It´s Rarely Simple

Martin Scott
Numerus – Germany

martin.scott@numerus.com

ISPOR – Barcelona – 14th November 2018

numerus

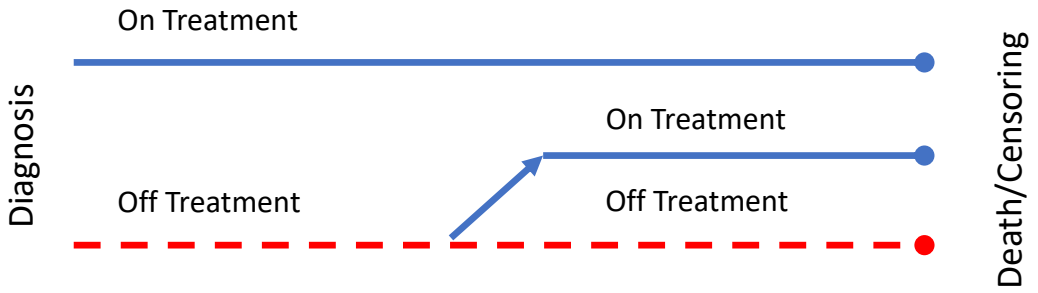
First Observational Study with Switching?

Whiskas Advert (1987)

"8 out of 10 said their cats preferred it"

numerus

Recap – NP-C Registry Delayed Initiation (Switching) to Zavesca



Like a standard RCT problem but without the R

numerus

How Should We Analyse this?

- Possible methods
  - Inverse probability censored weighting (IPCW)
  - Rank-preserving stuctural 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

numerus

Let´s Be, Oh Dear, Simple

- Analyse using a time dependent covariate

numerus

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

numerus

But..

numerus

No Randomisation / No Control / No Visit Schedule

numerus

So Just Do ITT?

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

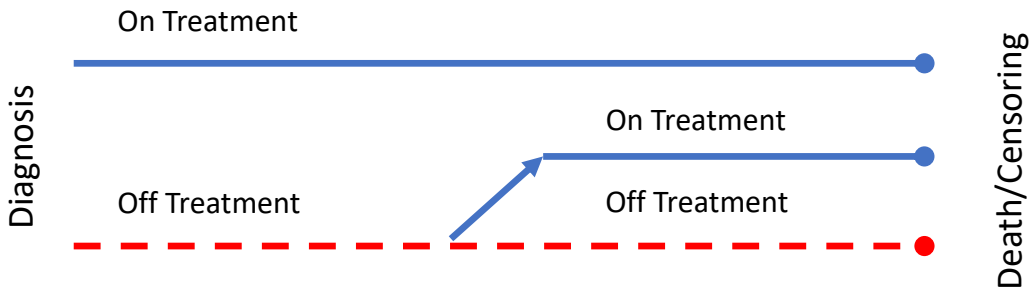
Ever took Zavesca

vs.

those who did not

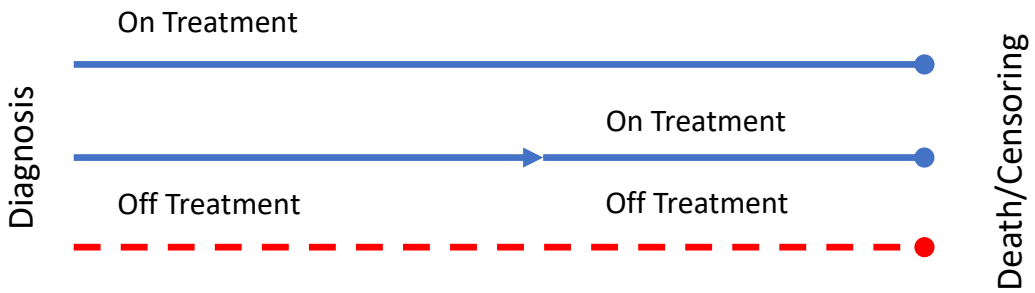
numerus

So Just Do ITT? No.



numerus

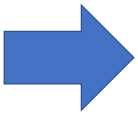
So Just Do ITT? No.



numerus

Let´s Be a Bit Less Simplistic

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



Unbiased (hopefully/unlikely) estimate of treatment effect

numerus

Is It Really That Simple?

