TO RE-CENSOR, OR NOT TO RE-CENSOR, THAT IS THE QUESTION: CRITICAL CONSIDERATIONS WHEN APPLYING STATISTICAL METHODS TO ADJUST FOR TREATMENT SWITCHING IN CLINICAL TRIALS

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OBJECTIVES

To determine when re-censoring should be incorporated in statistical analyses undertaken to adjust for treatment switching in randomised controlled trials, and to demonstrate the utility of inverse probability weighting (IPW) as an alternative to re-censoring. Treatment switching often has a crucial impact on estimates of the effectiveness and cost-effectiveness of new oncology treatments (Figure 1). Switching adjustment methods such as rank preserving structural failure time models (RPSFTM) and two-stage estimation (TSE) estimate 'counterfactual' (i.e. in the absence of switching) survival times and incorporate re-censoring to guard against informative censoring in the counterfactual dataset. However, re-censoring often involves a loss of longer term survival information which is problematic when estimates of long-term survival effects are required (Figure 2).

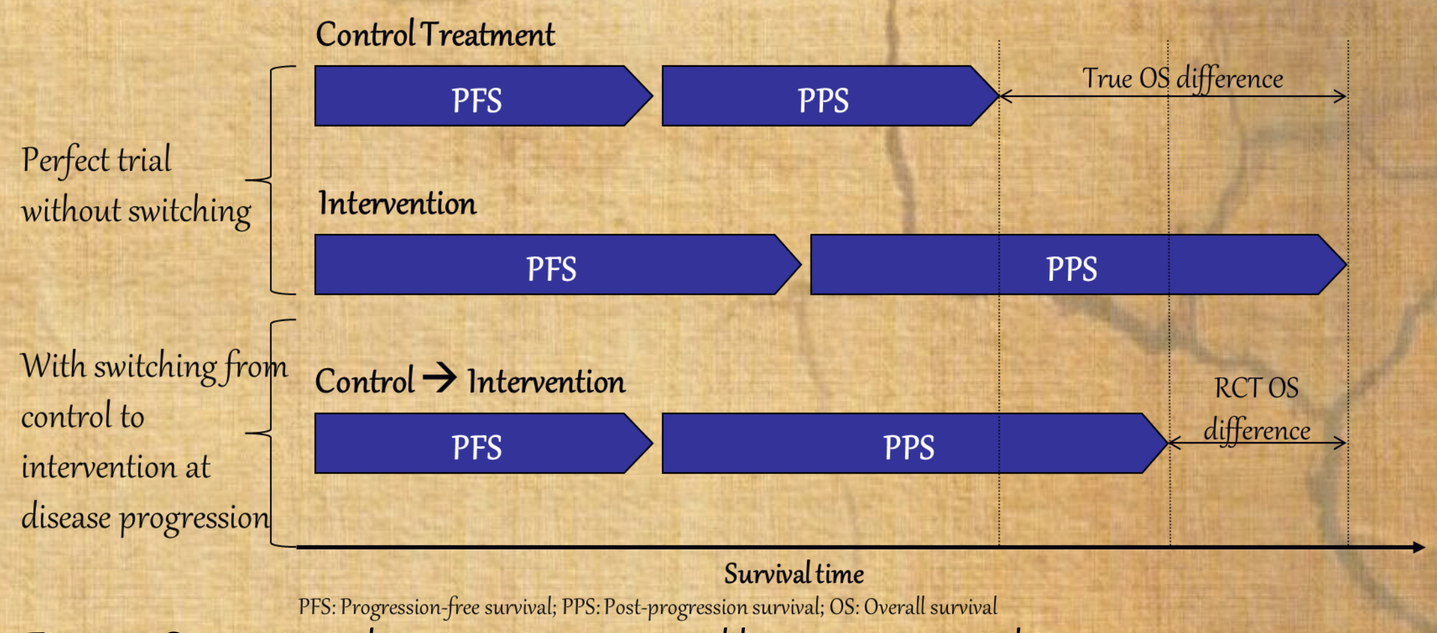

Figure 1. Contaminated treatment arms caused by treatment switching

METHODS

A simulation study was conducted, testing RPSFTM and TSE adjustment methods with and without re-censoring, and with IPW in place of re-censoring, across scenarios with various switch proportions and sizes and time dependencies of the treatment effect. Methods were assessed according to their estimation of true restricted mean survival in the control group (in the absence of switching) at the end of trial follow-up.

