INTRODUCTION TO SURROGATE ENDPOINTS: FROM TRIAL TO TREATMENT ACCESS

BALANCING CLINICAL INSIGHTS, REGULATORY DECISIONS AND HTA EVIDENCE

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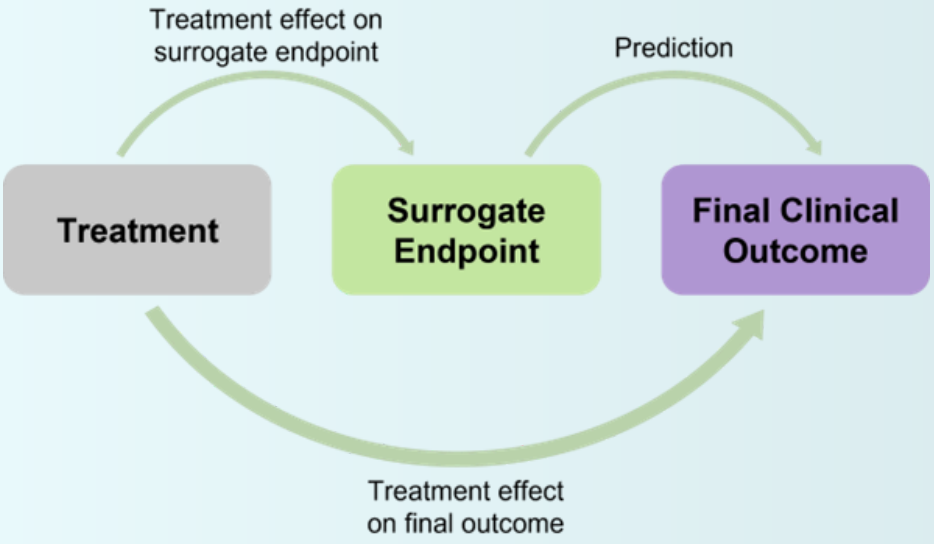
Introduction

A surrogate endpoint (SE) is a marker or intermediate outcome that is used as a direct substitute or predictor of how patients feel, function, or survive in clinical trials.[1] See the image below for an illustration of the relationship between surrogate endpoints and clinical outcomes in the clinical trial setting.



Surrogates are appealing because they can be measured earlier or with fewer resources than clinical outcomes, and therefore the use of SEs can accelerate the evaluation of new therapies and ensure timely treatment access. The flagship disease area for this application of SEs has been oncology. Overall survival (OS) remains the gold-standard clinical endpoint in oncology trials due to its objectivity and clinical meaningfulness, however due to dramatic improvements in patient survival collecting mature OS data in a clinical trial can be extremely slow. For example, as of 2023 thyroid cancer has a real-world median survival of 15 years,[2] and median survival in a clinical trial may be even longer due to restrictive eligibility criteria.

The most common SEs for OS in oncology trials are other time-to-event intermediate outcomes such as progress-free survival and metastatic-free survival.

With SEs playing an increasingly pivotal role in drug development, regulatory agencies such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) are licensing new health technologies based on these early indicators, particularly in therapeutic areas where long follow-up is needed.[3] The FDA is steadily accepting more surrogate measures over time.[4] Between 2010- 2012, the FDA approved 43.3% of new drugs on the basis of a surrogate endpoint, and the approval rate rose to approximate 60% between 2015 to 2017.[5] Beyond regulators, health technology assessment (HTA) bodies and payers rely on robust evaluation of surrogate-outcome relationships to inform coverage and reimbursement decisions and to inform real-world treatment access decisions.

Benefits and Limitations

Why Surrogate Endpoints Matter

- **Clinical Value:** SEs can shorten the time to meaningful trial results, providing earlier evidence of treatment efficacy when the true clinical endpoint may take years to mature.
- **Regulatory Impact:** Regulatory agencies, such as FDA and EMA, increasingly grant approvals on the basis of surrogate markers, particularly in oncology and rare disease areas.
- **Payer/HTA Decisions:** SEs help bridge the evidence gap between early trial data and the long-term outcomes needed for cost-effectiveness models.

Challenges in Using Surrogate Endpoints

- **Validity and Reliability:** Not all SEs predict long-term patient benefit; improvements in biomarkers or progression-free survival may not translate into longer OS.
- **Fragmented Evidence:** Clinical trials often report multiple SEs but analyze them individually, limiting their predictive power.
- **Payer Uncertainty:** HTA bodies may be cautious, especially if evidence of surrogate validity is weak, delaying coverage or restricting patient access.