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

numerus

Increasing Patients at Risk

Time	# deaths	At risk
0	0	50
1	1	50
2	4	40
3	6	7
4	13	14
5	13	18
6	16	17
7	19	25
8	22	28
9	25	35
10	27	23

Decreasing subjects at risk

Increasing subjects at risk

14th November 2018

numerus

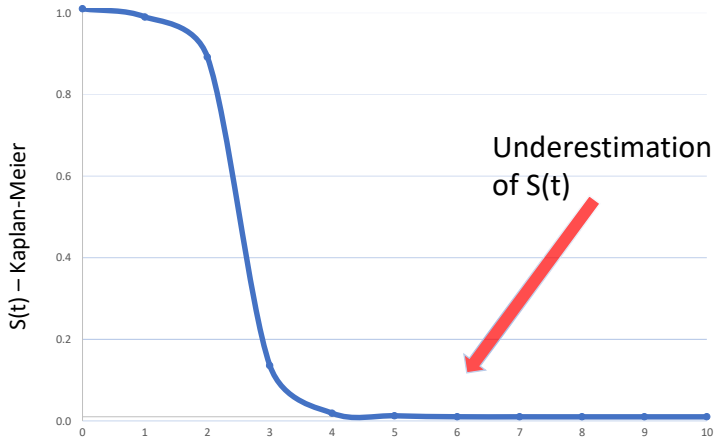
Increasing Patients at Risk

Time	# deaths	At risk
0	0	50
1	1	50
2	4	40
3	6	7
4	13	14
5	13	18
6	16	17
7	19	25
8	22	28
9	25	35
10	27	23

13 deaths from 7 patients at risk!?!

numerus

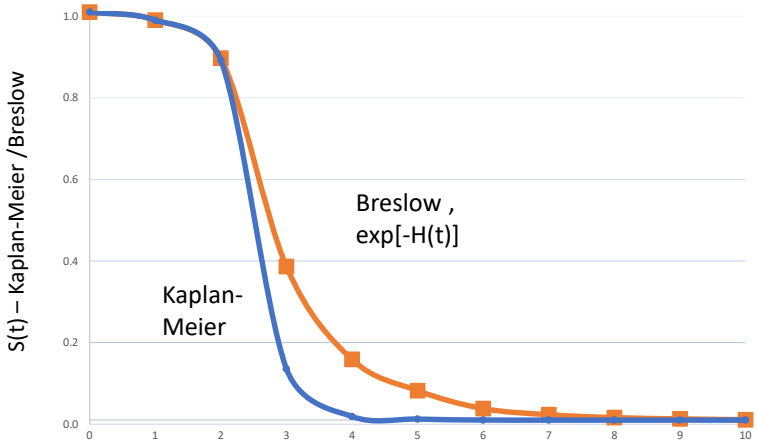
Kaplan-Meier Underestimates Survival



Time	# deaths	At risk	KM
0	0	50	1.00
1	1	50	0.98
2	4	40	0.88
3	6	7	0.13
4	13	14	0.01
5	13	18	0.00
6	16	17	0.00
7	19	25	0.00
8	22	28	0.00
9	25	35	0.00
10	27	23	0.00

numerus

Kaplan-Meier Underestimates Survival



Time	# deaths	At risk
0	0	50
1	1	50
2	4	40
3	6	7
4	13	14
5	13	18
6	16	17
7	19	25
8	22	28
9	25	35
10	27	23

numerus

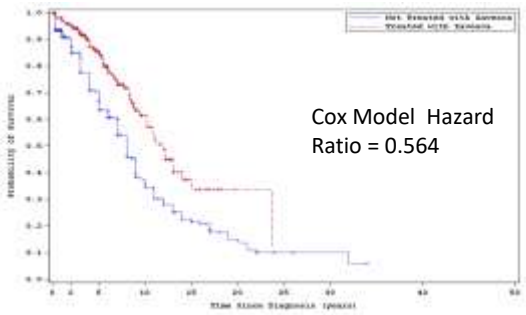
Adjusted Survival Curves

- 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

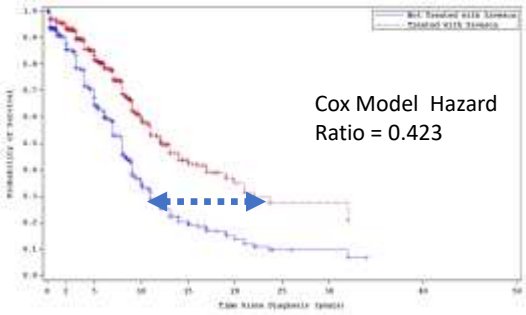
numerus

Adjusted Survival Curves

Unadjusted



Adjusted



Adjustment using Corrected Group Prognosis (CGP) Method

numerus

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.

numerus

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

numerus