



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

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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**



Treatment switching

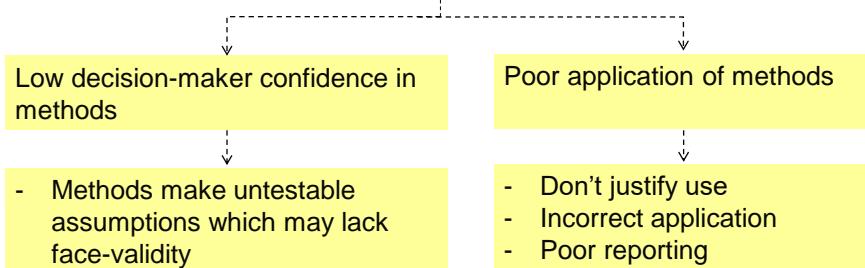
- But...
 - <50% TAs include adjustments for switching
 - ≈60% of adjustment analyses rejected
- Reliance on ITT, or upon poor adjustment analyses, has severe consequences
 - Inappropriate recommendations
 - Sub-optimal resource allocation
 - Lost lives, lost QALYs

➔ Why aren't we using adjustment analyses more?



Treatment switching

Why aren't we using adjustment analyses more?





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

Two-stage e

- Generate

IPCW

- Results i

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

to derive HR

to derive HR

val analysis



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. what if
 - does it matter?
2. Two-stage
 - Comparison

Myth-bust #2

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

o switchers similar?

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



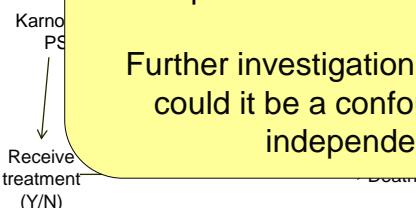
Unmeasured confounding and missing data

1. Why is the data missing? i.e. can it be observed by the clinician?
2. Does the missing variable affect the outcome?

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?



on *everything*
as introduced
be useful for
or not we
have any
confounders)



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