How Can Payer Requirements Be Satisfied when Treatment Switching Occurs?

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KEY POINTS . . .

The survival benefit of an investigational therapy can be underestimated when treatment switching occurs in clinical trials.

Various statistical methods are available to adjust for confounding introduced by treatment switching.

Different health technology assessment (HTA) agencies have different views on the value of these statistical adjustment methods.

Demonstrating statistically significant and clinically meaningful gains in overall survival (OS) remains the gold standard to provide evidence of the benefits of new anticancer drugs [1]. In clinical trials involving patients with advanced or metastatic cancer, however, it is very common for participants to switch from the treatment to which they were initially randomized to other licensed, unlicensed, or investigational therapies [2,3].

This practice is referred to as treatment switching, noncompliance, or treatment crossover (not to be confused with crossover trial design). For both ethical and practical reasons, and especially if no other non-palliative treatments are available, this option may be built into oncology trial protocols. Patients randomized to the control group may, for instance, be allowed to switch to experimental treatment upon disease progression [4]. Switching may also be recommended by the independent data monitoring committee when a trial is stopped early for apparent benefit, or happen spontaneously at the discretion of the patient and their treating physician. Obviously, such switches can affect the patients' outcomes and therefore estimates of the treatment effect on OS that are subsequently used in economic evaluations [5].

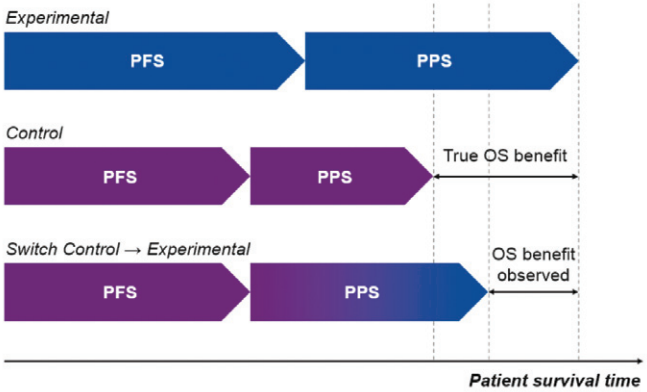
In general, health technology assessment (HTA) bodies compare current standard of care, a situation in which the investigational treatment is not available, to a possible forthcoming scenario in which the new intervention can be offered [2]. If the agency decides to recommend the new treatment, it would be perfectly possible for future patients to first receive the novel drug and subsequently be treated with other products that were already used in clinical practice. Therefore, the switch from experimental to control therapy in a clinical trial represents a situation that may actually occur in reality. Yet, as the control arm of the study represents the state of the world in which the new product would not be recommended, switches from control to the experimental therapy would not be possible and are therefore irrelevant to the decision problem defined in an HTA.

When a switch from control to experimental treatment occurs in a clinical trial, a standard intent-to-treat (ITT) analysis, in which data are analyzed according to the arms to which patients were initially randomized, will underestimate the OS benefits of an experimental product provided switchers benefit from it (see Figure 1). Various statistical methods that represent alternatives to the ITT analysis are available to adjust OS estimates for the confounding introduced by treatment switching, but different HTA agencies have different views on their value [2]. Here we review the perspectives of the UKs National Institute for Health and Care Excellence (NICE) and the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany. In addition, we explore the view from the industry as this situation creates additional considerations for researchers in planning their trials to ensure that patients get the treatment they need while maintaining robustness of the study results.

A Selection of Stats

In the presence of treatment switching, the ITT analysis will provide a confounded estimate of the 'true' treatment effect—that is, the effect that would have been observed if switching had not been permitted. Alternative statistical methods that seek to estimate the true treatment effect are available, ranging from simple to complex techniques [4-7]. Simple or naïve methods have been commonly used in HTA submissions. For example, data from patients who switched can be censored at the point of switching or excluded entirely from the analysis. However, it is very likely that the probability of switching is influenced by the patient's prognosis. This approach can therefore undermine the trial's randomization process that aimed to create two comparable groups of patients. For this reason, simple methods are highly prone to selection bias and should be avoided.

