Analysing HTAs: Surrogate endpoints in the respiratory domain and applied in ophthalmology

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Introduction

The present study critically analysed and compared historical health technology assessments (HTAs) for therapeutic products related to idiopathic pulmonary fibrosis (IPF) and interstitial lung disease (ILD). The primary objective was to investigate the application and critique of surrogate endpoints (SEs) in these HTAs, to shed light on their influence in clinical and economic evidence packages. SEs are defined as biomarkers or intermediate outcomes that can substitute for a final patient-relevant outcome, such as mortality and health-related quality of life. This evaluation will offer valuable insights that could help to support and refine the validation process of SEs in IPF and ILD.
We will perform an extensive review of selected analogous therapeutic products from various regions, followed by a methodical analysis of the results, driving factors, and the role and methods of SE validation in decision making. The implications of our findings will be assessed through a systematic literature review (SLR)-supported SE validation in glaucoma and diabetic macular oedema (DME). This study will explore the potential broader use of these findings across other disease areas.

Objectives

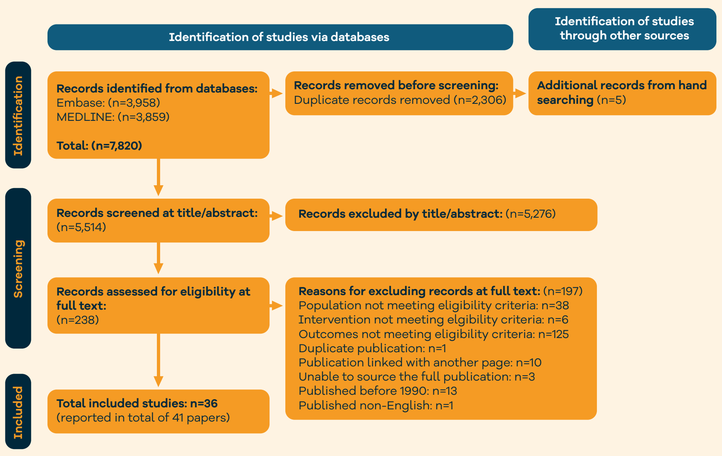
The present study aimed to evaluate historic HTAs for therapeutic products relating to IPF and ILD therapeutic domains. The objective was to shed light on the application and HTA body critique of SEs in clinical and economic evidence packages, facilitating insights that could help to refine the validation of SEs in IPF, ILD, as well as in glaucoma and DME.

Methodology

Analogous therapeutic products were selected based on pre-defined criteria, of which, five were identified for review. Publicly available HTA reports and methodological guidelines for these products were searched and evaluated from various countries, including Canada, England, France, Germany, the Netherlands, Scotland, Spain, Sweden, the USA, and Wales.

Key information was extracted into a data extraction table, detailing the outcomes, primary decision drivers, and role of SEs in informing decision making (Figure 1). Thematic learnings were then derived from each HTA submission and methodological review. The findings were subsequently tested for feasibility through an SLR-supported SE validation in glaucoma and DME.

Figure 1: PRISMA flowchart of the mapping review



To perform the SE validation, this study built upon the methodology and knowledge gained from the IPF and ILD surrogacy work. The National Institute for Health and Care Excellence (NICE) and Institute for Quality and Efficiency in Health Care (IQWiG) were identified as the HTA bodies with the most stringent SE guidelines and targets. These were followed when performing the analysis, to ensure that it was executed to the highest standard.

The approach for validating potential SEs to establish true endpoints was directly informed by Buyse et al (2007) (1). The authors recommended that a three-step approach be adopted.

The first step should be performed at the arm-level, whereby the correlation coefficient between the SE and primary endpoint is evaluated using Pearson's correlation. In line with the IQWiG guidelines (2), a correlation coefficient of 0.7 should be achieved by the surrogate, before progression can be made to the second step of the analysis. If the SE fails to achieve this target, then it is not classed as a viable SE.

The second step should be performed at the trial level, at which point the treatment effects of the SE and the primary endpoint are correlated using Pearson's correlation. The target correlation score for an SE to be classed as a viable surrogate for the primary endpoint is 0.85.

