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EDITORIAL



# The notion of Surrogacy in Health Technology Assessment: an insight in the processes of Germany, UK and France

## Introduction

The notion of Health Technology Assessment (HTA) has evolved significantly since its inception and currently it is acclaimed as the holy grail of decision-making in the pharmaceutical sector[1]. The elaboration of an HTA report constitutes a resource and time-demanding process. In this saga, overall survival (OS) has been acknowledged as the gold standard in elucidating the value of an oncology treatment modality, broadcasting what matters the most to patients and the community[2]. OS along with health-related quality of life (HRQOL), falls under the "patient-centered clinical endpoints". Patient-centered clinical endpoints describe the endpoints that measure a direct patient clinical benefit, such as individuals' survival or feeling of well-being[3]. In principle, clinical trials should focus on OS. However, in certain cases, it is hard or even unattainable for companies to submit mature OS data since the evolution in the pharmaceutical sector has led to significant survival gains. In this sense, the time-frame of a single trial is usually[4] insufficient to capture the full spectrum of OS. Moreover, the design of trials, as in the case of cross-over studies, further hampers the use and the clarity of OS as an endpoint. In this backdrop, much effort may be devoted to validate surrogate endpoints; however, surrogate endpoints are used specifically because they are more easily accessible. Discovery and validation of surrogate endpoints, which can be gathered at an early stage of the disease and most significantly, can demonstrate strong predictive causality with OS.

In oncology, surrogate endpoints are tumor-centered clinical endpoints that infer clinical benefit to the patient and are employed as a proxy for a patient-centered clinical endpoint. These endpoints refer to biological markers, either laboratory or histology ones, such as tumor response, circulating tumor cells, disease-free survival (DFS) and progression-free survival (PFS), which can define therapeutic response to an intervention. The rationale of surrogate endpoints is nested in the prediction of survival well in advance, thus perpetuating to fewer patients and shorter and cheaper trials. In some cases, as in the cases of crossover to subsequent treatments, the use of surrogate endpoints is justified. A validation must precede, which constitutes an intricate but obligatory process. Many surrogate endpoints, which meet the criteria of being assessable earlier in a patient's life, have been assessed. Nevertheless, a simple correlation does not suffice[3] (Table 1).

The surrogate endpoints, according to Prentice, must meet four operational criteria:

- The treatment must demonstrate a substantial effect on the surrogate endpoints.
- The treatment must also demonstrate a substantial effect on the primary endpoint.
- The surrogate endpoint must demonstrate strong and consistent correlation with-and also predict- the net effect on the primary endpoint (i.e. given that the surrogate falls under a specific threshold).
- The full effect of treatment upon the true endpoint must be mediated by the surrogate endpoint.

Nevertheless, Prentice criteria assume an in-depth apprehension of the underlying biological mechanisms, which is not always readily available[5]. Various approaches have been proposed. EunetHTA further elaborated on a policy framework for the validation of surrogate endpoints, which consists of three steps:

1. Analytical validation: Can we accurately measure this biomarker (accuracy: reliability, reproducibility, sensitivity and specificity) measured?
2. Qualification: Assume that a consistent association exists between the endpoints and the clinical endpoint of interest.
3. Utilization: What is the proposed utilization pattern of the use of the surrogate endpoint[6]?

It is imperative that surrogate endpoints must be validated with regards to a certain therapeutic class, for a certain disease, at a specific cancer stage. A universal rule of thumb does not exist and researchers should resist the temptation of an unconditional extrapolation. The case of Fluorouracil (5FU) is an illustrative one. For advanced colorectal cancer, only DFS was validated as a surrogate for OS. This relationship cannot be presumed for other medicines even for the same condition, or for the same product at another disease stage, contrary to the common assumption that a correlation between PFS and OS exists unconditionally across the whole oncology spectrum. For instance, PFS was validated as a surrogate for OS in ovarian cancer, but in the advanced breast cancer setting, it failed to meet the surrogacy criteria at the trial level, despite a significant effect on PFS and Time to Progression (TTP) at the individual level[7,8].

We should also underline that the debate of surrogate *vs.* primary endpoints has infiltered all health care sectors, as in the case of cardiology. Usually, trials which report superior outcomes based on surrogate endpoints, are not continued by primary prominent outcomes trial. It was also noted that approximately half of the positive surrogate trials were not validated[9]. Cardiovascular surrogate outcome trials may be more appropriate for excluding benefit from the patient perspective than for identifying it.