Frameworks and Methods for Evaluating Surrogate Endpoints

Despite these challenges, a substantial body of work has been developed to rigorously assess and validate SEs. Prentice (1989) first formalized the concept, framing SEs as substitute outcomes that can be used in clinical trials to compare treatments with respect to a true endpoint, typically a disease occurrence.[6] Building on this foundation, Taylor and Elston proposed a three-level hierarchical framework for evaluating surrogates:[7, 8]

- **Biological plausibility:** Evidence of a causal mechanism linking the surrogate endpoint to the true endpoint. Assessed using epidemiological evidence, animal models, mechanistic studies, etc.

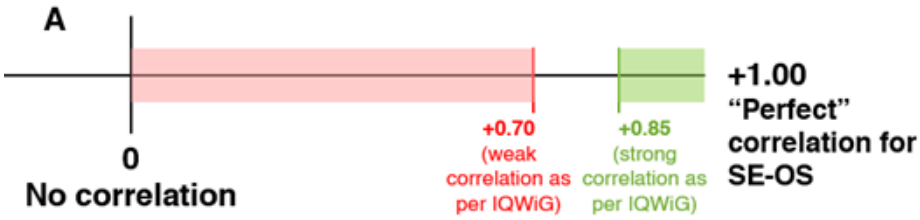
- **Patient-level association:** Evidence that the surrogate can predict patient prognosis. Assessed by evaluating the association between the two endpoints within a single trial.

- **Trial-level association:** Evidence that the surrogate can predict treatment benefit. Assessed by evaluating the association between treatment effects across multiple trials.

Subsequent methodological advances by researchers such as Bujkiewicz et al. have extended surrogate evaluation through Bayesian and multivariate meta-analytical frameworks to better capture complex surrogate-outcome relationships.[9,10] Additionally, agencies such as the National Institute for Health and Care Excellence (NICE) and the Institute for Quality and Efficiency in Health Care (IQWiG) have developed methodological guidelines and assessment criteria,[11,12] demanding transparent, systematic, and statistically rigorous validation of SEs which are to be used for regulatory approval and HTA decision-making.

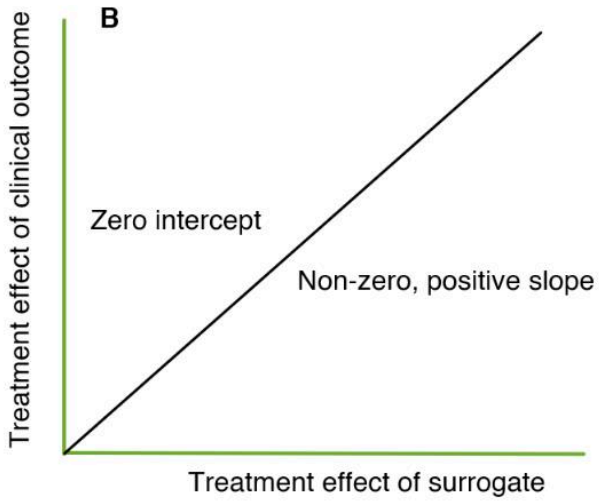
The strength of association, also known as the strength of surrogacy, is measured by a correlation coefficient and plays a critical role in establishing an SE's validity. A correlation relationship is considered perfect between the true treatment effect of the clinical endpoint and a SE when the following conditions are met:

1. the correlation estimate reached ±1 implies a perfect linear association between the treatment effects on an intermediate endpoint and OS.[11] See **image A** below for correlation relationship.



2. the intercept estimate of the surrogate equation equal to 0 which suggest an absence of treatment effect on final outcome when there was no effect on the surrogate endpoint.[11] See **image B** below for surrogate equation with intercept estimate equal 0.

3. the slope estimate of the surrogate endpoint does not equal to zero.[11] See **image B** below for surrogacy equation with slope estimate not equal to zero.



These foundational analytical methodologies and validation approaches to evaluate surrogate endpoints have been applied across several tumor types and population groups: advanced or metastatic melanoma,[13,14] esophageal or gastroesophageal junction cancer,[15] metastatic hormone-sensitive prostate cancer,[16] or high-risk localized and locally advanced prostate cancer,[17] enabling a transferrable, scalable strategy for evaluating SE credibility.

The Way Forward

SEs are reshaping how therapies move from clinical trials to regulatory approval and, ultimately, to payer decisions. The challenge is not whether to use SEs, but how to ensure that they are evaluated rigorously enough to guide real-world access and policy. By advancing methods that integrate multiple SEs and strengthen trial-to-OS prediction, stakeholders can improve both the speed and reliability of evidence for patients, regulators, and payers alike.

Keep a look out for future blog posts on further details of surrogacy validation methods, such as leave-one-out cross validation and surrogate threshold effect.

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