If the SE fails to achieve a 0.85 correlation coefficient, Buyse et al recommends performing a surrogate threshold effect (STE) analysis (Step 3). This estimated STE would then represent the minimum treatment effect required to predict a statistically significant non-zero effect on the primary endpoint (i.e. it would identify the size of treatment effect required to see a benefit on the primary endpoint).

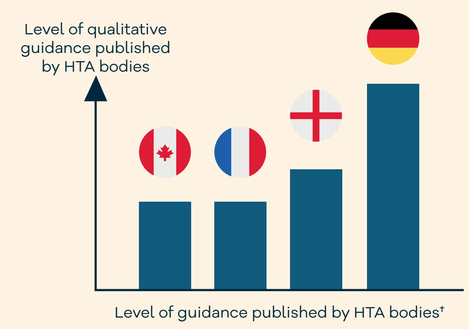
After the SE validation was conducted, a base case analysis was run using the rigorous framework outlined by IQWiG (2) and NICE (3). Sensitivity analyses were then performed to explore the impact of these results on the robustness of the outputs.

Analyses performed included restricting the publication year to studies released in 2005, 2010, and 2012 (to reflect the previous 10 years of publications). These restrictions allowed us to explore recent trends that were relevant to current clinical practice. The most recent studies helped to identify improvements in data collection methods and reporting techniques.

Results

The review of HTAs revealed considerable variations in the application of SEs and their subsequent critique by HTA agencies.
Key learnings included HTA agencies' preference for final patient-relevant endpoints, as well as the recognition that SEs could be used to facilitate shorter trials and faster access to treatments. Additionally, the Canadian Agency for Drugs and Technologies in Health (CADTH) (4) and Haute Autorité de Santé (HAS) (5) have provided minimal prescriptive advice on establishing the surrogate-to-final outcome relationship; however, IQWiG and NICE's Decision Support Unit have developed more detailed criteria to demonstrate the association between the treatment effect on the surrogate and the final endpoints (Figure 2)†. Notably, Germany did not approve the use of SEs for any of the drugs evaluated, owing to an absence of validation.

Figure 2: HTA body published guidance



†Charts created based on the qualitative interpretation

The surrogacy validation exercise undertaken in glaucoma and DME was determined to be feasible and resulted in intuitive outcomes; however, performing the analysis adhering to IQWiG and NICE guidelines presented challenges. Firstly, the correlation coefficients required may not have been reflective of a real-world scenario and therefore, could lead to the rejection of valid SEs. Discussions with clinicians suggested that coefficients of 0.5 and 0.7 were acceptable (at the arm- and trial-level). Secondly, only small data sample sizes relating to SE and the primary endpoint were identified, which may have increased the potential of skewed outputs and uncertainty in the analysis.

Conclusion

The present study highlights the potential role of SEs in HTA submissions and underscores the necessity for their meticulous validation in the IPF/ILD therapeutic domain, in ophthalmology and beyond. The successful feasibility test further signifies the potential for broadening the application of these findings across other disease areas.
The real-world application of the gold standard methodology and criteria for classification as an SE ensures that the highest standards are met; however, it also has its challenges, such that outliers in a limited evidence base can lead to correlation coefficients being skewed below the target correlation threshold (0.85).
Additionally, the use of unvalidated SEs may lead to clinical uncertainty and higher cost-effectiveness estimates, which could result in negative recommendations.
Overall, this shows that HTA agencies need to develop further guidance to assist in SE validation, as country-specific HTA methodological guidelines will help to meet market-specific needs. There is also a need for more standardised considerations of SE use across HTA agencies, and between regulatory and HTA bodies.
It is also crucial that these guidelines are generalisable to a clinical setting. HTA bodies should consider the data available, as well as clinical opinion when evaluating the strength of a candidate SE.

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Abbreviations

CADTH: Canadian Agency for Drugs and Technologies in Health; DME: Diabetic macular oedema; HAS: Haute Autorité de Santé; HTA: Health technology assessment; ILD: Interstitial lung diseases; IPF: Idiopathic pulmonary fibrosis; IQWiG: Institute for Quality and Efficiency in Health Care; NICE: National Institute for Health and Care Excellence; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SE: Surrogate endpoint; SLR: Systematic literature review; STE: Surrogate threshold effect; VF: Visual field