In 2016, the Evidera payer strategy team undertook research to determine the market access implications of surrogate endpoint selection and the optimal approach for their use within clinical development programs. These insights were generated through analysis of case study examples from key therapy areas and primary research with three payers per market in Germany, England, and the U.S.

The importance of this research is evident from the fact that almost half of all novel therapies approved by the U.S. Food and Drug Administration (FDA) in the past five years have relied on using surrogate endpoints within pivotal clinical trials for the demonstration of patient benefit. Similar surrogate endpoints have been widely accepted by the European Medicines Agency (EMA) for the regulatory approval of novel therapies.

Acceptability of a surrogate endpoint at the regulatory level is not, however, a guarantor of relevance to payers to support pricing and market access decision making. Payers generally require a surrogate endpoint to demonstrate a validated correlation with the final clinical endpoint, with a clear justification for use within a specific therapy area or patient group.

### Three main payer challenges in the use of surrogate endpoints

1. **Perception of surrogate endpoints as a cost-free shortcut by the industry***
   - Manufacturers need to take a longer strategic approach
   - Actual value and limitations must be considered
   - Need for an evidence development strategy understanding the advantages and disadvantages

2. **Low correlation of the surrogate endpoint to the final clinical endpoint***
   - Gap between the surrogate endpoint and final clinical endpoint creates uncertainty
   - Better understanding on how to manage the gap is needed

3. **Lack of patient relevance and validation***
   - Manufacturers must ensure enough time is allocated – start ahead of time

* Based on Evidera study with six national payers per market 2015/2016
WHEN IS A SURROGATE ENDPOINT ACCEPTABLE FOR PAYERS as a clinically relevant measure of therapeutic benefit? Our research indicates disparity between payers in Germany, England, and the U.S. as to how a surrogate endpoint should be validated, in which indications a surrogate may be justified, and which surrogate endpoints are acceptable measures of clinical value.

In clinical trials, a surrogate endpoint (or marker) is a measure of effect of a specific treatment that may correlate with a hard clinical effect but does not necessarily have a guaranteed relationship.

Regulatory approval and pricing and reimbursement decisions often need to be based on surrogate endpoints for the following key reasons:

1. **Efficacy data based on clinical endpoints require a large sample size and long follow-up**
   - This can present a challenge for therapies in chronic diseases and/or having a small expected effect size

2. **Treatments are becoming more effective, therefore endpoints are reached later**
   - Longer follow-up is needed to observe the outcome
   - Only a small effective size for the clinical outcome when observed early

3. **There can be ethical issues in stopping a trial early once the investigational product is proved to be superior based on other outcomes**

4. **Unbiased clinical endpoints sometimes cannot be observed due to**
   - Crossover to the efficacious therapy
   - Emergence of many possible subsequent therapies

In principle payers agree that the use of surrogate endpoints is at times unavoidable.

<table>
<thead>
<tr>
<th>Market</th>
<th>Are surrogate endpoints sometimes the only way to demonstrate value?</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>🇺🇸</td>
<td>Yes, proxies are sometimes needed when a longer follow-up is required to observe the outcome, due to increasingly effective treatments resulting in endpoints being reached later</td>
<td>Example: OS in cancer where treatments are becoming more effective and so endpoints are reached later, “The median OS gets pushed further and further out which is a good thing but how do we determine what the OS is and how do we compare treatment A to treatment B?”</td>
</tr>
<tr>
<td>🇬🇧</td>
<td>Yes, with rare conditions when it is not possible to see outcomes in the short-term</td>
<td>More pressure to treat people when you have an innovative drug and there is lack of an alternative Must still be linked to the final endpoint, and correlating in a clinically meaningful way</td>
</tr>
<tr>
<td>🇩🇪</td>
<td>Yes, specifically in viral diseases such as HCV though even any QoL endpoint is better than laboratory data</td>
<td>Not only the validation is critical but also the rationale for the selected endpoint, e.g., with HCV it cannot be mortality but the need for liver transplant or occurrence of HCC</td>
</tr>
</tbody>
</table>

* Based on Evidera study with six national payers per market 2015/2016
The FDA and EMA will often accept evidence from clinical trials that show a clear benefit on a surrogate marker, subject to an acceptable benefit/risk ratio for patients. Payers, however, consistently seek a surrogate endpoint to be patient-relevant with a strong correlation to a hard clinical endpoint. Across markets, payers have varying opinions as to when a surrogate endpoint is patient-relevant and how validity in terms of correlation with hard clinical outcomes should be demonstrated to support positive health technology assessment (HTA).

### CASE STUDY: IQWiG’S OPINION ON THE VALIDITY OF SURROGATE ENDPOINTS IN ONCOLOGY

In principle, the use of surrogate endpoints is considered acceptable if validated. However, comprehensive data are required to validate a surrogate endpoint, preferably a meta-analysis of several randomized trials showing sufficient certainty of results. In order to demonstrate validity, a high correlation between effects on the surrogate and the patient-relevant endpoint is usually required (0.9 is considered as a potential threshold).

