nicholas Latimer is funded by a National Institute for Health Research Post-doctoral Fellowship. These slides presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Treatment switching

- 40% of NICE TAs are in cancer
- Treatment switching is an issue in over 55% of oncology technology assessments
  - 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**

2

Treatment switching

- But…
  - <50% TAs include adjustments for switching
  - ≈60% of adjustment analyses rejected

- Reliance on ITT, or upon poor adjustment analyses, has severe consequences
  - Inappropriate recommendations
  - Sub-optimal resource allocation
  - Lost lives, lost QALYs

➔ **Why aren't we using adjustment analyses more?**

Treatment switching

Why aren't we using adjustment analyses more?

Low decision-maker confidence in methods

- Methods make untestable assumptions which may lack face-validity

Poor application of methods

- Don't justify use
- Incorrect application
- Poor reporting

Addressing some of these issues

Important issues that I won't cover…

1. Method selection. It is not sensible to present analyses using only one adjustment method, without properly describing why other methods are not appropriate

2. Reporting. Analyses should always be comprehensively reported, e.g.

- What covariates were included and why
- What was assumed about the durability of the treatment effect
- Analyses with and without re-censoring
- What range of weights came out of weighting analyses

➔ Work is ongoing on reporting standards for adjustment analyses

Addressing some of these issues

Areas that I will cover…

Areas where methods are being mis-understood, or used sub-optimally:

1. Enforced use of hazard ratios
2. Assessment of the common treatment effect assumption
3. Unmeasured confounding and missing data

Enforced use of hazard ratios

- Adjustment methods usually used to estimate hazard ratios (HR)

→ Rely upon proportional hazards assumption in survival/economic models

→ Economic models that rely on PH are often unpopular

→ Therefore, adjustment analyses may be unpopular

➔This is not necessary!

Enforced use of hazard ratios

RPSFTM

- **Generate** **to derive HR**

Two-stage e

- **Generate** **to derive HR**

IPCW

- **Results i** **val analysis**

Myth-bust #1

Methods do not necessarily produce adjusted HRs

If we do an adjustment analysis it does not mean that we must use HRs in our economic model

Common treatment effect (CTE) assumption

- The RPSFTM relies upon the CTE assumption
- Has been rejected due to its reliance on CTE

- It is impossible to test this assumption **BUT**

➔ **Analysis of the CTE assumption has been sub-optimal**

Common treatment effect (CTE) assumption

1. Sensitivity
   → e.g. w
   → does
2. Two-sta o switchers
   → Comp similar?

Myth-bust #2

We do not have to just accept (or not) the common treatment effect assumption

It is not a case of *"we don't believe the CTE assumption so there's no point looking at the RPSFTM"*

Further investigation is required

Unmeasured confounding and missing data

- IPCW and two-stage (TSE) methods rely upon "no unmeasured confounding" (NUC) assumption

→ Put *everything* in the models

→ Unless *everything* is measured in the trial, don't believe in these methods

➔ This is not necessary and may be wrong

➔ Need to consider what constitutes a confounder

Unmeasured confounding and missing data

1. Why is the data missing? i.e. can it be observed by the clinician?
2. Does t… …ffect?

…on *everything*

…as introduced …be useful for …r or not we …have any …l confounders)

Karno… PS

Receive… treatment (Y/N)

Myth-bust #3

IPCW and TSE shouldn't be thrown out "just" because a potentially important variable is missing.

Further investigation is required – could it be a confounder? Is it independent?

Conclusions

- If we want adjustment methods to be used more we need to use them better
- There are lots of quite simple things that we can do that can increase the likelihood that adjustment analyses will be believed/used