Figure 1. Treatment switching from control to experimental therapy may lead to underestimation of the true OS benefit of the experimental product.



OS indicates overall survival; PFS, progression-free survival; PPS, post-progression survival.

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Occasionally, more complex statistical techniques, such as the rank preserving structural failure time model (RPSFTM) and inverse probability of censoring weights (IPCW) method, have been used in HTA submissions. The RPSFTM method uses complete observations on patients to adjust survival time after crossover in order to estimate what would have happened if patients had not received the experimental treatment (also known as counterfactual survival times). In the IPCW approach, patients are artificially censored at the time of switching and the weight/influence of uncensored patients with similar prognostic characteristics is increased based on covariate values and a model of the probability of being censored. Additional statistical techniques that are available from the literature include iterative parameter estimation, structural nested models, and two-stage methods.

None of these complex methods are optimal in all circumstances. Each method has its limitations and relies on a set of strong—often untestable—assumptions. The clinical and statistical plausibility of each method will depend on the context in which it is applied. Whereas the standard RPSFTM assumes that the treatment effect is equal for all patients no matter when the treatment is received (relative to the time for which the treatment was taken, known as the common treatment effect assumption), the IPCW relies on the assumption that there are no unmeasured confounders that affect both switch and survival. Therefore, study and switching characteristics must be considered on a case-by-case basis to assess which adjustment method is likely to be most appropriate.

The NICE Way

Treatment switching is addressed in section 5.7.8 of NICE's 2013 Methods Guide [8]. In short, it states that adjusting for switching is acceptable, advises against the use of naïve methods, and requests the applicant to appropriately justify the chosen approach based upon methodological assumptions and trial characteristics.

Whilst NICE is supportive of the use of an appropriately identified and justified adjustment analysis, it is critical that the choice of method should not be made arbitrarily, and supportive analyses should be run to demonstrate the plausibility of key assumptions. Providing evidence to support the validity of the adjusted OS times (perhaps from external trials or registry data) may increase the confidence that review group and appraisal committee members have in adjusted analyses [9]. It is by no means guaranteed that an adjustment analysis will be accepted, if the analyses undertaken are not appropriately justified and if the appraisal committee does not believe the results are credible.

The Methods Guide does not offer detailed guidance around specific complex techniques; however the NICE Decision Support Unit has issued a technical support document providing an analysis framework to help researchers identify adjustment methods that are likely to be appropriate on a case-by-case basis [2].

IQWiG Seeking Certainty

IQWiG's perspective on statistical adjustment differs. The benefit assessment of pharmaceuticals in accordance with German law relies heavily on the demonstration of positive causal effects of a new drug over an appropriate comparator therapy on patient-relevant outcomes. Progression-free survival is generally not regarded as a patient-relevant outcome, but as a surrogate requiring proper validation [10]. Given the complexity of surrogate validation, unbiased data on OS becomes crucial.

There are some experiences from IQWiG assessments on oncology drugs involving treatment switching [11]. Manufacturers are likely to face issues if they perform a first data cut only after a significant proportion of patients in their pivotal trial have crossed over and, perhaps as a result, statistically significant differences in OS cannot be demonstrated. In addition, wide confidence intervals—as may be generated by the switching adjustment methods—are problematic in view of the German benefit assessment approach of IQWiG. A statistically significant difference (based on the 95% confidence interval…) is needed in order to qualify for an added benefit [12].

In summary, rather than relying on the results of statistical correction methods, the institute seems to prefer evaluating the level of bias that was introduced by treatment switching in subsequent data cuts. It then bases its decision on results obtained in the latest 'unbiased' data set—at least until the uncertainty introduced by the correction methods is properly addressed within the dossier [11,13].

