

Performing HTA and economic evaluations in Belgium – link with the European HTA Regulation

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Overview

- FYI – update Belgian guidelines for **economic evaluations**
 - Some elements to think about to be well prepared?
- Link with HTA Regulation
 - Joint Scientific Consultation (**JSC**)
 - Joint Clinical Assessment (**JCA**)
 - **Guidance documents**

Even if you don't fall under this regulation – the same principles can be applied!

you will receive the slides... (with all the **extras**)

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Belgian guidelines for economic evaluations

■ Class 1 drugs

Reglementering

 [K.B. van 21.12.2001 \(geldig voor alle dossiers ingediend voor 1 april 2018\)](#)

 [KB van 1 februari 2018 \(geldig voor alle dossiers ingediend vanaf 1 april 2018\)](#)

■ Class 1 implants and medical devices

 [K.B van 25.06.2014: Procedures, termijnen en voorwaarden inzake de tegemoetkoming van de verplichte verzekering in de kosten van implantaten en invasieve medische hulpmiddelen](#)

→ General principle: 5th criterion –
cost-effectiveness

(~guidelines for economic evaluations and BIA)

1° de **therapeutische waarde** ;

2° de **prijs** van de specialiteit en de door de aanvrager voorgestelde vergoedingsbasis ;

3° het **belang** van de specialiteit in de medische praktijk in functie van de therapeutische en sociale noden, met inbegrip van de relevantie en de adequaatheid van de grootte van de verpakking in dagdosissen in functie van de beoogde therapie ;

4° de **budgettaire** weerslag voor de verzekering, rekening houdend met de begrotingsdoelstellingen ;

5° de **verhouding tussen de kosten voor de verzekering en de therapeutische waarde**.

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Extra

Belgian guidelines for economic evaluations

■ Update – published soon...

■ Be well prepared...

- Focus on incremental elements
- ...
- Good estimate of the **relative** treatment effect

Can't you calculate the **cost-effectiveness**??

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Link to new HTA regulation

- Source: https://ec.europa.eu/health/health-technology-assessment/regulation-health-technology-assessment_en (other languages → Regulation on HTA EN ...)

- January 2018: Proposal EC

- December 2021: Regulation adopted

REGULATION (EU) 2021/2282 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 15 December 2021

on health technology assessment and amending Directive 2011/24/EU

- January 2022: Regulation enters into force
- January 2025: (progressive) application (art. 7)
 - January 2025: cancer drugs & ATMPs
 - January 2028: orphan drugs
 - January 2030: full scope

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Extra

Article 7

- **FYI:** Health technologies subject to joint clinical assessments

1. The following health technologies shall be subject to joint clinical assessments:

- (a) medicinal products as referred to in Article 3(1) and Article 3(2), point (a), of Regulation (EC) No 726/2004, for which the application for a marketing authorisation is submitted in accordance with that Regulation after the relevant dates set out in paragraph 2 of this Article, and for which that application is in compliance with Article 8(3) of Directive 2001/83/EC;
- (b) medicinal products authorised in the Union for which a joint clinical assessment report has been published, in cases where an authorisation is granted pursuant to the second subparagraph of Article 6(1) of Directive 2001/83/EC for a variation to an existing marketing authorisation which corresponds to a new therapeutic indication;
- (c) medical devices classified as class IIb or III pursuant to Article 51 of Regulation (EU) 2017/745 for which the relevant expert panels have provided a scientific opinion in the framework of the clinical evaluation consultation procedure pursuant to Article 54 of that Regulation, and subject to selection pursuant to paragraph 4 of this Article;
- (d) in vitro diagnostic medical devices classified as class D pursuant to Article 47 of Regulation (EU) 2017/746 for which the relevant expert panels have provided their views in the framework of the procedure pursuant to Article 48(6) of that Regulation, and subject to selection pursuant to paragraph 4 of this Article.

2. The dates referred to in paragraph 1, point (a), shall be as follows:

- (a) 12 January 2025, for medicinal products with new active substances for which the applicant declares in its application for authorisation submitted to the European Medicines Agency that it contains a new active substance for which the therapeutic indication is the treatment of cancer and medicinal products which are regulated as advanced therapy medicinal products pursuant to Regulation (EC) No 1394/2007 of the European Parliament and of the Council ⁽¹⁾;
- (b) 13 January 2028, for medicinal products which are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000 of the European Parliament and of the Council ⁽²⁾;
- (c) 13 January 2030, for medicinal products referred to in paragraph 1 other than those referred to in points (a) and (b) of this paragraph.

