Ascenian

May 2023

SURROGATE ENDPOINTS

IN EU JOINT CLINICAL ASSESSMENTS

Table of Contents

Ascenian

Introduction

By January 2025, all oncology products, advanced therapy medicinal products (ATMPs) and medical devices will be mandated to undergo joint clinical assessment (JCA), with extension for all orphan drugs in 2028 (1).
Currently guidelines are produced to set out the expectations on presented evidence for JCAs, process and consultation requirements.

Clinical outcome assessments (COAs) in HTA provide the measure of the clinical benefit of the targeted treatment on how patients feel, function, or survive (2). Expectations of the demonstration of clinical outcomes for the purpose of HTA is directed by method and evidence guidances set out by individual HTAs.

In January 2023 EunetHTA 21 published the guidance on Outcomes Endpoints and the associated evidence expectations for the purpose of executing JCAs. The guidance is purposed to inform how Member States may consider outcomes/endpoints during scoping and national evaluation processes to assign a clinical added value.

This guidance looks at definitions of outcomes, clinical relevance, safety, validity, reliability and interpretability of outcomes measurement instruments, as well as specific considerations to definitions of outcomes commonly used in oncology.

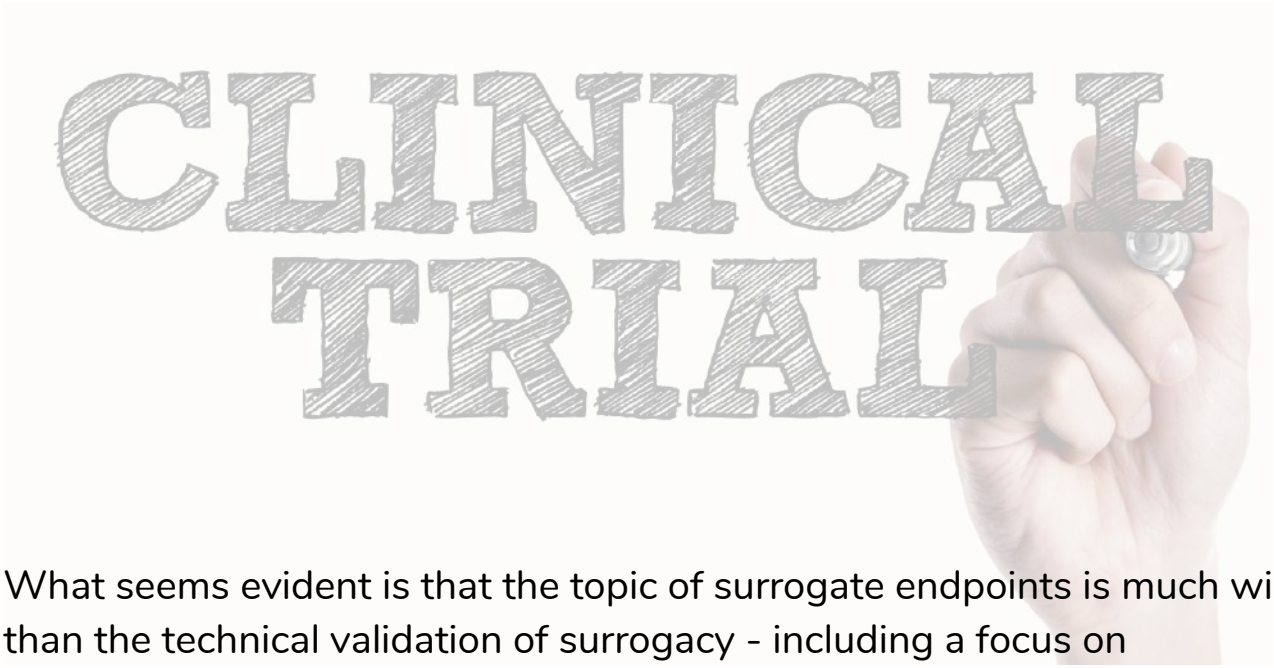
Here we like to provide an insight into the consideration of surrogate endpoints in the guidance published for the JCAs. A surrogate outcome is an outcome that is intended to replace an outcome of interest that cannot be observed in a trial. It is a variable that provides an indirect measurement of effect in situations in which direct measurement of a patient-centred effect is not feasible or practical (1).

