TRIALS

ORAL PRESENTATION   **Open Access**

Evaluation of methods to adjust for treatment switching in clinical trials

Richard Fox[1*], Lucinda Billingham[1,2], Keith Abrams[3]

Introduction
Treatment switching in clinical trials dilutes estimates of treatment effect which is problematic in decision making, especially in an economic context. In one example 75% of patients crossover from the randomised treatment which emphasises the need to address such bias. We consider methodologies that compensate for this bias.

Methods
The methods assessed are; intention to treat (ITT), per-protocol (PP), adjusted Cox model [1], causal proportional hazards estimator [2], rank-preserving structural failure-time models (RPSFT) [3], iterative parameter estimation (IPE) [4], parametric randomisation based method [5], and the less well known inverse probability of treatment weighting (IPTW) [6].

Data
Survival data having an underlying Weibull distribution was simulated and designed such that probability of switching for patient subgroups could be varied within treatment-arms. Other subgroup characteristics could be controlled and 24 scenarios with varied levels of bias were analysed. A review of submissions to the National Institute of Clinical Excellence was performed and used to inform the scenario parameters.

Results
The RPSFT and IPE methods returned the lowest biases, <8%, in all scenarios. The estimates of the parametric randomisation based method were often far less variable than other methods but were subject to erratic behaviour with extreme biases observed. The other methods

performed poorly in general, with biases of up to 50% not uncommon. In particular the IPTW method over-compensates in most scenarios.

Conclusion
Under these conditions the results clearly identified the RPSFT and IPE methods as most consistent and accurate, with the latter the more consistent of the two. None of the other methods returned consistent results, and as such cannot be recommended.

Further avenues of investigation include exploring the effect of other underlying survival distributions, extending from univariate models to adjust for other covariates, and extending from situations where just control-arm patients switch to scenarios with multidirectional cross-over.

Author details
[1]Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, B15 2TT, UK. [2]MRC Midland Hub for Trials Methodology Research, University of Birmingham, Birmingham, B15 2TT, UK. [3]Centre for Biostatistics and Genetic Epidemiology, University of Leicester, Leicester LE1 6TP, UK.

References
1. Law , Kaldor J: **Survival analyses of randomised clinical trials adjusted for patients who switch treatment.** *Stat Med* 1996, **15**:2069-2076.
2. Loeys T, Goetghebeur E: **A causal proportional hazards estimator for the effect of treatment actually received in a randomised trial with all-or-nothing compliance.** *Biometrics* 2003, **59(1)**:100-105.
3. Robins J, Tsiatis A: **Correcting for non-compliance in randomised trials using rank preserving structural failure time models.** *Communication in Statistics-Theory and Methods* 1991, **20(8)**:2609-2631.
4. Branson M, Whitehead J: **Estimating a treatment effect in survival studies in which patients switch treatment.** *Stat Med* 2002, **21**:2449-2463.
5. Walker S, White I, Babiker A: **Parametric randomization-based methods for correcting for treatment changes in the assessment of the causal effect of treatment.** *Stat Med* 2004, **23**:571-590.

[1]Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, B15 2TT, UK
Full list of author information is available at the end of the article

BioMed Central

6. Hernan M, Brumback B, Robins J: **Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men.** *Epidemiology* 2000, **11**(5):561-570.