It’s Rarely Simple

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First Observational Study with Switching?

Whiskas Advert (1987)

“8 out of 10 said their cats preferred it”
Recap – NP-C Registry Delayed Initiation (Switching) to Zavesca

Like a standard RCT problem but without the R

How Should We Analyse this?

• Possible methods
  • Inverse probability censored weighting (IPCW)
  • Rank-preserving structural failure time modelling (RPSTM)
  • Two stage modelling

• Problem when assumptions are violated
  • IPCW – no unmeasured confounders
  • RPSTM – randomised groups and common treatment effect
  • Two stage model – no unmeasured confounders and existence of a second baseline from which the effect of switching can be estimated
Let’s Be, Oh Dear, Simple

- Analyse using a *time dependent covariate*

Criticism of Time Dependent Treatment

- Lack of inclusion of confounders at time of switching can cause selection bias and ruin the randomisation

Randomised groups are no longer balanced for predictors of prognosis – the treatment effect is confounded

VS
But..

No Randomisation / No Control / No Visit Schedule
So Just Do ITT?

• An ITT approach (whatever that means in this context)

Ever took Zavesca  
vs. 
those who did not

So Just Do ITT? No.
So Just Do ITT? No.

Let’s Be a Bit Less Simplistic

• We used an extended Cox Model with time dependent treatment including potential confounders at baseline (i.e. predictors of treatment and prognosis)
  • Selection bias - remember this is not an RCT!

Unbiased (hopefully/unlikely) estimate of treatment effect
Is It Really That Simple?

- Who has ever done an time dependent treatment analysis?
- Did you have any challenges?
- Any problems?

14th November 2018

Increasing Patients at Risk

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Decreasing subjects at risk

Increasing subjects at risk

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Increasing Patients at Risk

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13 deaths from 7 patients at risk!?!?

Kaplan-Meier Underestimates Survival

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Underestimation of $S(t)$
Kaplan-Meier Underestimates Survival

Adjusted Survival Curves

- Survival curves don’t necessarily reflect treatment estimate from model if left unadjusted for imbalances caused by predictors of prognosis
  - Would also be the case in RCTs but randomisation (normally) removes the necessity for adjusted curves
Adjusted Survival Curves

Unadjusted

Adjusted

Cox Model Hazard Ratio = 0.564

Cox Model Hazard Ratio = 0.423

Adjustment using Corrected Group Prognosis (CGP) Method

Summary

• It’s not all about RCTs – observational studies also have to provide answers to urgent scientific questions
• In the absence randomisation and data on confounders at time of switching all analyses (complicated or otherwise) will be biased
• Time dependent covariate models are regarded as naive and too simplistic, but they might be the only option
• ...and even then, it’s not as straightforward as you may first think.
Recommendations

• Determine what should be estimated
• Think Estimands – “hypothetical”, “treatment policy”,...
• Collect the data on potential confounders (where possible)
• Utilise methods such as propensity scores, IPCW and Two-Stage Models where applicable

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Switching to Whiskers Works!

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