Estimating Comparative Effectiveness When Patients Are Switching Treatments: A Real-World Challenge

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Treatment switching makes estimation of comparative effectiveness a challenge in observational studies. Even though useful analytical methods abound, these rely on assumptions that can't easily be tested and on data that are not always collected.

Switching happens

A patient will be naturally inclined to initiate, change, or discontinue their treatment if they (or their physician) are not happy with the results, are experiencing adverse reactions or tolerability issues, or when better treatment options become available. This is true of both clinical trials and in the real world. Flexibility in treatment, whilst beneficial for the individual patient, poses challenges to prescribers and payers. How can they compare the effectiveness of treatments when patients are switching? "Not easily" is the glib answer. Treatment switching in any clinical trial setting complicates comparisons of therapies. Payers need to know what the "bang" is in their "bang-for-bucks" pharmacoeconomic calculations and/or the added benefit over standard treatment options. But how are these stakeholders to evaluate comparative effectiveness in messy, real-life situations?

Challenges

Importantly, and for good reason, treatment switching is limited in most randomized controlled trials. As the study label implies, switching treatments, if it does arise, usually happens under controlled conditions. However, the same cannot be said of patients in real-world, observational settings. Here switching is mainly left up to the patient and their treating physician, which usually makes it more difficult to address. This poses severe challenges for payers who are increasingly reliant on the use of observational "real-world" data to inform their decisions.

Treatment switching shouldn't necessarily be regarded as a problem. Patients change treatments in randomized controlled trials for a variety of reasons, (eg, their disease may progress or they may suffer a treatment-related adverse event). If they switch to another treatment that is widely available then, from a pragmatic perspective, this does automatically lead to a health technology assessment (HTA) complication. The switch simply reflects what would have happened in reality. Problems only arise if patients switch to treatments that are not widely available and not part of the standard treatment pathway. In such cases we cannot observe from unadjusted trial results what effect the switch has had.

In observational studies the problems are similar, but more extensive. Non-standard treatment pathways remain problematic, such that any meaningful interpretation of these without the necessary statistical adjustments is difficult. Moreover, there are usually no (or much less stringent) eligibility criteria, no randomization, and a lack of a clearly defined baseline. Patients may initiate the treatment of interest at different time-points in relation to their disease. Hence, before attempting to address treatment switching, we first need to consider how to conduct a statistical analysis comparing 2 or more treatments when we know that patients might have very different characteristics affecting their prognosis (leading to channelling bias, confounding by indication).

Intention-to-treat...?

Randomized controlled trials are typically analyzed following the intention-to-treat principle. Intention-to-treat analyses aim to provide an unbiased comparison of randomized groups, but do not make any adjustments for treatment changes. Hence, it's implicitly assumed that switching occurs randomly. While it remains common for HTA agencies to rely on intention-to-treat analyses even if treatment switching results in unrealistic treatment pathways, many agencies have shown a willingness to consider adjustment analyses.[1-3] Simple techniques, such as censoring switchers, should be avoided due to a high chance of bias (see Table 1). Methods like inverse probability of censoring weighting and rank preserving structural failure time model represent an improvement, but

make strong assumptions that aren't easily tested and may seem unrealistic.

The introduction of the estimands framework as part of the upcoming revision of the ICH E9 guideline[4] highlights the limitations of the intention-to-treat approach in an randomized controlled trial setting. Importantly, it provides guidance on how scientific questions can be answered through greater transparency in, and alignment of, clinical trial objectives, design, conduct and analysis. Treatment switching is considered as a type of "intercurrent event" within the revised guidelines—event types which ICH feels deserve greater consideration.

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There is no "standard" analytical approach, such as intention-to-treat, in an observational data setting. Indeed, it's difficult to conceptually apply the intention-to-treat principle in a study that lacks randomization and "allows" for treatment switching. Can we reliably state the *apriori* intention of the treating physician? Observational studies would appear to benefit from adherence to the intercurrent event framework described in ICH E9 (which has strong parallels with HTA's PICOT methodology). However, complex analytical methods such as extensions of inverse probability of censoring weighting and rank preserving structural failure time model are likely to be needed here also.

