A Novel Methodology to Enhance Unanchored Indirect Comparisons: Assessment-Schedule Matching

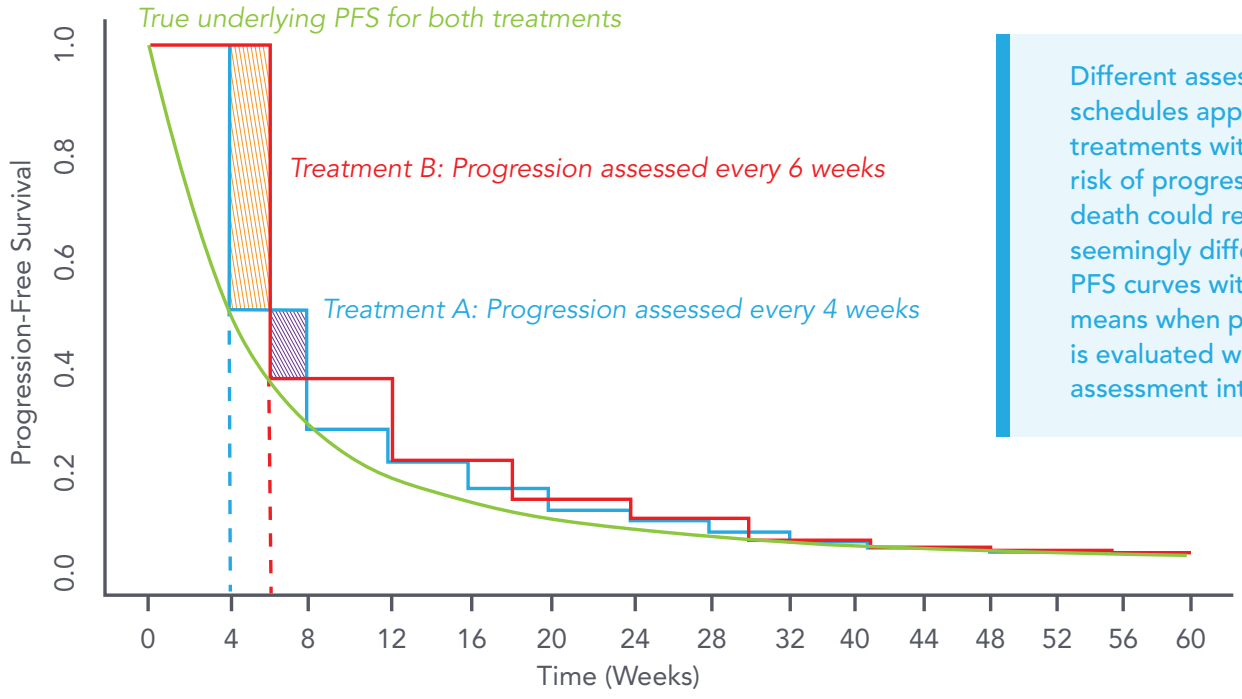
Context: Indirect Comparison of Treatments based on Single-Arm Trials

Health technology assessments (HTAs) of breakthrough therapies or in rare and orphan diseases are often based on evidence from phase II single-arm trials. These evaluations must include comparative evidence on the relative benefits of the therapy, which are typically derived from network meta-analyses (NMAs) based on randomized trials. When the primary source of evidence is a single-arm trial, NMA is no longer possible and unanchored approaches for indirect treatment comparisons are required. Matching-adjusted indirect comparisons (MAICs) and simulated treatment comparisons (STCs) are the most common approaches used in this situation. These methods can adjust for differences in the populations of trials being compared to minimize bias due to confounding but may not be enough to ensure reliable comparisons in some situations. When the outcome being compared is assessed on a set schedule, assessment time bias (ATB) may occur if the studies evaluated the outcomes at different times.

Illustration of ATB: Comparisons of Progression-Free Survival in Oncology

Progression-free survival (PFS) – a key outcome assessed in oncology trials – brings another set of challenges to indirect treatment comparisons based on single-arm trials. Disease progression occurs continuously but can only be detected at scheduled visits in the trial. This is what gives PFS curves the step-function form as almost all events are recorded at the set visit times.

Studies can adopt different schedules of assessment depending on the length of treatment cycles. This in turn leads to progressions being detected at different intervals. Thus, even if two treatments had an identical risk of progression and death, the PFS curves observed in the two trials can appear different. This is illustrated in the figure below – the same underlying PFS curve in green produces the observed events in trials for treatments A and B. The trial investigating treatment A assessed progressions every four weeks while trial B evaluated patients every six weeks, creating an artificial difference in the observed PFS curves of the two trials. In this illustration, the trial investigating treatment B would falsely appear to have more favorable PFS. We have found that even a small difference in schedules can distort comparisons of PFS.