Relying entirely on surrogate endpoints poses serious problems. There is an array of composite surrogate endpoints, which are perceived to be interchangeable. Time to

**Table 1.** Surrogate endpoints.

| Oncology | Surrogate | Primary |
|---|---|---|
| | Progression-free survival (PFS) | Overall survival |
| | Invasive-disease free survival (IDFS) | Overall survival |
| | Disease-free survival (DFS) | Overall survival |
| | Time to progression (TTP) | Overall survival |
| | Response rate (RR) | Overall survival |
| Cardiology | Left ventricular ejection fraction | Survival after MI |
| | Blood pressure | MACE, stroke |
| | Coronary angiography | MACE |
| Neurology | f Aβ plaque reduction as measured by PET imaging (Alzheimer) | Cognitive improvement, functional improvement, overall clinical response (ADAS-cog), Neuropsychological Test Battery in Alzheimer's Disease (NTB) |
| | Rate of striatal dopamine transporter loss as measured by SPECT 123I-b-CIT uptake (Parkinson) | Improvement in function, and less somnolence and edema. Unified Parkinson's disease Rating scale (UPDRS) |
| | P50 (schizophrenia) | Positive and negative syndrome scale (PANSS) |
| Infectious diseases | Viral load | Cure |
| Lupus nephritis | Complete renal response (CRR), defined as 1) a response in the urine proteinuria (protein-creatinine ratio) and 2) preservation/improvement of renal function (estimated glomerular filtration rate) | SLEDAI-2K<br>BILAG<br>ECLAM<br>SLAM-R |
| Osteoporosis | Bone mineral density | Fracture |

tumor progression is not the same as PFS, since it does not include patients who died from other causes. This is further compounded by the lack of an exact definition of PFS and DFS. The same variability is also encountered with regard to the definition of tumor progression. Radiological endpoints are susceptible to measurement error and bias[10].

In a recent study by Smith et al., which was published in the Journal of Medical Economics, the chapter of surrogate endpoints, as integral parts of the HTA assessment in Germany, France and UK was debated[11]. The three agencies use divergent approaches pertinent to surrogate endpoints. IQWiG issued detailed methods for the validation of surrogate outcomes and the correlation with the primary endpoint, taking into consideration the biological plausibility and empirical evidence. IQWIG implements a strict framework, and no surrogate endpoints are defined as valid. On the contrary, the appraisal technology guidelines of NICE, focus on the decision uncertainty, which is also embedded in the economic evaluation. Moreover, NICE is most likely to delineate the level of evidence, strength of association and the magnitude of the effect. HAS Sante is correlated with the least level of validation[12].

The authors assessed the reimbursement status of 42 oncology products between 2015 and 2018. 40.4% of indications (34 of 84) received a positive reimbursement decision across G-BA in Germany and Haute Autorité de Santé (HAS) in France. The first indication was associated with a significant negative effect on the quality added benefit of reimbursement. The submission of comparative data demonstrated a statistically significant positive benefit ($p < .001$). The availability of OS data demonstrated a substantial predictive capacity with reimbursement compared to a lack of OS or PFS data. The authors proceeded to assess the OS and PFS individually. When OS maturity and OS statistical significance were analyzed individually, authors reported a significant positive effect on added benefit ($p < .001$). In the case of availability of PFS data only, only maturity demonstrated a statistically significant positive effect ($p < .001$). However, data suggest that this correlation is unclear and oscillates consistently. The authors concluded that HRQOL data correlated with a significant positive effect on approval ($p < .001$). Of interest is the fact that the proportion of positive full reimbursement remained stable, approximately at around 50% of total applications. The submission of PFS data (without any OS) failed to demonstrate correlation with positive recommendation ($p = .991$), while on the contrary, mature data regarding PFS demonstrated a statistically significant correlation with fully reimbursement from both NICE and HAS ($p = .017$). This study concluded there is an increasing trend over time toward HTA submissions with immature OS data. However, this is negatively associated with HTA reimbursement decisions. Specifically, the authors results underlined that for added benefit ratings, mature OS takes hold as the most important endpoint to HTA agencies, despite the embedded intricacy in collating such data on time.

## The way forward

It is increasingly common for health authorities to rely on surrogate endpoints, which is attributed to the feasibility of gleaning them in time. Nevertheless, OS data is still reckoned as the superior endpoint regarding assessment outcomes. Authors concluded that a clear need exists regarding streamlining of the evidence expectations of European Medicines Agency and HTA bodies. This cooperation can also encompass another HTA area, the evidence development, while concomitantly safeguarding the safety of patients. Therefore, agencies and the industry must strive for efficient and feasible approaches of gathering real-world data, while safeguarding patients' safety. This includes research for more clinically meaningful endpoints which will enable shorter clinical trials, which will in turn benefit the patients by allowing swift access to new medication as well. Notably, FDA's accelerated access (AA) program which is intended to accelerate faster access of patients with serious diseases to potentially innovative therapies, published a list of reasonably likely surrogate endpoints that can be used to support an AA application[13].

Moreover, clinical trials should adopt a more efficient design, enabling the elaboration of meaningful outcomes. This also interlaces with another issue frequently encountered in the field of HTA, the transferability of data across countries.

From a medical perspective point of view, we should also ponder that on a global level, cancer rates are rising, which necessitates universal, swift and equal access to cancer treatments[14]. Nevertheless, the positioning of a product in an earlier stage of the disease may augment the disparities between the existing and anticipated data. From an ethical point of view, a delay stemming out of waiting for more data, may perpetuate to forsaken utility. Nevertheless, a forsaken utility may also occur due to a hasty adoption of a treatment modality, which does not have the necessary hard endpoints, compared to the gold standard. We should also deliberate on the specificities of cancer as a disease, and the grave effects it exerts on both patients and their social networks as well.

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### Author contributions

PP designed and drafted the article.

OP and MJP provided study material and revised the initial article.

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