**SUPPLEMENTARY MATERIAL**

**Treatment Switching: statistical and decision making challenges and approaches**

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**N:\HEDS\Health Economics\Nick Latimer\International XO meeting\Figure 1 MSM Revision v1.tif**

**N:\HEDS\Health Economics\Nick Latimer\International XO meeting\Figure 2 Two-Stage Revision v1.tif**

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**DESCRIPTION OF RE-CENSORING**

The Two-Stage method and the RPSFTM involves shrinking survival times for patients who switched treatments. Usually, not all patients die during the defined follow-up period for a clinical trial – a substantial proportion are still alive at the end of trial follow-up. Since patients cannot contribute to analysis of the trial data after this point, they are in effect being censored from the analysis at the end of trial follow-up. This process is called “administrative censoring”. Administrative censoring is generally not associated with bias, because the trial cut-off date is the same for all patients, and the date of recruitment to the trial for each patient is random: hence the point at which a patient is subject to administrative censoring should not be related to prognosis. However, in the Two-Stage and RPSFTM adjustment methods, when we shrink survival times for switchers, we estimate shrunken death times for those who died during the trial, and shrunken administrative censoring times for those who were administratively censored. The extent to which these death and administrative censoring times are shrunken depends upon the estimated effect size, and if and when switching occurred. Given that we know that switching is likely to be associated with prognosis, this means that whilst administrative censoring times are not related to prognosis, shrunken administrative censoring times may be, and the shrunken administrative censoring times could therefore be associated with bias. ‘Re-censoring’ has been suggested as a solution to this problem.

Re-censoring involves breaking the dependence between censoring time and treatment received by re-censoring adjusted survival and censoring times at the minimum of the observed censoring time and the observed censoring time multiplied by the inverse of the estimated treatment effect (in the form of a ‘time ratio’ or ‘acceleration factor’, whereby a time ratio of greater than 1 indicates that the experimental treatment extends survival). Whilst re-censoring may avoid the bias associated with adjusted censoring times being related to prognosis, it generally involves a loss of longer term information. In circumstances where the treatment effect is not constant over time this can lead to biased estimates of the longer term treatment effect.