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Acceptability of Surrogate Endpoints by Health Technology Assessment bodies – Results from a systematic review of Transparency Committee assessments in France

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Objectives

Health Technology Assessment (HTA) bodies are increasingly facing Surrogates Endpoints (SE) when assessing drugs as part of the reimbursement process, when results on a final primary clinical outcome are not available yet or not measurable at the regulatory approval stage.

The objectives of our study were to assess SE acceptability by the Transparency Committee (TC), France's HTA body, and how they impact opinions' main criteria (clinical benefit [SMR] and clinical added value [ASMR] compared with the existing strategy). In its doctrine, the TC differentiate SE that are statistically demonstrated and correlated with a final clinical outcome and "intermediate criteria", not correlated but deemed relevant.

Methods

An internal Public Health Expertise's database comprising the contents of all TC transcripts published between November 2019 and October 2022 was automatically searched with text algorithm to identify cases where SE acceptability and their impact on reimbursement decisions were discussed.

Debates and key information from the transcripts and associated opinions (study design and methodology, patients' characteristics, results, SMR/ASMR) were extracted and analyzed.

Results

70 transcripts corresponding to 50 opinions (9.0% of opinions published over the period) were identified, and 48 of them were focused on one product assessed in a therapeutic indication (two of them were collective reevaluations of the gliptin and gliflozin drugs in diabetes mellitus – excluded from the analysis).

Most of these opinions assessed treatments as adjuvant or neoadjuvant in oncology, rare diseases and infectiology (Figure 1) and the SMR were mainly high and the ASMR levels reported were mainly IV/V (Figure 2).

Figure 1. Opinions' therapeutic areas

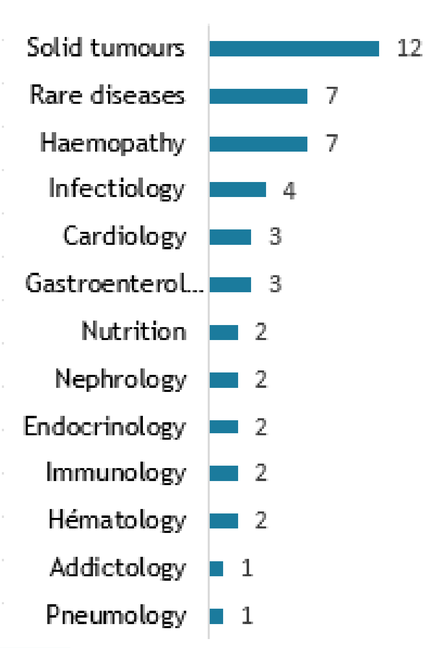
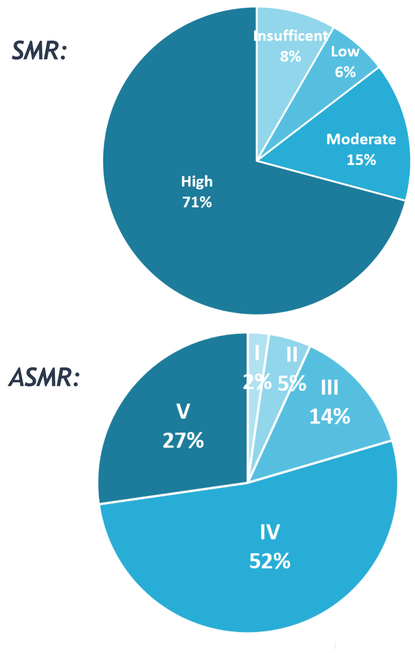


Figure 2. Opinions' SMR and ASMR

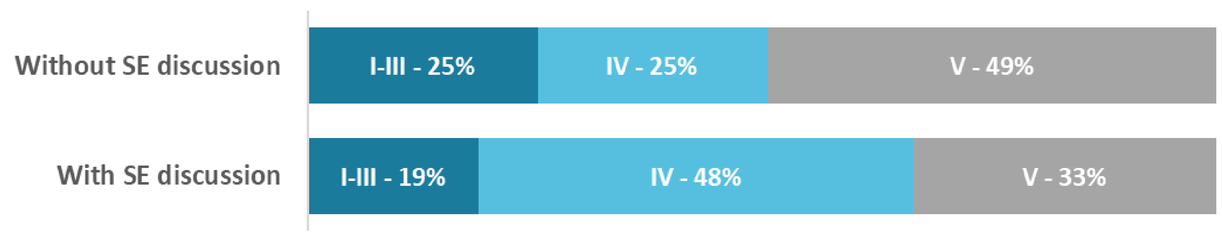


No opinion was identified with a statistical demonstration of the surrogacy according to the methodology recommended by HTA (Buyse method). The TC opinions analysed referred to "intermediate outcomes" of a clinical endpoint.

TC assessments for which SE were discussed were not significantly associated with a higher rate of ASMR V versus opinions without SE discussion, and ASMR I-III were also granted (Figure 3).

Opinions with insufficient SMR and ASMR V were mainly driven by methodological limitations, the design of clinical studies, treatment's size effect, the choice of comparator, the safety profile, while the acceptability and the relevance of SE was more considered and challenged for opinions with ASMR I-III and ASMR IV.

Figure 3. Repartition of ASMR according to the existing discussion of SE by the TC



The acceptability of SE by the TC depends on its capacity to be a good predictor of morbi-mortality outcomes and/or the natural evolution of the disease and symptoms.

The relevance of SE is also assessed according to the medical need, the complexity of measuring clinical outcomes in the disease according to the clinical trial framework, the medical consensus on this SE and previous opinions published by HTA.

In this context, immunogenicity data is well-accepted as SE in the assessment of the vaccine efficacy. In cystic fibrosis, the forced expiratory volume (FEV) was recently considered as a valid outcome of the pulmonary function, as well as the viral load in the treatment of human immunodeficiency virus (HIV).

Many recent TC opinions on innovative drugs using SE in early stages in oncology and rare diseases have successfully achieved ASMR I-III:

- Disease-free survival (DFS) or progression-free survival (PFS) in breast cancer HER2+, endometrial cancer, lymphoma
- Oxaluria level in primary hyperoxaluria type 1 and bile acids level in progressive familial intrahepatic cholestasis

In contrast, TC recently considers a lack of demonstration of the surrogacy between morbidity/mortality and LDL-c levels in familial hypercholesterolemia (FH), leading to ASMR V and IV (severe form of FH) for anti-PCSK9.

Conclusions

The use of SE should not be discarded for market access in France. But there is no set rule: the relevance of SE is assessed for each situation depending on the medical need, emphasizing the importance of consulting experts and previous opinions to anticipate their acceptability. Innovative treatments using SE can reach ASMR I-III if they demonstrate their superiority in a robust clinical trial including the relevant comparator.

One of the other findings is that the statistical demonstration of the surrogacy was never discussed in the opinions analysed. Nevertheless, the TC may accept "intermediate outcomes" considering the assessment's context. EUHTA's work on SE and potential impact on their acceptability will be key to monitor in the following years.

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