The Industrial Balance

The HTAs of dabrafenib (Tafinlar®) in the UK and Germany probably provide the best case example of the divergent views NICE and IQWiG have on switching adjustment methods. In the pivotal BREAK-3 study comparing dabrafenib versus dacarbazine for the treatment of BRAF V600E-positive unresectable or metastatic melanoma, GlaxoSmithKline's ITT analysis for OS resulted in a hazard ratio [95% CI] of 0.61 [0.25 - 1.48] but, at the time of this first data cut, already 28 out of 63 (44%) dacarbazine patients had switched treatments. Whilst NICE was critical of the methods used by the manufacturer to handle treatment switching, it acknowledged that statistical methods can be used when treatment switching occurs and took the adjusted results using the RPSFTM method into account in its technology appraisal [14].

Conversely, IQWiG rejected the methods in this case. It stated that *"the crossover adjustments conducted by the company were not relevant for the benefit assessment because they were based on strong assumptions, the fulfilment of which cannot be checked with the available data"* [15]. As we know, several of the assumptions of these adjustment methods are impossible >

to perfectly test. However, this was not a wholesale dismissal of adjustment methods; later in the report (in a section published only in German) IQWiG state that the real issue was that no justification of the adjustment method was presented to them. Further investigation would have been required. Still, the need for a statistically significant advantage—also with adjustment methods—remains. Indicating a need for discussion from the institute's view, *"benefit assessment in studies with allowed treatment switching"* was the key topic at the 2014 IQWiG in dialogue sessions [16].

Key Challenges and Recommendations

For the pharmaceutical industry, this situation poses significant challenges. Four categories of challenges that can be related to treatment switching include:

1. Ethical
- Is it ethical to prevent a patient randomized to the control arm of a trial from switching to the experimental treatment?
- Could treatment switching bias (not allowing an unbiased estimate of the true OS treatment effect) misguide clinical practice for future patients?

2. Practical
- Would patients still participate in trials if treatment switching was not allowed?
- Realizing that pre-specification of the adjustment method may not be possible, do data collection practices need to alter?

3. HTA agency needs
- While NICE prefers mature (and, if necessary, adjusted) OS data to be included in economic evaluations, IQWiG has a preference to evaluate unbiased data sets with limited uncertainty. Considering the issue of multiplicity, when should a manufacturer ideally plan to perform data cuts?

4. Expertise
- How can we ensure useful dialogue between companies and HTA agencies when both may have limited in-house knowledge/experience with these complex adjustment methods?

Our Recommendations

Ideally, but seldom practically possible, a superiority trial in oncology should allow the manufacturer to demonstrate a statistically significant and clinically meaningful difference in OS between treatments arms within a reasonable amount of time. Given the approach of some HTA bodies such as IQWiG, it may be unavoidable to schedule early and multiple interim analyses to obtain unconfounded trial results. Yet, conservative stopping rules should be adopted to ensure that randomized controlled trials will be unblinded early for apparent benefit only when a sufficient number of events have occurred, stringent statistical significance levels have been reached, and OS data are sufficiently mature.

If practically and ethically possible, it is useful to prevent patients from switching from the control group to the active treatment arm. The application of switching adjustment methods often drastically alters point estimates for the treatment effect which, in turn, feeds into the base case economic model evaluated by HTA agencies. Where it is not possible to prevent switching, statistical methods may be required to adjust trial results for the confounding introduced by treatment switching.

Pre-specifying the exact methods that will be applied in the statistical analysis plan may be difficult, and not all agencies may take results obtained with these techniques into account. It is therefore sensible to identify in advance a range of adjustment methods that will be applied, along with a range of supplementary analyses that will be run. In addition, data collection practices could be altered. For example, if data were collected on all potentially important patient characteristics over the entire duration of the trial, rather than on some characteristics up until a pre-specified disease-related time-point, the no unmeasured confounders assumption associated with the IPCW adjustment method is more likely to be satisfied.

