



Understanding Payer Sensitivities when Considering the Use of Surrogate Endpoints to Substantiate Clinical Value Propositions

Country Differences between England, Germany, and the U.S.

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A surrogate endpoint can be defined as an indicator variable substituting for a clinically meaningful endpoint that reflects how a patient feels, functions, or survives.¹ This can include behavioural or cognitive scores, physiologic variables that are indicators of normal biological or pathogenic processes, pharmacological responses to therapeutic intervention, and biomarkers. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.²

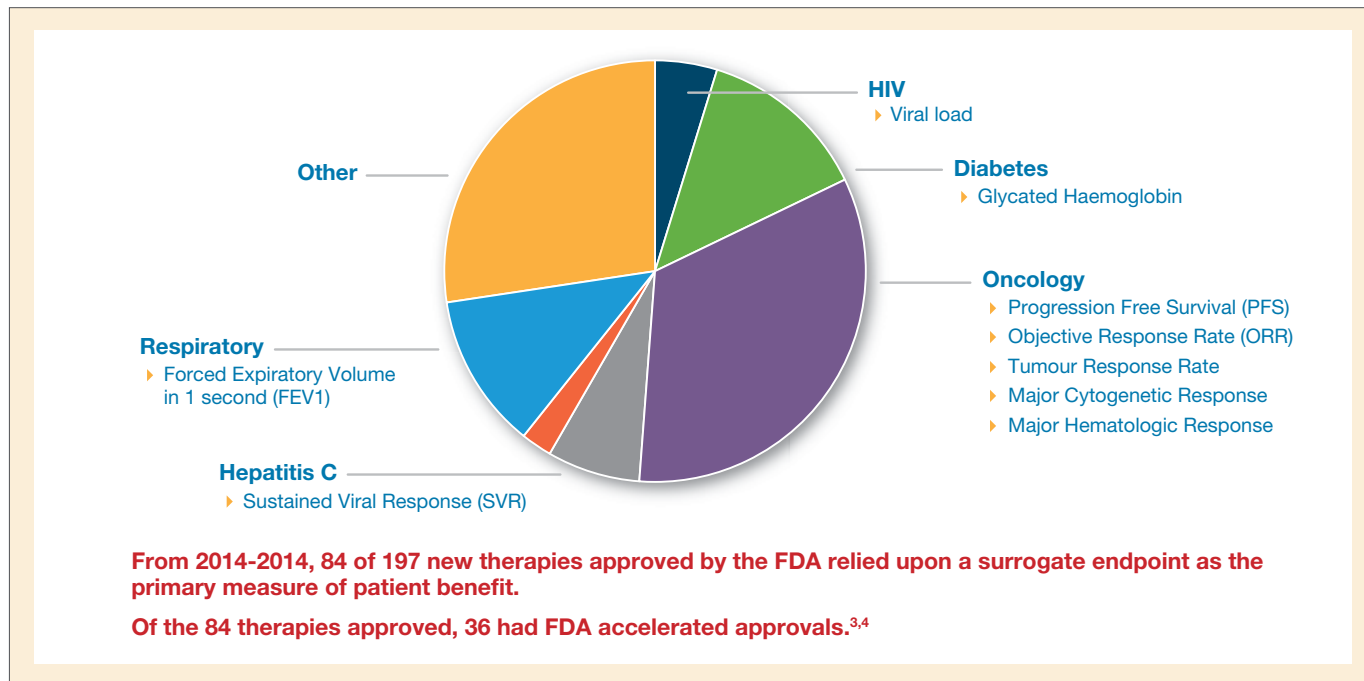
The use of surrogate endpoints in payer and health technology assessment (HTA) evaluations has consistently sparked controversies. Although in many cases a clinical study with a primary surrogate endpoint may be sufficient to achieve regulatory approval, this may be challenged

by payers and HTA agencies due to uncertain correlation with a clinically meaningful endpoint. The expectations from payers and HTA agencies as to when a surrogate endpoint is acceptable and specific requirements to ensure validity for decision making can vary considerably across markets, creating clear challenges for manufacturers.