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Key Principles

- Evidence submission – **one time** by HTD (art.1 §1)

- Joint work

- Scientific, clinical aspects

JCA

- Driven by Member State HTA bodies

- Ensure **use** of joint work in **national HTA** processes (art.13)

- Member States remain responsible for: (art.1 §2)

- Drawing conclusions on added value for their health system
- Taking decisions on pricing & reimbursement

1. A joint clinical assessment shall result in a joint clinical assessment report that shall be accompanied by a summary report. Those reports shall not contain any value judgement or conclusions on the overall clinical added value of the assessed health technology and shall be limited to a description of the scientific analysis:

- of the relative effects of the health technology as assessed on the health outcomes against the chosen parameters which are based on the assessment scope as set out pursuant to Article 8(6);
- of the degree of certainty of the relative effects, taking into account the strengths and limitations of the available evidence.

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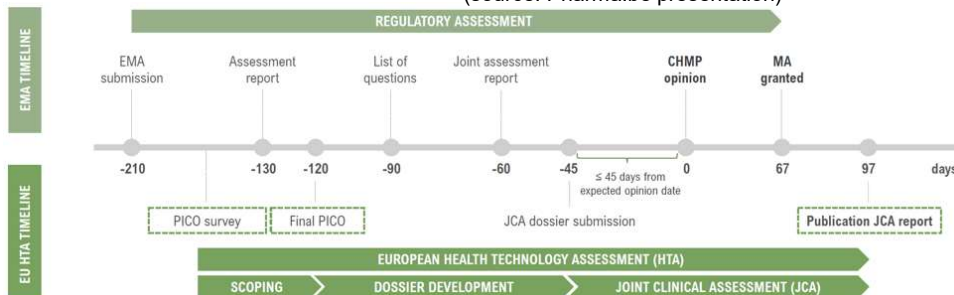
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Ambitious timeline

- **Art.11** 1. On the basis of the dossier submitted by the health technology developer and the assessment scope as set out pursuant to Article 8(6), the assessor, with the assistance of the co-assessor, shall prepare the draft joint clinical assessment and summary reports. The Coordination Group shall endorse the draft reports in accordance with the timeframe set out pursuant to Article 3(7), point (e). Those timeframes shall be:

- for medicinal products, no later than 30 days following the adoption of a Commission decision granting a marketing authorisation;

- **EMA & EU HTA timeline** (source: Pharma.be presentation)



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Joint scientific consultation

Article 17:

JSC

1. For health technologies referred to in Article 16(2), health technology developers may request a joint scientific consultation.

Relevant PICO?

- Remark: article 18 → preference RCTs

Avoidable uncertainty? (see further)

4. The assessor, with the assistance of the co-assessor, shall prepare the draft joint scientific consultation outcome document in accordance with the requirements set out in this Article and in accordance with the guidance documents and procedural rules established pursuant to Article 3(7), points (d) and (f), and Article 20. For medicinal products, in accordance with international standards of evidence-based medicine, directly comparative clinical studies which are randomised, blinded and include a control group shall be advised whenever appropriate.

- Advice, however...

ANNEX I

Dossier specifications for medicinal products

- (e) if a health technology has been subject to a joint scientific consultation, the explanation from the health technology developer on any deviation from the recommended evidence;

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The Development of Methodological and Procedural Guidance Sub-Group (MPG SG)

Belgium

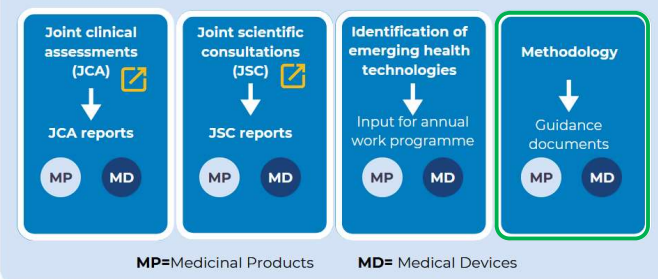
- Mattias Neyt & Frank Hulstaert (KCE)

Disclaimer:

- Internal procedure
 - every meeting – reminder of Col and confidentiality
- information is only presented for guidance documents that are already made public

MEMBER STATE COORDINATION GROUP ON HTA

SUBGROUPS (Source: learning.eupati.eu)



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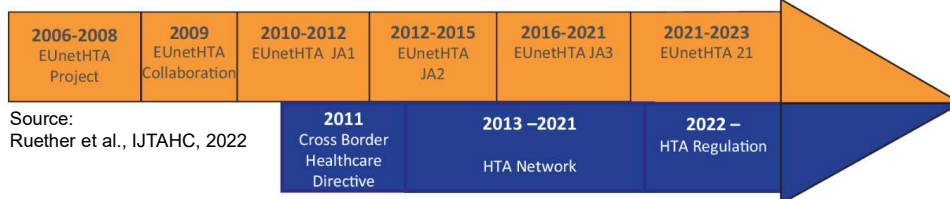
Guidance documents

