Methods used to adjust for cross-over in clinical trials: Insights from Scandinavian health technology assessments

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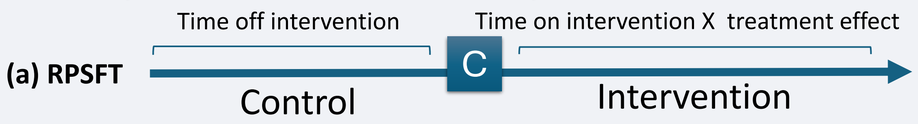
Background

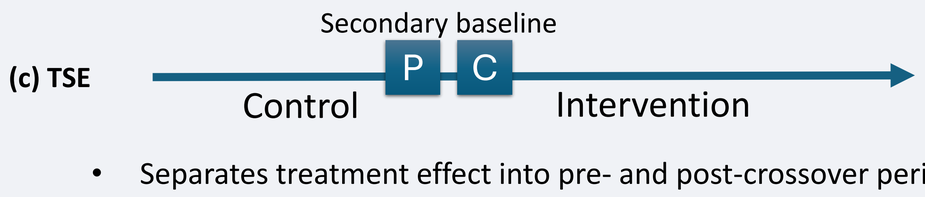
In clinical trials, crossover—where patients switch from the control to the treatment group—can confound treatment efficacy assessment, posing challenges for health technology assessments (HTAs) (1). This often occurs in long-term trials when control patients seek treatment due to perceived benefits shown during the study. Crossover can dilute the observed treatment effect, complicating the accurate assessment of efficacy. Adjusting for crossover isolates the treatment's impact, providing a clearer picture of effectiveness. Common adjustment methods include Rank-Preserving Structural Failure Time (RPSFT), Inverse Probability of Censoring Weights (IPCW), and the Two-Stage Estimation (TSE) method, each estimating treatment effects as if crossover had not occurred (1,2).

Figure 1. Adjustment Methods and Assumptions for Crossover in Clinical Trials.



- Estimates survival as if crossover had not happened.
- Assumes the treatment effect is constant over time.

- Weights individuals based on their likelihood of crossover.
- Assumes no unmeasured confounders.



- Separates treatment effect into pre- and post-crossover periods.
- Assumes no unmeasured confounders at secondary baseline.

C : crossover, P : progression

This project investigates the use of methods to adjust for cross-over in clinical trials within HTAs in Scandinavia (Sweden, Norway, and Denmark), utilising a proprietary database of Nordic HTA decisions.

Methods

We analyzed HTA reports from Sweden, Denmark, and Norway, focusing on decisions using one of three standard methods to adjust for cross-over: RPSFT models, IPCW, and TSE. Decisions were identified using a keyword search in the Nordic HTA database, NMA*i*. This proprietary database provides a robust and complete dataset of HTA decisions in Scandinavia, enabling detailed comparisons across different methodologies and healthcare systems.

Results

A total of 44 HTA reports from Sweden, Denmark, and Norway were identified in the NMA*i* database, spanning from 2014 to 2024. Of these, 29 reports (65%) were submitted within the last five years (2020-2024), indicating increased use of cross-over adjustment methods in HTA submissions. **Table 1** presents the descriptive statistics of HTA submissions by country and the cross-over adjustment methods used.

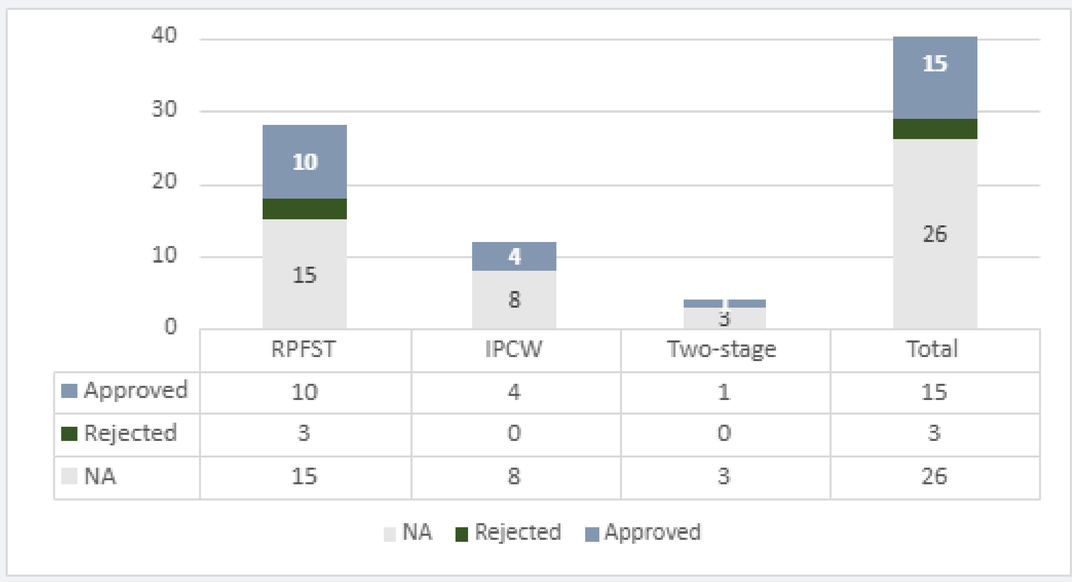
RPSFT model was the most commonly applied method, accounting for 64% of submissions, with Sweden and Norway showing the highest usage rates (67% and 72%, respectively). In contrast, IPCW represented 27% of the cases, with higher adoption in Denmark (45%). TSE method was the least used, appearing in 9% of reports, distributed evenly across the three countries.

Table 1. HTA Submission Statistics by Crossover Adjustment Methods.

Keywords	Sweden	Norway	Denmark	Total
RPFST	10 (67%)	13 (72%)	5 (45%)	28 (64%)
IPCW	3 (20%)	4 (22%)	5 (45%)	12 (27%)
Two-stage	2 (13%)	1 (6%)	1 (10%)	4 (9%)
Total	15 (100%)	18 (100%)	11 (100%)	44 (100%)

Table 2 shows the approval status of these HTA submissions by crossover adjustment methods. Among submissions using RPSFT, 36% were approved, 11% were not approved, and 54% had no available decision. For IPCW submissions, 33% were approved and 67% had no decision. TSE submissions had a 25% approval rate, with 75% lacking a decision. This distribution highlights a substantial proportion of applications without a final decision, especially for methods other than RPSFT, underscoring the need for further evaluation and regulatory consistency in the use of cross-over adjustment methods.

Table 2. Approval Status of HTA Submissions by Crossover Adjustment Methods.



Discussion and conclusion

This analysis shows that the RPSFT is the most commonly used crossover adjustment method in Scandinavian HTAs, likely due to its simplicity and single primary assumption—that the treatment effect is constant over time. While this assumption may not always hold, RPSFT's straightforward application makes it accessible for routine use. In contrast, IPCW, though effective for creating a pseudo-population without crossover, requires the challenging "no unmeasured confounders" assumption, possibly limiting its adoption. TSE, which avoids the constant treatment effect assumption, also relies on assumptions about confounders at the secondary baseline, making it complex to apply consistently. In conclusion, while RPSFT remains the most widely accepted method for crossover adjustment in Scandinavian HTAs, further research and standardization are necessary to enhance the integration of IPCW and TSE methods. Establishing consistent practices across Nordic countries could improve the comparability of HTA outcomes, particularly with the upcoming joint HTA initiatives.

References

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