In 2016, the Evidera Market Access Strategy team undertook an investigation on the impact of surrogate endpoints in pricing and reimbursement decision making

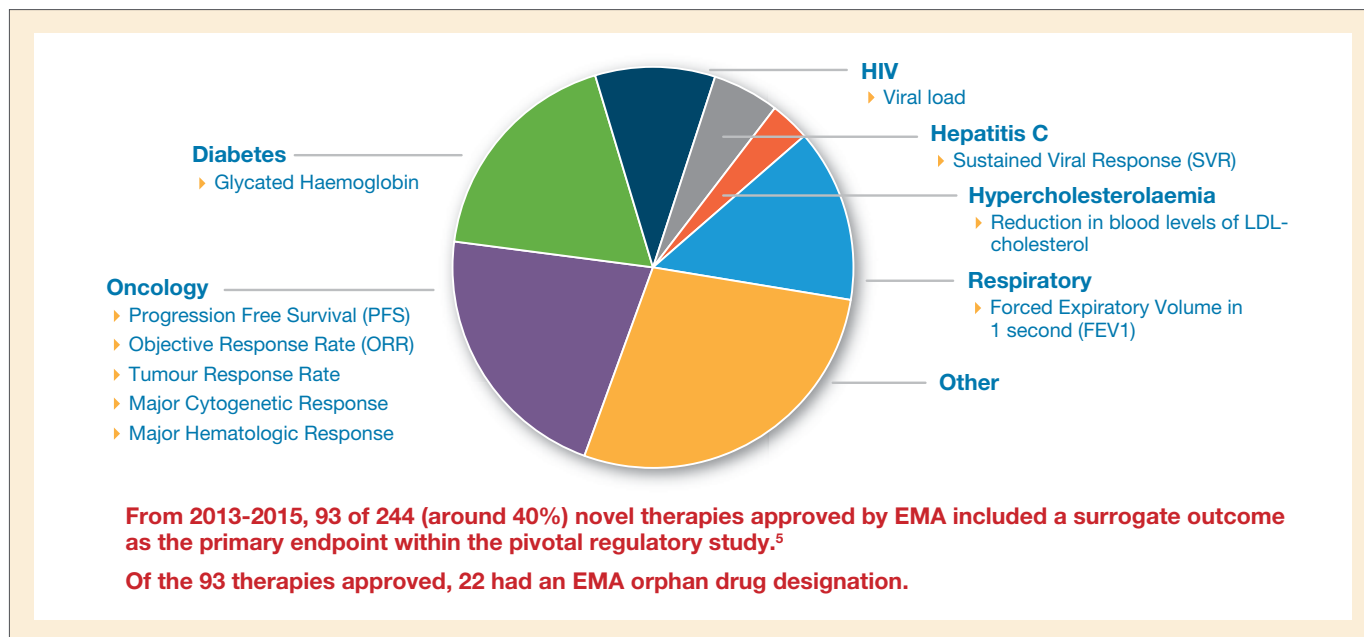
Almost half of all novel therapies approved by the U.S. Food and Drug Administration (FDA) in the past five years have relied on surrogate endpoints for demonstration of patient benefit.^{3,4}

Graphic 1. Review of Key Therapy Areas within FDA Approvals with Surrogate Endpoints



Surrogate endpoints have been widely accepted by the European Medicines Agency (EMA) for the regulatory approval of novel therapies.⁵

Graphic 2. Review of Key Therapy Areas within EMA Approvals with Surrogate Endpoints



with payers in the U.S., England, and Germany. The aim of the research was to identify payer perceptions on the use of surrogate endpoints, differences in acceptability across specific surrogate markers and indications, and expectations for ensuring the validation of a surrogate

marker as a patient-relevant measure of therapeutic effect.