- For all EUnetHTA 21 deliverables the future EU HTA Regulation will serve as a basis and the past EUnetHTA Joint Action 3 experiences will be taken into account. With the deliverables, EUnetHTA 21 is supporting the development of guidance documents to be adopted by the Coordination Group and/or drafting of implementing legislation by the European Commission, thus facilitating the subsequent implementation of the HTA regulation.



eunetha

<https://tools.eunetha.be/guidelines.html>



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HTA - Guidance

- Source: <https://health.ec.europa.eu/health-technology-assessment/key-documents>

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- Guidance on the validity of clinical studies for joint clinical assessments
- Scientific specifications of medicinal products subject to joint clinical assessments

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- Guidance on outcomes for joint clinical assessments
- Guidance on reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analyses in joint clinical assessments

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- Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons
- Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons

However, it is important that the selection of trials and synthesis methods is made with caution and is rigorously examined by assessors in collaboration with healthcare professionals and statisticians.

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Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons

Adopted on 8 March 2024 by the HTA CG pursuant to Article 3(7), point (d), of

Regulation (EU) 2021/2282 on Health Technology Assessment

The document is not a European Commission document and it cannot be regarded as reflecting the official position of the European Commission. Any views expressed in this document are not legally binding and only the Court of Justice of the European Union can give binding interpretations of Union law.

■ Statements about:

- RCTs → preferred
 - Anchored indirect comparison → exchangeability
 - Population-adjusted indirect comparison
 - Observational evidence & Single-arm trials
- } → Requirements (~often unverifiable and unattainable)

■ Important to make link with other guidance document (~validity)

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Extra

■ FYI: Summary

To assess the relative efficacy or effectiveness of a new intervention compared to one or more existing interventions (the comparators; e.g., the current standard treatment) in the presence of multiple sources of evidence, appropriate methods for evidence synthesis should be used. Randomised controlled trials (RCTs), provided they are well designed and have low risk of bias, are the gold standard for informing estimates of treatment effectiveness and should be used for evidence synthesis when possible. Thus, we assume that the evidence synthesis considered is based on adequate RCT data unless otherwise stated. The objective of this document is to describe the most commonly used methods for direct and indirect treatment comparisons, including their underlying assumptions, strengths and weaknesses. The document is not a methodological textbook and does not give a detailed description of the statistical techniques described. The guideline is aimed at assessors in the context of the EU regulation for the conduct of joint clinical assessment of health technologies (HTAR), although the relevance for other stakeholders is recognised. All methods for evidence

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... In situations where no direct RCT evidence on a comparison of interest is available or where multiple treatments must be compared simultaneously, indirect comparisons may be used. In general, direct comparisons are preferable to comparisons based on indirect evidence alone because the latter are associated with greater uncertainties. If indirect comparisons are required, in general only anchored indirect comparisons respecting randomisation are appropriate, which requires that the evidence network is connected. Useful approaches for anchored indirect comparisons include the Bucher method and the frequentist and Bayesian approaches for network meta-analysis. In cases where anchored indirect comparisons are not feasible, alternative methods are available, but it is unlikely that these adequately eliminate bias due to lack of randomisation.

If the similarity assumption is not met, methods for population-adjusted indirect comparisons might be considered, provided that the network is connected and IPD are available for some of the trials included. These methods require that all effect modifiers relevant for adjustment are measured. However, this is often unverifiable and unattainable. Therefore, it is imperative that the robustness of the results derived from population-adjusted indirect comparisons are thoroughly investigated to ascertain whether the population-based adjustment leads to an estimate of the treatment effect with higher certainty of results. The model and covariate selection strategies for adjustment must be prespecified and based on transparent criteria. Owing to the greater uncertainties associated with population-adjusted methods, a sufficiently large treatment effect estimate is required, which can be formally evaluated via testing of shifted hypotheses. This means that a conclusion can be drawn regarding an effect only if the confidence interval lies completely above or below a certain pre-specified threshold shifted away from the zero effect.