Big (bad?) data

The use of more sophisticated treatment-switching analytical techniques in order to obtain better (less biased?) treatment comparisons usually requires more data, better data, and greater assumptions. This appears to be borne out in reviews of methods used in observational studies—treatment switching is either ignored or handled by using relatively simple approaches. In defense of this arguably poor showing is that the data required to implement complex methods are not necessarily collected or not consistently measured in real-world clinical practice, resulting in substantial levels of missing data.

Further potential complications abound. Relevant data might come from multiple, independent sources which have collected patient data in different ways, at different times, in different regions, and/or with varying quality. For example, data on treated patients might exist in a drug registry, while untreated patient data might reside in a completely different source. The same patient might appear in more than one data source, potentially leading to double counting. Data sources might need to be linked if, for example, a critical field is present in one source but not in another. The resolution of these sorts of problems often requires the use of techniques such as probabilistic data linkage, especially in cases where health databases don't employ unique patient identifiers (as is the case in most countries, with the Nordics a notable exception). Unsurprisingly to those that have ever attempted it, formally combining independent patient-level health data is a complex exercise, often leading to patchy patient records. The whole can sometimes be less than the sum of the parts!

Table 1: Standard approaches when dealing with treatment switching

Method	Main Assumption
Intention-to-treat analysis	Switching occurs at random
Exclude/censor switches	No confounders that affect both the reason for switching and the treatment outcome
Include treatment as time-varying covariate	No confounders that affect both the reason for switching and the treatment outcome
Inverse probability of censoring weights	No unmeasured confounders
Rank-preserving structural failure time modelling	Randomized groups and common treatment effect
Two-stage model	No unmeasured confounders and existence of a second baseline from which the effect of switching can be estimated

Complexity

There's also the related issue of methodological transparency. Reimbursement authorities tend to have lower levels of comfort in their decision making when faced with higher levels of statistical complexity. Pushing the methodological envelope might lead to less-biased treatment comparisons, but that's of little use if you can't easily convey that message to persons lacking advanced degrees in biostatistics. Reimbursement authorities will struggle to approve what they don't understand. It requires little stretch of the imagination to suspect that this might also be a reason for the lack of use of more sophisticated treatment-switching methods in published observational data studies.

Target trial approach

Adhering to the philosophy of keeping things simple, the target trial approach[5] provides a step-by-step guide for analyzing observational data. The idea is that if we cannot run a randomized controlled trial (for whatever reason), the next best thing is to use observational data to try to emulate the trial that we would have run, if we could have. Importantly, the approach doesn't focus solely on the analytical methods used, which is further reflected in its 7 key components:

- Eligibility criteria
- Treatment strategies
- Assignment procedures
- Follow-up period
- Outcome
- Causal contrasts of interest
- Analysis plan

Used correctly, it can allow appropriate adjustments to be made for treatment switches in observational data. However, in the context of non-random switching, it relies on some of the previously outlined analytical approaches—unbiased estimates of the treatment effect will only be available if there's no unmeasured confounding in the data. Data collection is therefore critical. The success of the target trial approach depends a lot on collecting good quality data on all possible confounders over time. While it's still a relatively untried framework, the target trial is beginning to undergo evaluation in more practical settings.[6-8]

Final thoughts

Treatment switching complicates estimates of comparative effectiveness and is arguably a greater problem in observational studies. While real-world evidence researchers have a wealth of statistical and analytical tools at their disposal, a bigger challenge appears to lie with lack of good quality data.

Alongside improved data collection, general frameworks such as the "estimands" concept and target trial approach offer hope for the improved handling of treatment switching. This should lead to more accurate estimates of comparative effectiveness and, ultimately, better stakeholder decisions.

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