Most HTAs in Europe (3) set the preference for final patient-relevant outcomes and reliance on surrogate endpoints with biological plausibility and epidemiological evidence of the association between the surrogate and final endpoint. Within the European Union only IQWIG (Institute for Quality and Efficiency in Health Care) in Germany has set out more prescriptive requirements. Outside the European Union NICE in England, the Australian Pharmaceutical Benefits Advisory Committee, and the Canadian Agency for Drugs and Technologies in Health consider specific requirements for the acceptance of surrogate endpoints, e.g., meta-analyses of randomised controlled trials showing strong association between the treatment effect on the surrogate and final outcomes.

So, how does the guidance for the JCAs consider the acceptance of surrogate endpoints, and which requirements are set out?

(1) New HTA Regulation: key elements and next steps, Presentation 26 Oct 2021
(2) D4.4 – Outcomes Endpoints Practical Guideline, published Jan 2023
(3) Surrogate Endpoints in Health Technology Assessment: An International Review of Methodological Guidelines, PharmacoEconomics volume 38, pages1055–1070 (2020)

Guideline document for JCAs D4.4 on Outcomes (Endpoints)



What seems evident is that the topic of surrogate endpoints is much wider than the technical validation of surrogacy - including a focus on demonstrating patient relevant outcomes / shift in health states

Discussions around endpoints in JCA start from drafting of the PICO* questions and are pursued during the assessment phase.

Five methodological guidelines exist that specifically deal with endpoints. The existing guidelines describe the characteristics of different types of endpoints (clinical endpoints including health related quality of life, safety endpoints…) and issues relating to their measurement and presentation. Specificities related to surrogate endpoints are also discussed. These also provide recommendations for the selection and interpretation of clinical endpoints when conducting a relative effectiveness assessment. Several topics that are frequently raised during early dialogues (now Joint Scientific Consultations) guided the need for a separate guidance on endpoints:

- use of an intermediate outcome measure without demonstration of a link with a relevant clinical endpoint (for example, in the field of oncology, progression-free survival in situations where overall survival cannot be documented in the short or medium-term);
- the use of a surrogate endpoint and the demonstration of link with the respective morbidity and mortality endpoints;
- expectation of the validity of a scale as a measure of a clinical endpoint;
- information needed for interpretation of the results in term of clinical relevance;
- place of external recommendations and guidelines (for example from regulatory bodies or research project or patients' associations) for the choice of endpoints, in order to ensure clinical relevance.

The objectives of the guideline document:

1. to provide guidance for member states in defining relevant outcomes during the **scoping process.**
2. To help assessors in evaluating and reporting all the elements that member states need to determine the **clinical added value** of a health technology.

PICO: I – Intervention, C – Comparison, control or comparator[6], O – Outcome(s) (e.g. pain, fatigue, nausea, infections, death)

Ascenian

Surrogate endpoints – in the scoping process

Several outcomes are considered adequate in confirmatory clinical trials and in HTA methodology to measure the clinical benefit to the patient. Some outcomes may be fully acceptable as support for the risk/benefit ratio assessment but are less suitable for the needs of JCA. This may be the case for surrogate outcomes.

The guidance acknowledges that for diseases with expected long-term survival, it might be impossible to obtain mature mortality data from clinical trials at the time the JCA report is generated. If it is not feasible to measure a final outcome, then intermediate or surrogate outcomes may be acceptable if there is evidence of a strong association or correlation of effects on the surrogate or intermediate outcome with the effect on the final outcome (1,2).

Points on surrogate endpoints for the assessment in the scoping process

A validated surrogate outcome should only be used to replace a final patient-centred outcome of interest if absolutely necessary:

- If evidence for a patient-centred outcome such as morbidity, overall mortality and HRQoL is likely to be available, then this should be requested during the scoping process;
- Surrogate outcomes can be requested in addition to patient-centred outcomes where relevant. However, only surrogate outcomes for which validity has previously been clearly established should be requested where possible. This may not be possible at the scoping stage in many instances, although in some cases this might have been established by previous JCAs or in other literature on the same indication (2).