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... In any situation with non-randomised data, such as observational evidence and single-arm trials, or in the case of disconnected networks, complete access to the IPD is required in order to apply methods that can adequately adjust for confounding. Again, these methods require that a set of all covariates (confounders, prognostic variables, or effect modifiers) relevant for adjustment are measured. However, this is often unverifiable and unattainable. Therefore, it is imperative that the model and covariate selection strategies for adjustment are prespecified and based on transparent criteria. Use of propensity scores is a method frequently applied. The assumption of conditional exchangeability needs to be met and can be assessed by investigating positivity, overlap, and balance. If conditional exchangeability is not met, an adequate analysis is not possible and the results from the corresponding analysis are unlikely to provide a meaningful estimate of treatment effectiveness. If a propensity score approach is applied, the final target population has to be described in detail, especially if trimming or truncation methods are used. Owing to the greater uncertainty associated with non-randomised data, a sufficiently large treatment-effect estimate is required, which can be formally evaluated via testing of shifted hypotheses. Methods of sensitivity analysis that explore the potential impact of unmeasured confounders may also be applied to assess the robustness of the estimated treatment effects in this scenario.

... assumptions is required when making inferences. Input from a statistician with specific expertise in this area is advised for a critical assessment of the methodological approach used, assumptions potentially violated, and the corresponding uncertainty of results.

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Extra

■ FYI: III Conclusion

This guideline presents methods that are used to combine evidence to determine the relative clinical effectiveness of treatments. The guideline directs assessors towards the pathway that will ideally provide the best estimate of relative effectiveness with the least uncertainty. The most robust evidence comes from adequate RCTs with low RoB.

Pairwise meta-analyses combine data for which the treatment and comparator are the same in all the trials included. Both frequentist and Bayesian frameworks offer approaches that are suitable provided the underlying assumptions are adequately met. When direct evidence from RCTs is not available or more than two treatments are of interest and it is necessary to perform indirect treatment comparisons, uncertainty for the treatment-effect estimate increases. Indirect comparisons are commonly used in comparative effectiveness analyses for which there is a lack of trials or evidence gathered for all the comparators of interest. When conducting such analyses, the appropriate method to use is one that preserves randomisation (i.e., an anchored indirect comparison). NMA can combine both direct and indirect evidence within the network. Various frequentist and Bayesian methods have been proposed for this purpose. The more evidence that is included in a network for one treatment, the more precise the estimates may be, but as complexity increases so does the potential for violation of the assumptions, which can influence the certainty of results. Whatever the method used, prerequisites and assumptions related to that method must be clearly specified and justified.

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If IPD are available, further analyses can be undertaken. Approaches that account for differences in population characteristics between studies are available. MAIC reweights the outcomes to an alternative population, which may differ from the target population of the assessment. Furthermore, this method relies on accounting for all relevant effect modifiers in the model, which is difficult to ensure, and therefore, in general not an adequate analysis. The same applies to STC, which is a regression-based approach that extrapolates the outcomes to an alternative population. ML-NMR is a recent extension of regression-based approaches that combines IPD evidence with aggregated evidence.

A number of statistical approaches has been proposed for dealing with cases in which non-randomised evidence (e.g., single-arm trials, comparative observational studies and registry data) is used to inform an estimate of relative effectiveness. Although it is possible to provide summaries of evidence syntheses generated in this way, the certainty of the results provided by these techniques remains controversial. Results from such analyses are more likely to suffer from bias and are more likely to underestimate the true uncertainty and to depend on untested assumptions in comparison to syntheses with RCT evidence alone. Therefore, any analyses extending the network using single-arm or non-randomised evidence should include sensitivity analyses and an examination of the assumptions and should provide appropriate caveats for users. The use of single-arm or non-randomised evidence usually threatens the internal validity of results. Therefore, it is incumbent on the assessor to judge whether this evidence is sufficient for adequate estimation of the relative treatment effectiveness. For some interventions, single-arm or non-randomised evidence may be the only evidence available for consideration. However, it may well be that this evidence is insufficient for estimation of the relative treatment effectiveness in the context of JCA.

■ Misunderstanding



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Reflection from an HTA point of view

Replacing RCTs with real world data for regulatory decision making: a self-fulfilling prophecy?

Real world data are advocated as an alternative approach to RCTs for closing knowledge gaps on drugs, but **Beate Wieseler and colleagues** argue that this approach is the wrong remedy for current challenges in drug development

Beate Wieseler, ¹ Mattias Neyt, ² Thomas Kaiser, ¹ Frank Hulstaert, ² Jürgen Windeler¹ *BMJ* 2023;380:e073100

Key messages

- Enthusiasm is growing for the use of observational real world data as a basis for regulatory, clinical, and health policy decision making
- But such study designs are ill suited to measure the treatment effects of new drugs
- Promoting the use of observational studies from routine practice data sources might hinder efforts needed to improve the feasibility of randomised controlled trials
- To ensure high quality and efficient healthcare, the conduct of RCTs, including those in routine care, should be made easier, faster, and cheaper

Impact promotion RWD/RWE on feasibility RCTs

- Check feasibility of randomization
- Non-RCT: a choice or necessity?