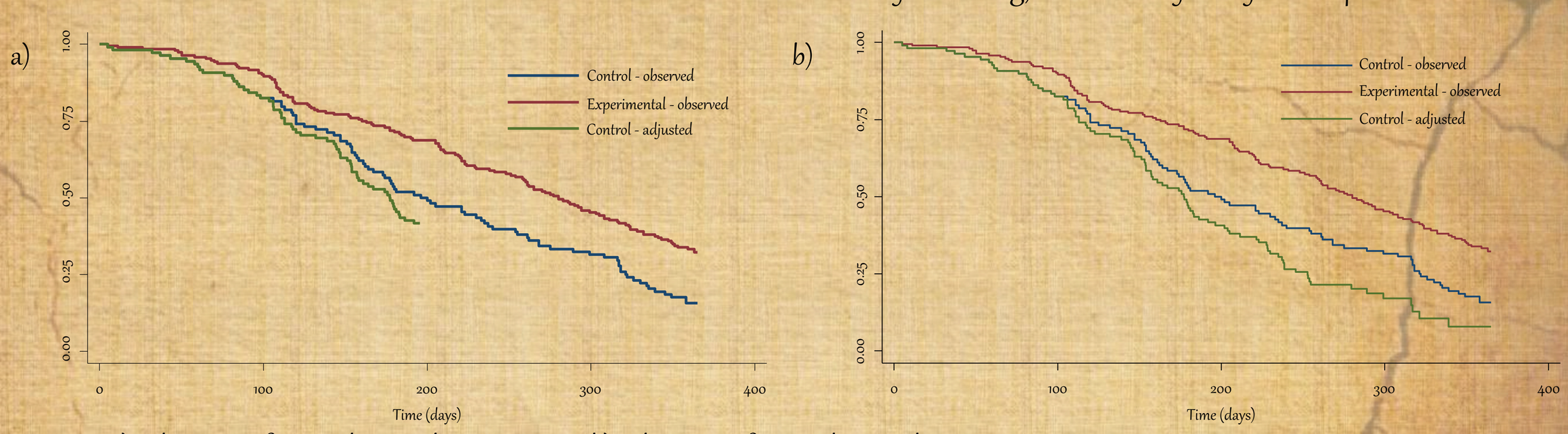

Figure 2. a) Adjustment for switching with re-censoring; b) Adjustment for switching without re-censoring

RESULTS

- RPSFTM analyses that incorporated re-censoring consistently produced negative bias (under-estimating control group mean survival and therefore over-estimating the treatment effect), with percentage bias ranging from -0.2% to -8.97%. TSE analyses that incorporated re-censoring usually produced negative bias (percentage bias range 0.0% to -4.1%). (Figure 3)
- RPSFTM and TSE methods that did not incorporate re-censoring consistently produced low-ranging positive bias (percentage bias 0.0% to 6.5%, over-estimating control group mean survival and therefore under-estimating the treatment effect). (Figure 3)
- RPSFTM and TSE analyses that incorporated IPW instead of re-censoring performed well when they resulted in weights with a low coefficient of variation (approximately 1.00) (percentage bias range 0.0% to 2.9%). They performed poorly when estimated weights were associated with a high coefficient of variation (greater than 4.0) (percentage bias range -7.3% to 5.0%). (Figure 3)