Different assessment schedules applied to two treatments with identical risk of progression or death could result in seemingly different PFS curves with longer means when progression is evaluated with wider assessment intervals.

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A Solution: Assessment-Schedule Matching

Assessment-schedule matching (ASM) offers a relatively simple and adaptable means of accounting for assessment time bias. Using patient-level data from one of the trials being compared, ASM aligns the timing of events to the schedule of the comparator's trial. The ASM method involves three steps – to adjust the timing of the first visits, for example this is done as follows:

Step 1: Forward Shift

In the illustration above, this step pushes the times of individual disease progression in Treatment A from four weeks to six weeks because these events would only have been detected at that time in Treatment B.

Step 2: Correction for Death or Censoring

If the shifted time from Step 1 exceeds the time of recorded death or censoring for a given patient, it is assumed that the progression event would be missed at six weeks.

Step 3: Backward Shift

Shifting recorded progression events from the second scheduled assessment in Treatment A back to the first visit in Treatment B (six weeks) since a proportion of the week eight events would have occurred before week six and been detected at that time.

Acceptability of ASM in HTA Submissions

While ASM is a new approach, its use in HTAs is justifiable and necessary in certain situations. The direction and potential magnitude of the bias due to differences in assessment time can be assessed based on the designs of the trials and reported outcomes. The bias has been shown to occur even with small differences in schedules in a published simulation trial. The ASM method is peer-reviewed with a simulation study demonstrating that it effectively removes assessment time bias in all tested scenarios. In addition, the method is fully transparent, with programming code published in Pharmacoeconomics, which allows reviewing agencies to apply the method themselves; therefore it is advisable to apply in unanchored indirect treatment comparisons of PFS or other visit-based outcome assessments where schedules differ.

Evidera Experience and Selected Publications

Evidera's team of statisticians and modelers are innovative thinkers in alternative approaches to indirect treatment comparisons. We have successfully supported National Institute for Health and Care Excellence (NICE) submissions where targeted approaches have been applied for indirect comparisons. We leverage expert health economics, modeling, and literature review teams for scientific and strategic support in assessing the need and suitability of targeted comparisons, skillfully executing the analyses, clearly communicating the findings, and incorporating these into health economic assessments and agency submissions.

- **Kapetanakis V**, **Prawitz T**, Schlichting M, **Ishak KJ**, Phatak H, Kearney M, Stevens JW, **Benedict A**, Bharmal M. Assessment-Schedule Matching in Unanchored Indirect Treatment Comparisons of Progression-Free Survival in Cancer Studies. *Pharmacoeconomics 2019* Sep 26. doi: 10.1007/s40273-019-00831-3. [Epub ahead of print] Article available here: https://rdcu.be/bR0Qy
- **Ishak KJ**, **Proskorovsky I**, **Benedict A**. Simulation and Matching-Based Approaches for Indirect Comparison of Treatments. *Pharmacoeconomics*. 2015 Jun;33(6):537-549. doi: 10.1007/s40273-015-0271-1.
- **Caro JJ**, **Ishak KJ**. No Head-To-Head Trial? Simulate the Missing Arms. *Pharmacoeconomics*. 2010;28(10):957-967. doi: 10.2165/11537420-000000000-00000.
- **Kapetanakis V**, **Benedict A**, Schlichting M, Stevens J. Adjusting for Between-Trial Differences in the Schedule of Assessment for Disease Progression in Immuno-Oncology and its Impact on Indirect Treatment Comparisons. Workshop Presented at ISPOR's Annual International Meeting 2018, Baltimore, MD, USA.
- **Ishak KJ**, Phatak H, Masseria C. Making Sense of Novel Approaches for Indirect Comparison: Similarities and Differences of Simulation and Matching Based Approaches. Workshop Presented at ISPOR's European Meeting, 2015, Milan, Italy.
- **Ishak KJ**, **Proskorovsky I**, **Benedict A**, Chen C. Overcoming Incomplete Evidence Networks and Heterogeneity Issues with Simulated Treatment Comparisons. Workshop Presented at ISPOR's European Meeting, 2013, Dublin, Ireland.
- **Ishak KJ**, Eckert L, **Caro JJ**. Comparative Effectiveness Analysis using Simulated Treatment Comparison (STC). Workshop presented at ISPOR European Meeting 2011, Madrid, Spain.