(avoidable versus unavoidable uncertainty)

Alternative: ways to make RCTs, including those in routine care, easier, faster and cheaper

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Combine strengths of RCTs & RWD

- Pragmatic RCTs (e.g. KCE Trials programme)
- Link RCTs & information administrative databases (e.g. pressure ulcers report)
- Baseline adjustment relative treatment effect (e.g. tiotropium, DES, ... report)

Remark:

- definition RWD FDA versus EMA
- Efforts RCT vs. creating external control group

The FDA defines real world data as “data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources,” not restricting study designs. It defines real world evidence as “the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of [real world data],” which can be generated using different study designs “including, but not limited to, randomised trials” (eg, large simple trials, pragmatic trials), and observational studies (prospective or retrospective).⁷

European Medicines Agency (EMA)

The EMA defines real world data as “routinely collected data relating to a patient’s health status or the delivery of healthcare from a variety of sources other than traditional clinical trials,”⁸ thus restricting the study designs that can be used to generate real world data. The EMA has published inconsistent information on this restriction of study designs—it previously noted that data from pragmatic (randomised) trials would be included if collected under conditions of normal clinical care, citing the randomised Salford Lung Study as an example.⁸ But, in a more recent publication, real world data and evidence seem to be restricted to non-interventional preauthorisation or postauthorisation studies or sources other than RCTs.⁹ The Data Analysis and Real World Interrogation Network (DARWIN EU), the EMA’s main tool for the provision of real world data, is also limited to observational data sources and non-interventional studies.¹⁰

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- Assessment of certainty
 - Descriptive at EU level
(factual, no value judgement)
→ valid scientific principles
are required

Guidance on Validity of Clinical Studies



V1.0

04 July 2024

Adopted on 19 September 2024 by the HTA CG pursuant to Article 3(7), point (d), of
Regulation (EU) 2021/2282 on Health Technology Assessment

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Certainty of effectiveness results

- Three concepts:
 - Internal validity
(~RoB assessment tool)
 - External validity
(~PICO, descriptive)
 - Statistical precision
(statistical testing)

Requirement for reporting

- Any effectiveness result in a JCA report must be accompanied by a description of its certainty.

The certainty of effectiveness results is determined by three concepts: internal validity (i.e., the extent to which a study is free from bias [also called systematic errors], a concept analogous to Risk of Bias [RoB]); external validity (i.e., the extent to which study results provide a basis for generalisation to the target population, a concept which encompasses generalisability and applicability); and statistical precision (i.e., the uncertainty associated with study results due to random sampling variability). These three concepts assess three different dimensions of the certainty of results [7-9], which, for example, means that shortcomings in internal validity cannot be remedied by higher statistical precision. Furthermore, evidence that has high internal validity does not necessarily have high external validity. The three different dimensions of the certainty of results overlap with domains of different frameworks for the assessment of the quality of evidence. For instance, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) domains of risk of bias, indirectness and imprecision correspond to internal validity, external validity, and statistical precision, respectively [10].

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Extra

• Internal validity 2.2 Internal validity

Following international standards of evidence-based medicine, the internal validity of a study has a paramount role in determining the overall certainty of the study results [8,11]. The **classical hierarchy of evidence** [12] includes several types of studies, from **case-reports and nonclinical data (level 5 evidence, the lowest level of evidence)**, **case-control studies (level 4)**, **retrospective (or lower-quality) cohort studies (level 3)**, **prospective (or higher-quality) cohort studies (level 2)**, up to **randomised controlled trials (RCTs; level 1, the highest level of evidence)**. Classification of study design alone (see Section 3) **is insufficient for a full assessment of internal validity** [13,14], but has **practical value** for a **preliminary sorting** between higher- and lower-quality evidence and for **selecting a suitable RoB assessment tool**.

➤ E.g. RCTs → Cochrane Collaboration's RoB 1 instrument

Requirements for reporting

- For outcomes with evidence coming from **RCTs**, assess **RoB using the Cochrane RoB 1 tool**. **RoB should be assessed for each outcome** required in the assessment scope.
- For outcomes sharing the same characteristics (e.g., data collection, blinding aspects, or evaluation) RoB can be assessed on an overall level (i.e., grouped).
- **RoB judgement** should be provided for both, **each individual domain** (i.e. type of bias) and overall.

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➤ E.g. Comparative non-RCTs

Requirements for reporting

- For outcomes with evidence coming from **comparative non-RCTs**, assess RoB using **ROBINS-I**. **RoB should be assessed for each outcome** required in the assessment scope.
- The RoB of outcomes sharing the same characteristics (e.g., data collection, blinding aspects, or evaluation) can be assessed on an overall level (i.e., grouped).
- **RoB judgement** should be provided for both, **each individual domain** (i.e. type of bias) and overall.