(1) D4.4 – Outcomes Endpoints Practical Guideline, published Jan 2023
(2)European Network for Health Technology Assessment. Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints [Internet]. 2015. Available on: https://www.eunethta.eu/wp-content/uploads/2018/02/WP7-SG3-GL-clin_endpoints_amend2015.pdf?x69613

Surrogate endpoints – in the appraisal

The association of surrogate and final outcome along levels of evidence - Demonstrate that the surrogate outcome corresponds to the patient-centred outcome (L1). Demonstrate consistent association (L2) and evidence biological plausibility (L3).

As detailed in 'Endpoints Used in Relative Effectiveness Assessment: Surrogate Endpoints' (1), appraisal of the association between the surrogate and the final outcome should take into account the level of evidence:

	Level 1	Level 2	Level 3
01 WHAT	Evidence demonstrating that t**reatment effects on the surrogate outcome correspond to effects on the patient-centred outcome** (from clinical trials).	Evidence demonstrating a **consistent association between the surrogate outcome and the final patient-centred outcome**	Only evidence of **biological plausibility of an association between the surrogate outcome and the final patient-centred outcome**
02 HOW	**Meta-analysis of several randomised controlled trials; and establishment of correlation between effects on the surrogate outcome and the patient-centred outcome.**	**Interventional, epidemiological or observational studies**.	**Pathophysiological studies and/or an understanding of the disease process.**

(2)European Network for Health Technology Assessment. Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints [Internet]. 2015. Available on: https://www.eunethta.eu/wp-content/uploads/2018/02/WP7-SG3-GL-clin_endpoints_amend2015.pdf?x69613

Ascenian

Guidance to manufacturers and assessors of JCAs

The guideline document for JCAs D4.4 on Outcomes (Endpoints) sets out expectations for manufacturers on the submission of data and evidence when surrogate endpoints have been used, and also provides requirements to assessors for the JCA assessment and reporting.

Manufacturer

2. Demonstrate the strength of the association between the surrogate outcome and the patient-centred outcome and the treatment effect.

1.Presence of a surrogate endpoint

HOW

Regression analysis for single studies, or meta-regression in the case of multiple studies. Demonstration at both the individual level and the trial level.

IN ADDITION

Scientific literature which demonstrates the link.

3. For all outcomes requested in the assessment scope, the manufacturer should provide, in addition to the previously reported follow-up, the latest available data cut, regardless of how immature it is.*

*The presence of surrogate outcome data, regardless of their validity, does not change this requirement. For example, if an intervention is expected to impact OS, the latest data cut on OS should always be presented, even if the length of follow-up or the number of events is insufficient.

From: D4.4 – Outcomes Endpoints Practical Guideline, published Jan 2023

Guidance to manufacturers and assessors of JCAs

The guidance provided to assessors of JCAs will focus on the demonstration of the correlation of the surrogate endpoint to the patient-centred endpoint (as defined in the scoping exercise) as much as on any remaining evidence uncertainty.
The guideline document for JCAs D4.4 on Outcomes (Endpoints) sets out that the assessor should consider the following for the JCA report:

Assessors of JCAs

Association

- The level of evidence for the association between the surrogate outcome and the final patient-centred outcome.
- Details on whether this association is based on biological plausibility and/or empirical evidence.
- A description of whether this association has been studied in the disease stage, population and intervention of interest.
- In cases for which the association between the surrogate outcome and the final patient- centred outcome has previously been examined but for a different disease stage, population or intervention, the assessment report should consider the implications for the validity of this association in the current population and intervention of interest.

Strength

- The strength of the association between the surrogate outcome and the patient-centred outcome.
- The strength of the association between the treatment effect on the surrogate outcome and the patient-centred outcome.

.

Uncertainty

- Any uncertainties associated with the evidence and quantified if available.
- The limitations of the use of a surrogate outcome should be explicitly explained.
- An indication of whether a patient-centred outcome is likely to be available at a later date.
- Clearly outline any remaining areas of uncertainty.

From: D4.4 – Outcomes Endpoints Practical Guideline, published Jan 2023

How will national HTAs use the JCA reports?

National HTA will require data meeting the methodology set out at national level, if it has not been part of the JCA guidance or included in the JCA scoping process. Most critical will be consideration of the JCA report in the value assignment (if applicable) and in pricing.

Article 13 of the HTA Regulation regulates that **member states will give due consideration to the Joint Clinical Assessment report.**

Annex the published Joint Clinical Assessment report to the HTA report at Member State level.

Provide information on how the Joint Clinical Assessment has been considered in the national process.