References

[1] Johnson P, Greiner W, Al-Dakkak I, Wagner S. Which metrics are appropriate to describe the value of new cancer therapies? Biomed Res Int 2015;2015:865101. [2] Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. 2014. Available from: http://www.nicedsu.org.uk. [Accessed September 7, 2015]. [3] Daugherty CK, Ratain MJ, Emanuel EJ, et al. Ethical, scientific, and regulatory perspectives regarding the use of placebos in cancer clinical trials. J Clin Oncol 2008;26:1371-8. [4] Ishak KJ, Proskorovsky I, Korytowsky B, et al. Methods for adjusting for bias due to crossover in oncology trials. Pharmacoeconomics 2014;32:533-46. [5] Jönsson L, Sandin R, Ekman M, et al, Drummond M. Analyzing overall survival in randomized controlled trials with crossover and implications for economic evaluation. Value Health 2014;17:707-13. [6] Latimer NR, Abrams KR, Lambert PC, et al. Adjusting survival time estimates to account for treatment switching in randomized controlled trials--an economic evaluation context: methods, limitations, and recommendations. Med Decis Making 2014;34:387-402. [7] Watkins C, Huang X, Latimer N, et al. Adjusting overall survival for treatment switches: commonly used methods and practical application. Pharm Stat 2013;12:348-57. [8] NICE. Guide to the methods of technology appraisal 2013. Available from: http://publications.nice.org.uk/pmg9. [Accessed September 7, 2015]. [9] Latimer, Nicholas R. Treatment switching in oncology trials and the acceptability of adjustment methods. Expert Rev Pharmacoecon Outcomes Res 2015;14:1-4. [10] Institute for Quality and Efficiency in Health Care. Validity of surrogate endpoints in oncology: Rapid Report. 21 November 2011. Available from: https://www.iqwig.de/download/A10-05_Executive_Summary_v1-1_Surrogate_endpoints_in_oncology.pdf. [Accessed September 7, 2015]. [11] Vervoelgyi V, Beckmann L. Institute for Quality and Efficiency in Health Care. Evaluation of treatment switching in the Institute's assessments. Presentation at IQWiG in dialogue 2014: Benefit assessment in studies with allowed treatment switching. Available from: https://www.iqwig.de/download/14-06-27_IQWiG_im_Dialog_Volker_Vervoelgyi.pdf. [Accessed September 7, 2015]. [12] Institute for Quality and Efficiency in Health Care. General Methods Version 4.2 (German version). Available from: https://www.iqwig.de/download/IQWiG_Methoden_Version_4-2.pdf. [Accessed September 7, 2015]. [13] Maervoet J, Skaltsa K, Ivanescu C, Van Engen A. Do health technology agencies accept methods for dealing with treatment switching? ISPOR 17th Annual European Congress; Presentation NI4. Available from: https://www.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp. [Accessed September 7, 2015]. [14] NICE. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. Oct 2014. Available from: http://guidance.nice.org.uk/ta321. [Accessed September 7, 2015]. [15] Institute for Quality and Efficiency in Health Care. Dabrafenib - Benefit assessment according to § 35a Social Code Book V (English extract). 23 December 2013. Dec 2013. Available from: https://www.iqwig.de/download/A13-35_Dabrafenib_Extract-of-dossier-assessment.pdf. [Accessed September 7, 2015]. [16] Institute for Quality and Efficiency in Health Care. IQWiG in dialogue 2014: Benefit assessment in studies with allowed treatment switching. Available from: https://www.iqwig.de/en/events/iqwig-in-dialogue/iqwig-in-dialogue-2014.6046.html. [Accessed September 7, 2015]. ■

Additional information:
The preceding article is based on the Issues Panel, "Should We Adjust Overall Survival Estimates for Treatment Switching in Oncology?" given at the ISPOR 17th Annual European Congress, 8-12 November 2014, Amsterdam, The Netherlands.

To view the presentation, go to: http://www.ispor.org/Event/ReleasedPresentations/2014Amsterdam#issuepanelpresentations