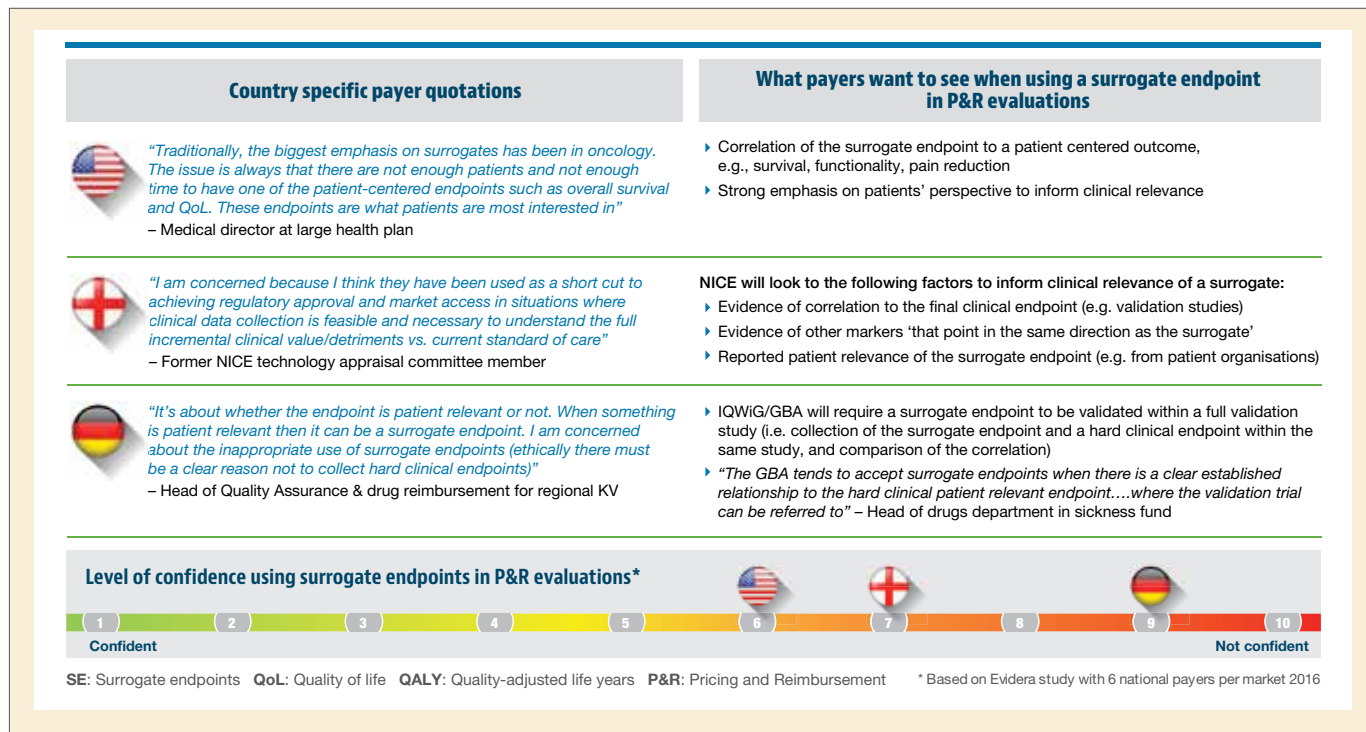
At the regulatory level, the FDA and EMA have issued guidance on how to define a surrogate endpoint.

At the payer level, payers consistently highlight that ideally the surrogate endpoint should have a close correlation with hard clinical outcomes to inform decision making. However, in practice, significant variability exists regarding the level of information that payers want to see when assessing surrogate endpoints in pricing and reimbursement evaluations.







Payers across the U.S, England, and Germany identify important challenges regarding the use of surrogate endpoints as a measure of clinical effect.