➤ E.g. Uncontrolled clinical trials (~e.g. single-arm trials)



Unlike comparative clinical trials, uncontrolled trials, when they are the only source of data submitted as evidence, **do not allow relative effectiveness assessment** (i.e., supplementary

Requirement for reporting

- Since **uncontrolled trials per se are of very limited value for performing relative effectiveness assessment**, RoB assessment is in general not required.
- When data from uncontrolled trials are **combined with an external source of data**, **certainty of evidence** for the resulting indirect comparison **must be assessed** and reported in the JCA.

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• External validity: importance of the PICO

appropriate to use the term 'external validity' [17]. A key question is how well the evidence matches the elements of the PICO question and, therefore, whether it can be applied to answer that question [18]. In statistical terms, a lack of external validity of clinical evidence threatens the overall certainty of results if, because of relevant effect modification, the effect in the population of interest could be different from the effects in the clinical studies.

Limitations to the external validity of the evidence can occur if: (i) the study population (based on eligibility criteria or actual recruitment) differs from the intended target population; (ii) the experimental intervention, control interventions and/or subsequent interventions differ from the target setting; or (iii) the study outcomes (e.g., surrogate outcomes) do not give information about the outcomes of interest. For the external validity of clinically relevant evidence, effect modification has to be taken into account [18]. Details on effect modification and subgroup analysis can be found in other HTAR guidance documents [5].

➤ Final judgement on external validity → made at national level

Requirement for reporting

- Different aspects of external validity (primarily any PICO mismatch between assessment scope and clinical study) should be addressed in a JCA, but the final judgment on the applicability of study results must be left to the discretion of each member state.



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Importance of guidelines & early dialogues

Figure 3

Level of agreement for each domain: Health Technology Assessment bodies (HTABs) vs. regulators (based on 31 procedures). *n* represents the total number of HTABs expressing an opinion for each domain. ■ full agreement ■ partial agreement ■ disagreement

E.g. QoL is not a requirement for EMA ...



Source: Tafuri, Br J Clin Pharmacol, 2016

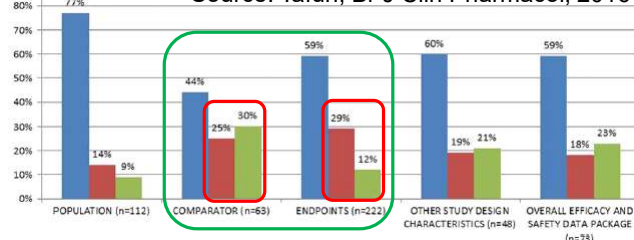
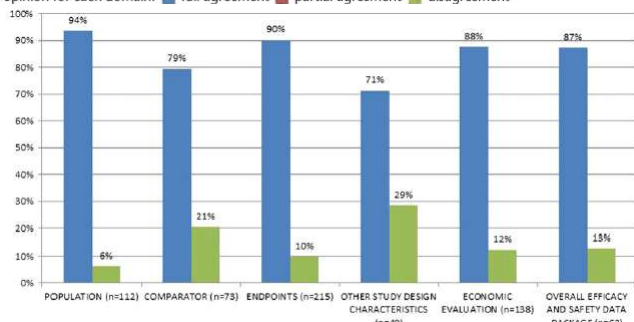


Figure 4

Level of agreement among Health Technology Assessment bodies (HTABs) for each domain (based on 30 procedures). *n* represents the number of multiple comparisons among HTABs expressing an opinion for each domain. ■ agreement ■ disagreement



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Guidance on outcomes for joint clinical assessments

Adopted on 10 June 2024 by the HTA CG pursuant to Article 3(7), point (d), of Regulation (EU) 2021/2282 on Health Technology Assessment

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3.1 General considerations for patient-centred outcomes

Points of attention for the assessment scoping process

- Outcomes relevant for HTA should be long-term or final where possible.
- If it is not feasible to measure final outcomes, 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 long-term or final outcome. A supposed impossibility of obtaining long-term data should not refrain MS from formulating the desired outcome during the scoping process (see also Section 3.3).
- Depending on the research question also short-term outcomes (collected for an appropriate study duration) are relevant, e.g. symptoms, HRQoL or adverse events.