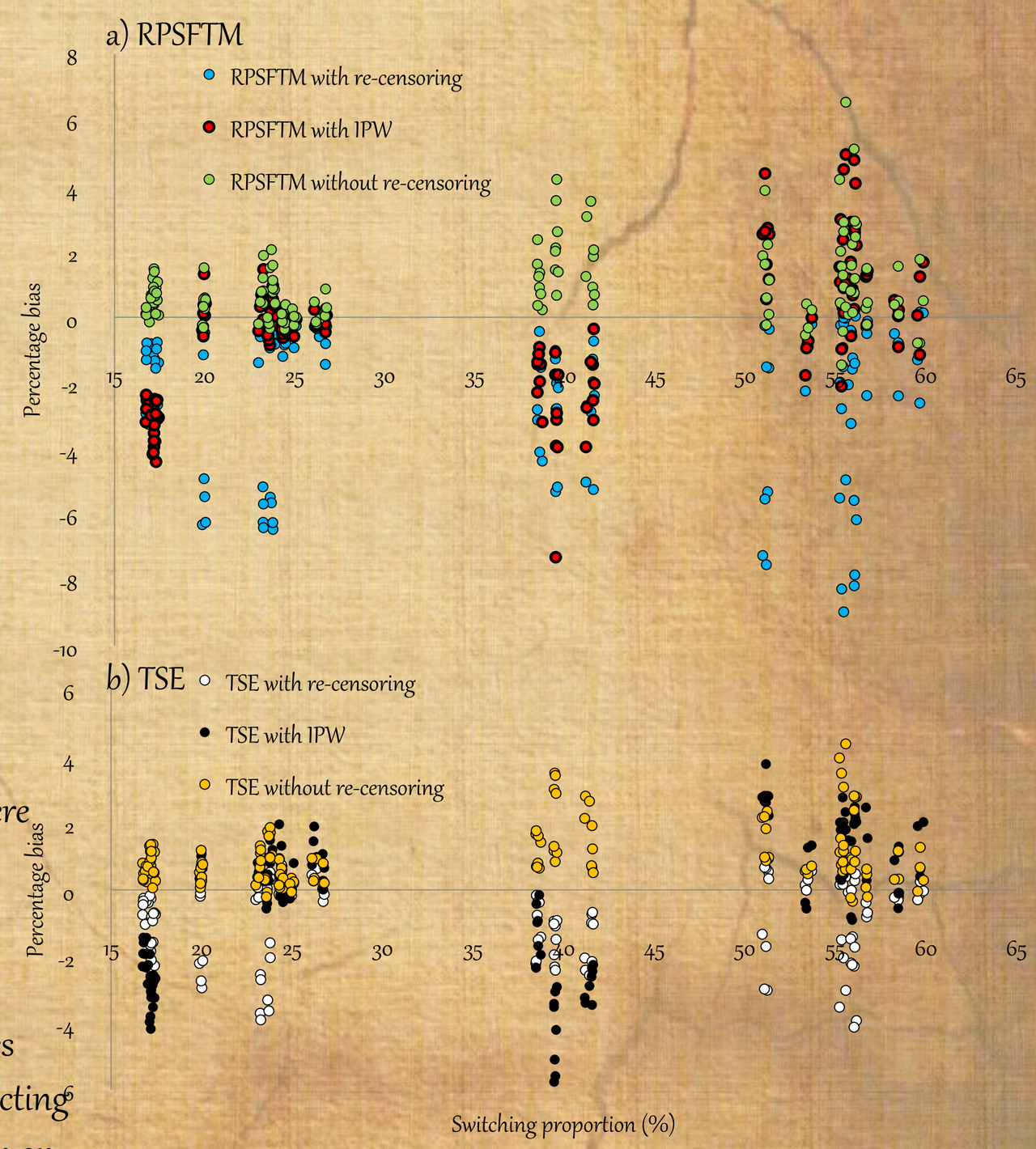

Figure 3. Percentage bias in each of 144 scenarios for a) RPSFTM; b) TSE

CONCLUSIONS

Re-censoring should not always be incorporated in adjustment analyses when the objective is to estimate the long-term treatment effect. Conducting analyses with and without re-censoring may provide useful information on the size of the true treatment effect. Re-censored analyses are prone to over-estimating treatment effects when the treatment effect reduces over time, and for an RPSFTM analysis this is compounded if switchers receive a reduced treatment effect. In contrast, analyses that do not incorporate re-censoring usually under-estimate the treatment effect. Using IPW instead of re-censoring represents a valid alternative when estimated weights have a narrow range.

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