Payers across all three markets identify a need for the validation of surrogate endpoints (in terms of the relationship with hard clinical outcomes) and support

Graphic 3.



Graphic 4.

Indication	Surrogate endpoint	Surrogate for	Acceptance in payer assessment	Key findings on payer perception
Hypercholesterolaemia	Level of LDLC	Coronary heart disease, cardiovascular (CV) risk		Payers recognize that "different methods of lowering LDL cholesterol have different clinical outcomes" and many plans are not covering PCSK9 inhibitors because of this. Other plans are restricting use within the labelled indication and awaiting further data on hard clinical endpoints to inform decision making
				Widely considered to be poorly correlated with cardiovascular risk. NICE review of PCSK9 inhibitors resulted in patient access schemes (PAS) and restriction to patients who are not adequately managed with current standard of care (SoC)
				Not acceptable for payers; very low perceived correlation with patient morbidity
HCV	Sustained Virological Response (SVR)	Survival, liver transplant		Widely accepted as a surrogate endpoint for survival, and "about as close as you are going to get to a clinically relevant endpoint". The only information not available is "downstream impact on liver function recovery and whether you are still at risk of cirrhosis"
				SVR 12 and SVR 24 are acceptable endpoints; valued as a surrogate for survival and as a driver of reduced transmission rates
				SVR cannot be equated with "cure" (as this is not validated as a surrogate outcome in line with IQWiG criteria), however SVR is accepted as a surrogate for reduced incidence of liver cancer

Key: Acceptability of surrogate endpoints in P&R assessment

HIGH
LOW
MEDIUM

* Based on Evidera study with 6 national payers per market 2015/2016

managing the increase in uncertainty within the decision making process. The three key challenges reported on the use of surrogate endpoints are as follows.

1. Considered as an industry shortcut within clinical development programs

- Can be seen as a route to rapid regulatory approval without consideration of the actual value/limitations of the surrogate endpoint for communicating the incremental clinical value vs. existing therapies within payer assessment
- Need for an evidence development strategy understanding the advantages and disadvantages of a surrogate endpoint to evaluate the need for additional data generation

2. Correlation of the surrogate endpoint to the final clinical endpoint

- A gap between the surrogate endpoint and the final clinical endpoint will create additional uncertainty for decision makers
- Payers request support from manufacturers to understand and manage this additional uncertainty within pricing and market access decision making

3. Ensuring patient relevance and validation

- Creating the supporting rationale for the relevance and validity of a surrogate endpoint (in terms of

what this practically means for how the patient feels, functions, or survives) often does not receive sufficient time or resources within a product development program

