The Assessment of Surrogate Endpoints and their Impact on HTA Recommendations

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Introduction

A surrogate endpoint (SE) is defined as a biomarker or an intermediate outcome that can substitute for a final patient-relevant outcome, such as mortality and health-related quality of life (1).
The use of SEs is becoming more common in pharmaceutical product development as they enable shorter clinical trials and quicker patient access to treatments that have been accepted by medicines regulators. However, limited information exists on the acceptance of SE data by Health Technology Assessment (HTA) agencies.
HTA agencies are under increasing pressure to accept data from SEs when making their recommendations despite traditionally requiring long-term comparative effectiveness data to inform assessments of new therapies. Whilst the use of SEs enables faster data acquisition, sole reliance on validated SEs can increase uncertainty and fail to fully capture the complete risk–benefit profile of a drug.

Objectives

The objectives of this study were to:

1. Assess the published HTA guidelines on the use of SEs
2. Analyse the correlation between SE acceptability by HTA agencies and the recommendations made by HTA agencies in Canada, England, France, and Germany regarding products that included SE data in their clinical trials

Methodology

The study approach consisted of two parts:

1 Part

Published HTA guidelines and guidance on the application of SEs in the markets of focus were reviewed. A targeted search of HTA agency websites was conducted to identify guidelines relating to the application of SEs in the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Gemeinsame Bundesausschuss (G-BA)/ Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), and the National Institute for Health and Care Excellence (NICE).

2 Part

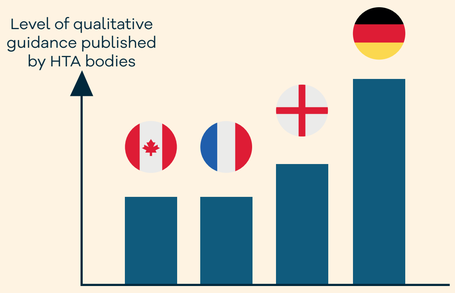
Secondly, the NICE website and all NICE-published Technology Assessments were screened between 2021–2022 (2). Therapies with trial data for a SE were then identified as the only primary outcome (PO), and corresponding HTA outcomes of those therapies were extracted from CADTH, G-BA, HAS, and NICE.

Markets of focus:

Part 1 results

An assessment was conducted to determine the level of guidance published on the use of SEs. All four HTA agencies published methodological guidelines and made specific reference to SEs; however, the guidance is not very prescriptive and illustrates the need for more definitive guidance for sponsors.
Key learnings included the preference of the HTA agencies for data for final patient-relevant endpoints, but also the recognition that there is a need to use SEs to enable shorter trials and quicker access to treatments. In addition, the HTA agencies expect sponsors to provide evidence to demonstrate the surrogate-to-final endpoint relationship, especially as SEs increase the level of uncertainty in coverage decisions.
CADTH and HAS 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 final endpoints.

G-BA/IQWiG will consider data from SEs if they have been validated with appropriate statistical methods. If a SE is not validated, there is the possibility of applying the concept of the surrogate threshold effect (STE). If the SE is neither validated nor accepted by the consideration of a STE, the results can be presented but are not regarded as proof of added benefit by the G-BA.
Similarly, NICE's Decision Support Unit document (3) provided methodological guidance on the process for validating a SE, the meta-analytic approach to SE evaluation and data requirements. Furthermore, the NICE Agenda for Change 2021 identified SEs as an area where more prescriptive advice is required in their methods update (4).



Note: †Chart created based on the qualitative interpretation of the level of guidance published by HTA bodies

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Part 2 results

From the 65 interventions that NICE reviewed over 2021–2022, only 20 included data from a SE as the sole PO (outcomes: 15 recommended [2 included in the Cancer Drug Fund], 4 restricted, 1 not recommended). Most SEs were accepted by NICE with some decisions critiqued. While most products were recommended, it is worth noting that most oncology submissions included overall survival (OS) data as a secondary endpoint.

When cross-referencing the medicines that included a SE as the sole PO compared with other HTA agencies, CADTH evaluated 11 interventions (outcomes: 8 recommended with restrictions, 3 not recommended). Most SEs were accepted by CADTH with clinical expert opinion also taken into consideration, although minimal critique on SEs was provided by CADTH. Furthermore, all products given a decision of 'recommended' had restrictions, including oncology submissions that provided OS data as a secondary endpoint.

HAS assessed 15 interventions and provided the following scores: SMR important: 10; moderate: 3; insignificant: 2. ASMR III: 3; IV: 4; V: 7; and 1 not applicable (NA). Most SEs were accepted by HAS; however, minimal critique was specifically provided on SE acceptance. Most oncology products that were recommended included OS data as a secondary endpoint, and those that did not receive insignificant SMR scores and a NA ASMR score.

G-BA reviewed 17 interventions and provided: considerable benefit: 1; minor added benefit: 4; unquantifiable benefit: 1; and no added benefit: 11. Not all SEs were accepted by G-BA as this HTA body requires a strong SE correlation with the final outcome to consider the results in its assessments. In addition, oncology products that included OS data as a secondary endpoint received a no added benefit rating, as the data were considered non-significant or found to have a lack of comparative data.

The analyses were limited to HTA agencies' clear documentation on SE acceptability, and critique. In addition, there are several other factors that could affect HTA appraisals that should be taken into consideration, including clinical benefit uncertainty, drug safety, and other aspects of study design (4).

Conclusion

The use of unvalidated SEs may lead to clinical uncertainty and higher cost-effectiveness estimates, which could result in negative recommendations. Therefore, there is a need for HTA agencies to develop further guidance to assist in SE validation as country-specific HTA methodological guidelines will help 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.

Many products that included validated SE data were ultimately recommended, yet there is a need to include additional robust evidence, such as that from key secondary endpoints to reduce uncertainty and achieve positive recommendations.

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Abbreviations

ASMR, Amélioration du service médical rendu; CADTH, Canadian Agency for Drugs and Technologies in Health; CDF, Cancer Drug Fund; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; HTA, Health Technology Assessment; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NA, Not applicable; NICE, National Institute for Health and Care Excellence; OS, overall survival; PO, primary outcome; SE, surrogate endpoint; SMR, Service Médical Rendu; STE, surrogate threshold effect