Complement the Joint Clinical Assessment with non-clinical analyses (e.g., on budget impact or cost-effectiveness).

Complement with additional clinical analyses that may be needed in their national HTA process (e.g., analyses related to national disease epidemiology or the specific national healthcare context).

Determine overall value of a new health technology for their healthcare system, and pricing and reimbursement decisions.

Diving deeper

Where to go from here? Know the options and examples, but think beyond the existing frameworks to demonstrate patient-centred value.

For those who don't know yet the most prominent frameworks on the validation of surrogate endpoints, the authors of the D4.4 have made some recommendations.
Ascenian believes they provide valuable practical guidance, and Market Access teams should be aware of those. Thinking beyond the obvious is critical in defining the most valuable support in patient-centred outcomes demonstration, including demonstrating value along the patient pathway.

01

Use of surrogate endpoints in healthcare policy

WHAT: Strategic perspective of the use of surrogate endpoints, broad framework.
HOW: Examples, visuals, top-level strategic considerations and decision framework

Use of surrogate end points in healthcare policy: a proposal for adoption of a validation framework, 2016, Ciani, Drummond et al.
https://www.nature.com/articles/nrd.2016.81

02

Australia - Pharmaceutical Benefits Advisory Committee.

WHAT: Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee. 2016.
HOW: Guidance on validation of patient relevance; critical strategic questions and patient pathway focused

https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf

03

Surrogate Endpoints in Health Technology Assessment

WHAT: Review of existing policies on surrogate endpoints
HOW: National guidelines summaries, systematic review, especially relevant for England, Germany, Australia and Canada.

https://www.researchgate.net/publication/342385594_Surrogate_Endpoints_in_Health_Technology_Assessment_An_International_Review_of_Methodological_Guidelines

04

Technical support document about multivariate meta-analysis produced by the NICE DSU.

WHAT: Technical document describing the use of multivariate meta-analytic methods for evaluation of surrogate endpoints.
HOW: Introduction and explanation of model; has been updated in 2022 for including a trivariate meta-analysis model

https://www.sheffield.ac.uk/nice-dsu/tsds/multivariate-meta-analysis

From: D4.4 – Outcomes Endpoints Practical Guideline, published Jan 2023

We have not included here the IQWIG guidance on the use of validated surrogate endpoints in submissions, but it can be found in the latest draft of the IQWIG methods paper : https://www.iqwig.de/methoden/allgemeine-methoden_entwurf-fuer-version-7.pdf

DSU - Decision Support Unit

Conclusion

Using surrogate endpoints in JCA submissions will require providing further evidence on the correlation to the patient-centred outcome as defined in the JCA scoping exercise. Guidance is available. The demonstration of correlation will be critical in the JCA assessment, and crucially important when member states associate a value rating to the JCA for the purpose of reimbursement and price. At the same time, new patterns are emerging on how value may be identified, and those should be taken into account when developing strategy on surrogate endpoint validation.

Preparation

- Focus early on the improvement of health states along the patient value chain
- National and Joint Scientific Advice will be important
- Assess price impact early

Think Strategically

- Know the patient pathway: substantiate value beyond treatment position
- Consider Michael Porter's model of Value in Health for demonstrating improvement in patient-centred health outcomes

Other solutions

- Develop a substantiation plan, including: Demonstration of value beyond stopping treatment, such as impact on QoL, long treatment needs of side effects and impact on follow-on treatments, when collecting evidence for substantiation of surrogate endpoints - Example Abemaciclib assessment in Germany (https://www.iqwig.de/presse/pressemitteilungen/pressemitteilungen-detailseite_62592.html)

Technical requirements in demonstrating the validity of surrogate endpoints on patient-centred outcomes are likely to stay, but demonstrating patient-relevant value along the patient pathway is likely to increase in value and recognition with HTAs - check Michael Porter's *Value in Health*!

Ascenian

Thank you very much for you attention.

We will monitor closely the implementation of the guidances on JCA. Worthwhile to consider is the definition of PICOs in the scoping process for JCA assessments. Also, monitor the national HTA assessments that recommend exploration of treatment effects and impact beyond the target positioning in the patient pathway.

We look forward hearing from you and your experiences.

Contact

Ascenian
Kuno-Fischer Str.6
14057 Berlin
Germany
www.ascenian-consulting.com
info@ascenian-consulting.com

Ascenian