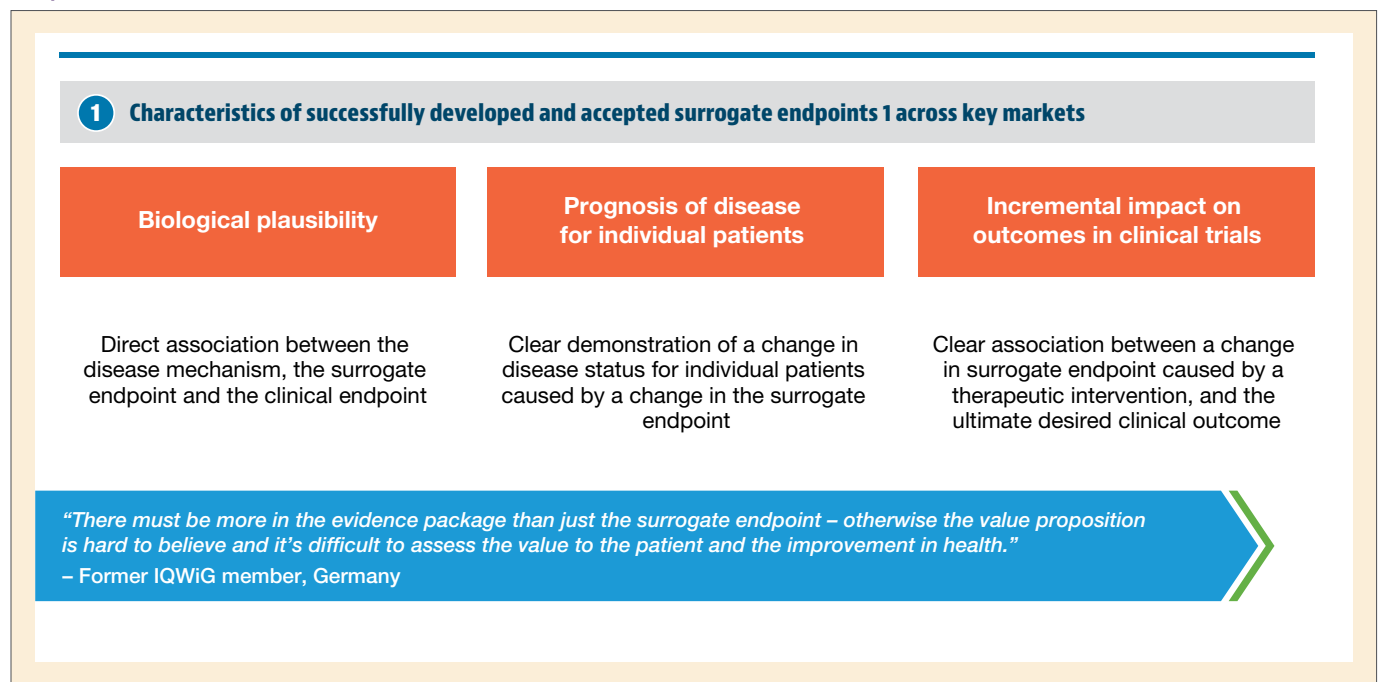
Our research demonstrates varying perceptions of payers across markets on the acceptability of specific surrogate endpoints within decision making and implications for pricing and reimbursement.
(Graphic 4)

For example, payers across markets accept sustained virologic response as a valid surrogate for patient relevant outcomes in Hepatitis C, however, low density lipoprotein is consistently challenged as a poor surrogate for cardiovascular outcomes/morbidity in the treatment of hypercholesterolaemia.

Conclusion

Despite differences between markets regarding the perception of surrogate endpoints, consistencies are evident in the characteristics of successfully developed and accepted surrogate endpoints. A clear chain of evidence linking a change in the surrogate parameter with a change in clinical outcomes, along with a rationale for the reliance on a surrogate endpoint for demonstrating the clinical benefit of a new therapy, are of key importance to ensure payer acceptance. ■

Graphic 5.



Graphic 6.

Payers require a clear rationale for the reliance on a surrogate endpoint for demonstrating the clinical benefit of a new therapy

2 When to rely on a surrogate endpoint?

- ✓ **A clear and transparent rationale as to why it is not feasible to collect hard clinical endpoint data**
 - ▶ E.g., requirement for a long follow-up that is not feasible within a clinical development program (especially important for innovative drugs where there are few alternatives, therefore there may be more pressure to make the drug available)

- ✓ **All criteria for the validity of a surrogate endpoint are met**
 - ▶ Consistency of the association between the surrogate and clinical endpoint
 - ▶ Consistency of the association between surrogate endpoints and patient-important outcomes (e.g., QoL, pain reduction, activities of daily living)
 - ▶ Evidence from trials in the same drug class that improvement in the surrogate endpoint has consistently led to improvement in the target outcome
 - ▶ Evidence from trials in other drug classes that improvement in the surrogate endpoint has consistently led to improvement in patient-important outcomes

"When thinking about using a surrogate, my advice is don't take shortcuts, and if there is a feasible way of collecting hard endpoint data, do this, otherwise have a justifiable reason for why you didn't do this or expect payers to penalise you."
– Former NICE Appraisal Committee member

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