3.3 Surrogate outcomes

What 3.3 Surrogate outcomes

3.3.1 General considerations

A surrogate outcome is an outcome that is intended to replace an outcome of interest that cannot be observed in a specific clinical study (4). 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 (32). A surrogate outcome may be a biomarker that is intended to substitute for a patient-centred outcome, or it may be an intermediate outcome. A surrogate outcome is expected to only predict the treatment effect of an outcome that is not observed in a clinical study. A biomarker is a surrogate which can be defined as a characteristic that is an objective measure of an indicator of normal biological processes, pathogenic processes or pharmacological responses to an intervention (33). Examples of biomarkers used as surrogacy for mortality and/or morbidity and/or disease remission include levels of cholesterol, haemoglobin A1C (HbA1C), and antibody titre after vaccination. An intermediate outcome is a surrogate outcome such as a measure of a function or of a symptom (disease-free survival, angina frequency, exercise tolerance) but is not the long-term or final outcome of the disease, such as survival or the rate of irreversible morbid events (stroke, myocardial infarction) (34).

Extra

■ 3.3 Surrogate outcomes

■ Problem

The use of surrogate outcomes in the assessment of the relative effectiveness of a health technology can be controversial since the validity of surrogate outcomes has rarely been fully established in a rigorous manner (35–38). Only a few surrogate outcomes have been shown to be true measures of tangible clinical benefit.

■ Points of attention for the assessment scoping process

Points of attention for the assessment scoping process

- Final patient-centred outcomes such as mortality, morbidity, and HRQoL should be requested during the scoping process.
- Requesting a validated surrogate outcome only to replace a patient-centred outcome of interest should only be done if absolutely necessary.
- 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.



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The use of PFS as a surrogate endpoint

■ Is PFS a valid surrogate for OS?

- SR Ciani (2014): in advanced solid tumors
 - “The strength of the association between the two surrogates and OS was generally low. The level of evidence (observation-level versus treatment-level) available varied considerably by cancer type, by evaluation tools and was not always consistent even within one specific cancer type.”
- SR Prasad (2015): in Oncology
 - “most trial-level validation studies of surrogate end points in oncology find low correlations with survival.” and that “the evidence supporting the use of surrogate end points in oncology is limited.”
- Gyawali et al. (2020): Evaluating the evidence behind the surrogate measures included in the FDA's table of surrogate endpoints as supporting approval of cancer drugs (breast cancer)
 - “The results from correlation studies evaluating pCR, DFS, ORR, and PFS suggest that the treatment effects on none of these surrogate measures were strongly correlated with treatment effects on OS.”

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- Can PFS be considered as a surrogate for QoL?

- QoL as an endpoint: 190/352 trials (54%), reported in 147/190 trials (77%)
- Correlation: weak



International Journal of Cancer

29 October 2018

Association between progression-free survival and patients' quality of life in cancer clinical trials

Abstract

Quality of life outcomes provide essential information for patients and physicians in oncology care. However, the validity of progression-free survival (PFS) as a surrogate for quality of life, and the inclusion and reporting of quality of life endpoints in clinical trials, is unclear. We performed a retrospective study of phase III clinical trials of drugs for advanced or metastatic solid tumors published between 2010 and 2015. Correlation coefficient (r) and area under the ROC curve (AUC) for association between PFS and positive quality of life were evaluated. Of the 352 Phase 3 trials included, 190 (54%) included a quality of life endpoint, of which 23% did not report pre-specified quality of life outcomes; a total of 125,962 patients were enrolled in studies lacking, or not reporting, quality of life outcomes. Among the 147 trials that reported quality of life outcomes, 99 (67%) reported no effect, 38 (26%) reported a positive effect and 10 (7%) reported a negative effect of treatment on patients' global quality of life. The association between PFS and improvement in global quality of life was weak ($r = 0.34$; $AUC = 0.72$), as was the association between PFS and improvement in any domain of quality of life. In conclusion, PFS benefit was not strongly correlated with improvements in patients' quality of life, and, despite the palliative intent of treatments in the advanced/metastatic setting, the availability of quality of life data from clinical trials of cancer drugs was poor.

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Extra

- 3.3 Surrogate outcomes

- What if no information on outcome of interest in scope

3.3.2 Association between surrogate outcomes and patient-centred outcomes

If the HTD is unable to provide data for an outcome of interest that has been specified in the scope, but another outcome (regardless of whether this has been requested in the scope or not) is believed to provide indirect information regarding the outcome of interest (i.e. is considered a surrogate outcome for the outcome of interest), this should be described in the dossier. The HTD should explain for which outcome of interest a surrogate is applied and demonstrate the strength of the association between the surrogate outcome and the outcome of interest and the association of treatment effects on the surrogate and the outcome of interest (see Section 3.3.3 for more details on level of evidence for surrogacy). For example, if the outcomes "mortality" and "HbA1C" are both specified as outcomes in a scope, the HTD is only required to demonstrate the strength of the association between HbA1C and mortality, if the data for mortality is not available or very limited (e.g. due to very limited events), and the HTD considers HbA1C to provide information about the technology's expected effect on mortality.