In cases where no high correlation is evident, surrogate threshold effect (STE) can be provided to support the validity if sufficiently large effects on the surrogate have been shown. It is not readily possible to transfer conclusions about the validity of surrogates across different diseases, disease grades, or different interventions.

**IQWiG’s opinion on the validity of surrogate endpoints in colon and breast cancer**

IQWiG concludes that the validity of tumor response parameters as surrogates for patient-relevant endpoints (overall survival) in colon and breast cancer remains unclear, driven by the low reliability of the validation studies.

None of the validation studies examined are believed to consistently fulfill recognized quality criteria, with several concerns, including:

- Different interventions or indications are often analyzed conjointly
- Either it is unclear how the data had been compiled, or its compilation proved to be non-systematic
According to IQWiG’s guidance, the validity of surrogate endpoints in oncology has to be assessed at multiple levels – where patient relevance is paramount

**STEP 1** Assess reliability of validation results
(high / limited / moderate / low reliability)

“Reliability” is assessed based on the following criteria:
- Application of a recognized approach described in the scientific literature
- Conduct of analyses to test the robustness and generalizability of results
- Systematic compilation of the underlying data for the validation
- Sufficient restriction of indications or degrees of disease severity
- Sufficient restriction of the interventions investigated
- Clear definitions of the endpoints investigated

A correlation of 0.9 is perceived as a potential threshold for a high correlation of effects on the surrogate and the patient-relevant endpoint (PRE).

**STEP 2** Assess correlation between surrogates and PRE
(high / medium / low correlation)

**STEP 3** If correlation is only medium, assess the effect on the surrogate vs. STE

- Based on the above information (reliability of results, the level of correlation between the surrogate and PRE, and the effect on surrogate if needed), IQWiG will make conclusions on the benefit of the new therapy on PRE from its effect on surrogate endpoint.
- This conclusion could be “proof of effect”, “indication of effect”, “hint of effect”, or “no effect”.

In cases where a high correlation is not evident, then the effect on surrogate endpoint vs. surrogate threshold effect (STE) will be examined (if available)
- Proof of support of benefit: if 95% CI of the effect on the surrogate > STE
- Indication of effect on PRE: if 80% of the effect on the surrogate > STE

Source: IQWiG Reports – Commission No. A10-05 Validity of surrogate endpoints in oncology (version 1.1), 21 Nov 2011;
PRE: Patient-relevant endpoint; STE: Surrogate threshold effect

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**PRACTICAL IMPLICATIONS OF SURROGATE ENDPOINT USE ACROSS MARKETS: THE ONCOLOGY CASE**

The debated case of Progression Free Survival (PFS) as a surrogate endpoint

In the U.S., payers confirm that the consideration of surrogate endpoints is widely accepted to inform formulary access. Payers recognize that PFS is an imperfect surrogate but are willing to accept the endpoint to support perceived value in the absence of mature overall survival (OS) data. On the other side, in Germany, PFS is generally widely challenged as a surrogate for overall survival and not considered patient-relevant.

**THE LIMITED PAYER ACCEPTANCE OF IMAGING AND TUMOR SIZE AS VALUED SURROGATE ENDPOINTS**

With regards to imaging and tumor response, payers are even more reluctant.

- German payers do not consider evidence from imaging and tumor size to constitute evidence that demonstrates patient benefit.
- England payers also state this type of evidence has low relevance for payer decision making due to “poor correlation with clinical outcomes.” Imaging and tumor size is valued as “supporting data for other more relevant endpoints,” for example “if there is a PFS benefit and immature OS benefit and we are looking at the overall argument for the likely OS benefit.” - Former NICE technology appraisal committee member
KEYTRUDA WAS ABLE TO ESTABLISH PATIENT BENEFIT BEYOND THE SURROGATE ENDPOINT

Keytruda (pembrolizumab, Merck) is indicated for:

- Advanced melanoma following treatment with ipilimumab, or after treatment with ipilimumab and a BRAF inhibitor in patients with BRAF mutation
- Metastatic non-small cell lung cancer (NSCLC) in patients whose tumors express PD-L1 and have failed treatment with other chemotherapeutic agents

The drug received regulatory approval for both indications in 2015 in the U.S. and the EU.

For the pricing and reimbursement processes of the melanoma indication in Germany, France, England, and the U.S., the manufacturer presented clinical effectiveness evidence from two clinical trials:

- KEYNOTE-001 was a combined Phase I and II study
- KEYNOTE-006 was a randomized, international, multicenter, Phase III trial vs. ipilimumab

In KEYNOTE-006, Keytruda was associated with statistically significant increases in both progression-free survival (first interim analysis) and overall survival (second interim analysis), compared with ipilimumab. Keytruda was also associated with statistically significantly higher overall response rates compared with ipilimumab.

Tumor response rate by computerized tomography (CT) and magnetic resonance imaging (MRI) has been widely used across clinical trials for new therapies in the treatment of metastatic melanoma as a surrogate for improving survival.

