Workshop report: Methods for adjusting for treatment switches in late-stage cancer trials

Ian White, 18 May 2012.

Organisation

This one-day workshop was organised by Ian White (MRC Biostatistics Unit & Cambridge HTMR) in conjunction with Paula Williamson (NW HTMR), Susie Dodd (NW HTMR), Sarah Walker (London HTMR), Chris Metcalfe (Bristol HTMR), Nicholas Latimer (University of Sheffield), Martin Pitt (Peninsula College of Medicine and Dentistry) and Xin Huang (Pfizer).

Funding was provided by the HTMR network.

This workshop was held at MRC head office, London, on 20th Feb 2012.

The final programme is attached.

Background

In late stage placebo-controlled cancer trials, it is common to give the experimental treatment to placebo arm patients at the point of disease progression. This treatment switching (also called cross-over or contamination) does not affect the estimated treatment effect on progression-free survival, but dilutes the estimated treatment effect on overall survival (if there is one), and reduces the power of intention-to-treat analysis. The dilution can be very strong in later follow-up: for example, in NICE guidance on the use of sunitinib for the treatment of gastrointestinal stromal tumours, interim analysis gave a hazard ratio of 0.49 (P=0.007) while final analysis had a hazard ratio of 0.88 (P=0.31). Dilution of treatment effects for overall survival is of special relevance to health economic assessments such as are widely done for NICE, because they require a real-life estimate of overall survival benefit when the treatment is given outside the clinical trial without switches.

Various methods have been used to correct for treatment switching: perhaps the two most favoured are the rank-preserving structural failure time model (RPSFTM) and inverse probability of censoring weighting (IPCW). RPSFTM respects the randomisation but its usual implementation fails to regain any power lost. IPCW does regain lost power but does not fully respect the randomisation and instead relies on an assumption of no unmeasured confounders.

Report on the workshop

26 people attended. Talks covered the following areas:

1. The nature and importance of the problem of treatment switching in late-stage cancer trials.
2. Poor reporting of treatment switching and other treatment changes in practice.
3. Methods for analysis, focussing on RPSFTM and IPCW, but also including the use of historical controls and extrapolation from progression-free survival to overall survival.

4. Simulation studies comparing the methods.
5. Health economic perspectives.
6. Experiences of people working in the pharmaceutical industry.
7. Experience of people doing NICE appraisals.
8. General discussion.

Key methodological points that came out of the discussion were:

1. It is useful to avoid switches if this is practically and ethically possible, both in the design (for example, by restricting circumstances in which the placebo arm will receive treatment) and in the analysis (for example, by defining progression-free survival as the primary outcome, if this is possible).
2. It is important to define clearly the question to be addressed in any analysis that attempts to adjust for switching. In particular, do we want to compare “treatment now” with “treatment on progression” or with “no treatment at all” (or both)?
3. All the analysis methods make assumptions which are untestable and often dubious: in particular, the RPSFTM assumes the treatment effect is the same whether treatment is given at randomisation or at progression, while IPCW assumes no unmeasured confounders.
4. The properties of the methods are reasonably well known and understood when their assumptions are correct, but less well known and understood when their assumptions may fail: simulations should help to shed light on this, but can be highly complex.
5. No one method is better than the others in all settings, so the choice of method must depend on the clinical context.
6. Pre-specification of analyses is important but hard to do, especially since IPCW becomes impossible if all patients who progress then switch.
7. There is a disconnect between licensing, which may be based on progression-free survival, and funding requirements, which are (in practice) largely based on overall survival.
8. The very wide confidence intervals produced by RPSFTM makes it very vulnerable to selective reporting.

The following needs were identified:

1. NICE needs to receive and disseminate guidance on the properties of the available methods and how suitable methods should be chosen and implemented.
2. Trialists need to be more aware of the issues and their implications for design and analysis.
3. Statisticians need code, especially in SAS and R, ideally as online resources.
4. All need a better understanding of how robust the methods are to their assumptions being violated.

5. Methodological needs include finding more powerful versions of the RPSFTM; exploring implications of the RPSFTM for restricted mean survival and for cost-effectiveness acceptability curves; and developing simpler simulation study designs; and exploring "false positive" properties of these methods when there is no treatment benefit on overall survival.

Proposed outputs

The following outputs were suggested:

1. Guidance for NICE. Nick Latimer is working with NICE to produce this, and will send draft guidance to members of the workshop for comment.
2. A session at next year's HTMR network methodology conference.
3. Input to the SPIRIT initiative on protocol items.
4. Most of the presentations from the workshop are available on the HTMR network website.
5. Two papers are already planned by Nick Latimer on his simulation study (one reporting the results, one reporting the implications for health economic evaluations), and a case study of the assessment of Everolimus has been drafted by Martin Pitt. Three further papers are proposed:
   a. A paper on the practical application of all the different methods for handling switches for the purposes of economic evaluations, with a review of methods used in NICE technology assessments. (Lead: Nick Latimer.)
   b. A paper on guidance for trialists (and regulators?), e.g. in BMJ "education and debate", explaining (using examples) why treatment switches are allowed and why they are a problem; how trials can (sometimes) be designed to avoid switches; how to identify the question of interest when there are switches; and what analysis options are available when there are switches (without mathematical details but stating the key assumptions). (Lead: Ian White?)
   c. A review article on the methods, for a methodological journal, reviewing & critiquing all the methods that have been used and identifying outstanding questions and possible future developments. (Lead: Ian White??)
6. Methodological work should continue, in particular that by Jack Bowden on improving the RPSFTM; exploration of extrapolating progression-free survival to overall survival; and exploration of the implications of the RPSFTM for cost-effectiveness analysis.

Appendix: workshop programme

Morning: Methods. Chair: Paula Williamson (North West HTMR)			
10:00	Ian White	Cambridge HTMR	Methods for handling treatment switching: rank-preserving structural nested failure time models, inverse-probability-of-censoring weighting, and marginal structural models
10:45	Susie Dodd	North West HTMR	Departure from treatment protocol in published RCTs: a review
11:00	**Tea / coffee**		
11:20	James Morden	Institute of Cancer Research	Methods for adjusting survival estimates in the presence of treatment crossover - Simulation studies
	Nick Latimer	University of Sheffield	
12:05	Neil Hawkins	ICON PLC & University of Glasgow	Methods for health economic models in metastatic cancer
12:50	**Lunch**		
Afternoon: Perspectives. Chair: Ian White			
13:50	Xin Huang	Pfizer & PSI	Adjusting the Crossover Effect in Survival Analysis Using a Rank Preserving Structural Failure Time Model: The Case of Sunitinib GIST Trial
14:35	Rob Hemmings **[was unable to attend]**	Medicines and Healthcare products Regulatory Agency	Treatment switches in cancer trials - problems, pitfalls and (no) solutions
15:20	**Tea / coffee**		
15:40	Martin Pitt & Martin Hoyle	Peninsula Technology Assessment Group	Dealing with treatment switches in cost-effectiveness analysis: the NICE experience
16:10	Claire Watkins	AstraZeneca	Discussants & general discussion
	Chris Metcalfe	Bristol HTMR	
17:00	**End**		