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Extra

■ 3.3 Surrogate outcomes

- Level of evidence for surrogacy:
 - Level 1, 2 & 3
 - Correlation: ≥ 0.85



The appraisal by MSs of the association between the surrogate and the long-term or final outcome should take into account all of the following levels of evidence (37):

- **Level 1:** evidence demonstrating that treatment effects on the surrogate outcome correspond to effects on the patient-centred outcome (from clinical trials); comprises a meta-analysis of several randomised controlled trials (preferably from a systematic literature review); and establishment of correlation between effects on the surrogate outcome and the patient-centred outcome in the respective disease stage and sufficiently restricted to the interventions investigated. While MSs can appraise the validity of a surrogate outcome submitted by the HTD with regard to their national decision-making process, it is highlighted in literature that this level can be considered as required (with evidence showing a sufficiently strong correlation) for demonstrating the validity of a surrogate outcome (39,40);
- **Level 2:** evidence demonstrating a consistent association between the surrogate outcome and the final patient-centred outcome (from interventional, epidemiological or observational studies);
- **Level 3:** only evidence of the biological plausibility of an association between the surrogate outcome and the final patient-centred outcome (from pathophysiological studies and/or an understanding of the disease process).

There is no universally accepted threshold for the establishment of sufficient correlations between the surrogate and the patient-centred outcome at trial level (i.e., correlation of the effects) and patient level (i.e., correlation of the outcomes). However, a correlation of at least 0.85 is described as "high" and can be used as a criterion for validation of surrogate outcomes (39).

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Extra

■ 3.3 Surrogate outcomes

- Requirements for JCA reporting

The assessor should consider the following for the JCA report:

- 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.
- 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.
 - Any uncertainties associated with the evidence and quantified this if data are 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.

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Reflection from an HTA point of view

- Source: <https://kce.fgov.be/en/do-innovative-medicines-against-cancer-always-have-a-real-added-value>

BENEFITS AND COSTS OF INNOVATIVE ONCOLOGY DRUGS IN BELGIUM (2004-2017)



■ DOWNLOADS

- Synthesis in English (50 p.) (2.77 MB)
- Scientific report in English (352 p.) (11.5 MB)
- Supplement in English (1142p.) (12.88 MB)

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- (Cost-)effectiveness: general findings and problems
 - Greatest uncertainty: impact OS
 - Lack head-to-head, immature data, surrogate endpoints, cross-over
 - Impact QoL – also large uncertainty
 - Not always measured (disease-specific & generic utility instrument), if measured – considered confidential (!)
 - Choice comparator
 - Confidential prices
 - Price/discount intervention (& comparator & FU treatments...)
 - Decision maker's ICER (transparency & accountability)

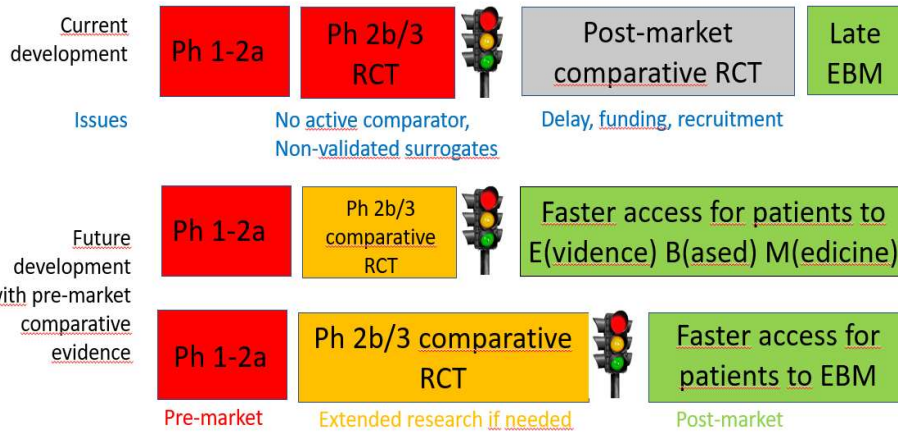
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Towards comparative evidence generation in phase 2b/3

Jointly approved by regulators and HTA/payers
with public (co-)financing of trial infrastructure



Have better evidence at market launch! (←→ MEAs) → perform better economic evaluations

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Important guidelines

- Belgian economic evaluation and BIA guidelines: publication of update expected soon...
- HTA Regulation guidance documents
<https://health.ec.europa.eu/health-technology-assessment/key-documents>
- EUnetHTA guidelines: <https://tools.eunetha.be/guidelines.html>
 - Measuring HRQoL
- Hopefully this helps to be better prepared...

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