While tumor response is not an acceptable endpoint to demonstrate patient benefit, the assessments in the HTA markets – Germany, France and England – provided positive overall benefit ratings for Keytruda. This was mainly due to the fact that most assessments took primarily into account the interim PFS and OS data and regarded the overall response rate (ORR) data as informative only. This clearly demonstrates the reducing importance of the surrogate endpoint where any hard endpoint data may be available.
**Case Study: Pricing and reimbursement outcomes for Keytruda for the treatment of metastatic melanoma**

<table>
<thead>
<tr>
<th>U.S.</th>
<th>NICE 1</th>
<th>HAS 4, 5</th>
<th>GBA 2, 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is tumor response rate an acceptable surrogate endpoint?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Is tumor response rate patient relevant?</td>
<td>Yes</td>
<td>Undecided in the case of Keytruda</td>
<td>No</td>
</tr>
<tr>
<td>Outcome</td>
<td>NICE valued the interim PFS and OS data and regarded ORR as informative. Overall accepted for NHS use.</td>
<td>March 2016: SMR important ASMT IV – based decision on interim OS and PFS</td>
<td>Feb 2016: GBA: No evidenced benefit in naive patients BRAF- V600-mutated and in BRAF-V600-wild-type, a significant incremental benefit. Based decision on interim OS and PFS.</td>
</tr>
</tbody>
</table>

**P&R decision and rationale**

**Keytuda**

- **Reimbursed by Medicare**
- **Reimbursed within NHS**
- **Reimbursed 100%**
- **Reimbursed by Social Security**

**Surrogate endpoints position**

- Covered via medical benefit
- NICE accepted due to positive interim PFS and OS
- ASMR IV
- Reimbursed given improved QoL and support from interim OS and PFS

**ORR accepted and seen as patient relevant**

- NICE valued the interim PFS and OS data and regarded ORR as informative. Overall accepted for NHS use.
- Mar 2016: SMR important ASMT IV – based decision on interim OS and PFS.
- Feb 2016: GBA: No evidenced benefit in naive patients BRAF-V600-mutated and in BRAF-V600-wild-type, a significant incremental benefit. Based decision on interim OS and PFS.

**ORR accepted and seen as patient relevant if it is the only patient benefit**

- NICE valued the interim PFS and OS data and regarded ORR as informative. Overall accepted for NHS use.
- Mar 2016: SMR important ASMT IV – based decision on interim OS and PFS.
- Feb 2016: GBA: No evidenced benefit in naive patients BRAF-V600-mutated and in BRAF-V600-wild-type, a significant incremental benefit. Based decision on interim OS and PFS.

**ORR not seen as patient relevant**

- GBA: No evidenced benefit in naive patients BRAF-V600-mutated and in BRAF-V600-wild-type, a significant incremental benefit. Based decision on interim OS and PFS.

**ORR not seen as patient relevant if it is the only patient benefit**

- GBA: No evidenced benefit in naive patients BRAF-V600-mutated and in BRAF-V600-wild-type, a significant incremental benefit. Based decision on interim OS and PFS.

**ORR not seen as patient relevant if it is the only patient benefit**

- GBA: No evidenced benefit in naive patients BRAF-V600-mutated and in BRAF-V600-wild-type, a significant incremental benefit. Based decision on interim OS and PFS.

**KEY LEARNINGS:**

- HTA’s accept submissions with the surrogate endpoint ORR if supported by other patient benefits – in the case of Keytruda interim PFS and OS data supported the patient benefit.

**KEY LEARNING:** Using surrogate endpoints to support pricing and reimbursement (P&R) for a novel drug requires a clear chain of evidence be established demonstrating a justified rationale for the absence of hard clinical endpoint data, and the validated correlation of the surrogate endpoint with hard clinical outcomes.

A surrogate endpoint is most likely to be an appropriate/acceptable endpoint for a pivotal clinical trial if the following factors are in place.

1. 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)

2. All criteria for the validity of a surrogate endpoint are met, including:

   - Consistency of the association between the surrogate and clinical endpoint
   - Consistency of the association between surrogate endpoints and patient-important outcomes (e.g., quality of life (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
Using surrogate endpoints in P&R requires that a clear chain of evidence is established demonstrating additional patient benefits on mortality/morbidity endpoints

<table>
<thead>
<tr>
<th>Characteristics of successfully developed and accepted surrogate endpoints across key markets</th>
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</thead>
<tbody>
<tr>
<td>Biological plausibility</td>
</tr>
</tbody>
</table>

- Direct association between the disease mechanism, the surrogate endpoint, and the clinical endpoint
- Clear demonstration of a change in disease status for individual patients caused by a change in the surrogate endpoint
- Clear association between a change in surrogate endpoint caused by a therapeutic intervention, and the ultimate clinical outcome within a trial

“There must be more in the evidence package than just the surrogate endpoint – otherwise the value proposition is hard to believe and to assess the value to the patient and its improvement in health” – Former IQWiG member, Germany

REFERENCES


REFERENCES (CONTINUED ON NEXT PAGE)
REFERENCES (CONTINUED)


