Health technology assessment methods guidance – medicinal products

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Glossary

A complete glossary for terms for health technology assessment (HTA) have been one of the key deliverables for the SUSTAIN-HTA project. SUSTAIN-HTA is a Horizon Europe initiative that builds a sustainable, pan-European infrastructure to support the uptake of innovative, fit-for-purpose HTA methods. It identifies HTA bodies' methodological needs, maps innovative tools, and strengthens HTA expertise through training, education, and targeted support.

The SUSTAIN taxonomy provides a comprehensive, standardised classification of 374 HTA-related terms across key assessment, regulatory, and decision-making domains to support consistent communication and methodological alignment. It was developed through a targeted review of EU HTA documents, extraction and analysis of terminology, and consensus-building among SUSTAIN-HTA partners from multiple HTA bodies and academic institutions.[1] Tarang Sharma, Technical Officer, Access to Medicines and Health Products, WHO Regional Office for Europe) is part of the Expert Advisory Group for the SUSTAIN-HTA project.

The SUSTAIN-HTA Taxonomy tool is available here which has a complete glossary of relevant terms used in this document: https://bu2f97-saifelayan.shinyapps.io/appd/

[1] Elayan S, Goettsch W, Facey K, Garrett Z, Elvidge J, Collins S, Oortwijn W, van Mun L. SUSTAIN-HTA D1.1: Taxonomy report. Utrecht (NL): SUSTAIN-HTA Consortium; 27 June 2024. Available from: https://sustain-hta.org/wp-content/uploads/2025/04/SUSTAIN-HTA_D1.1_Taxonomy-report.pdf

Introduction

1.1 Background and context

Health technology assessment (HTA) is defined by the European Union as a scientific, evidence-based process used by competent authorities to evaluate the relative effectiveness of new or existing health technologies[2]. The primary goal of HTA is to assess the added value of a health technology in comparison to other alternatives, thereby supporting informed decision-making in healthcare.

Greece first introduced its HTA system in January 2018, with implementation beginning in mid-2018[3]. This marked a significant development in national health policy, particularly in reimbursement decisions for medicinal products. HTA serves as a critical strategic mechanism to optimize the allocation of scarce healthcare resources, facilitate timely and equitable patient access to innovative medical therapies, and uphold the sustainability of the healthcare system by guiding cost-effective investments in new and emerging technologies.

The methods of the Regulation EU 2021/2282 on health technology assessment (EU HTAR)[1] are based upon the voluntary collaboration among Member States, initiatives such as The European Network for Health Technology Assessment (EUnetHTA).[4] EUnetHTA included four clinical domains (problem identification and current technology; technical characteristics of the technology; relative safety; relative effectiveness), as well as five non-clinical domains (cost and economic evaluation, ethical, organisational, social and legal aspects of the technology) and the EU HTAR focuses on the clinical assessment domains, through the development of EU-level Joint Clinical Assessments (JCA).

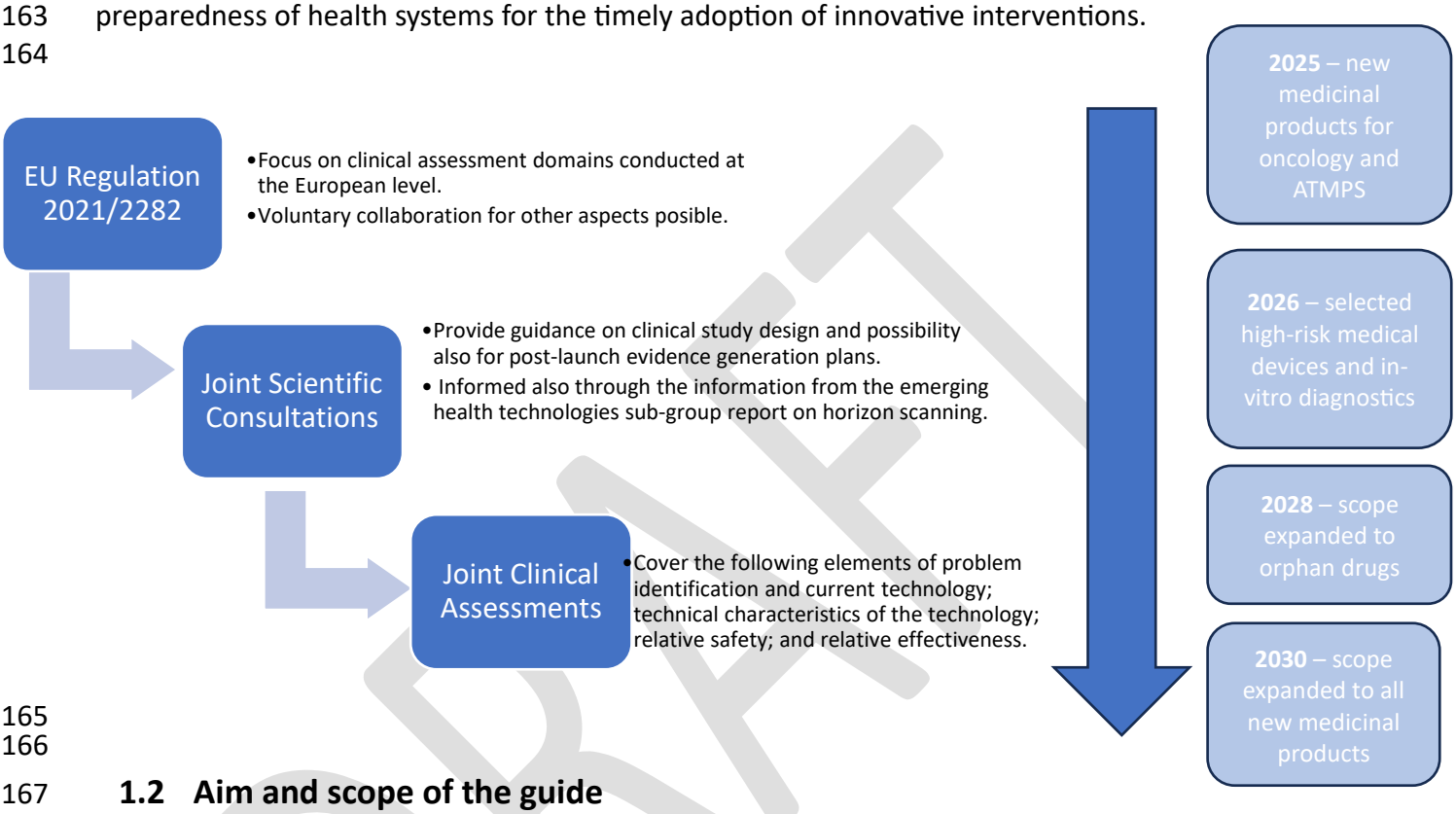
The non-clinical components of HTA will be addressed at the national level. Nonetheless, Member States may choose to engage in additional voluntary collaboration in these areas, including economic evaluations and other relevant considerations. The Regulation specifies that Joint Clinical Assessments (JCA) will be carried out by Member States through representatives of their existing HTA bodies. Initially, these assessments will focus on new medicinal products, such as cancer therapies and advanced therapy medicinal products (ATMPs) followed by certain high-risk medical devices and in vitro diagnostic medical devices, with the scope expanding to include orphan drugs from 13 January 2028, and subsequently, all new medicines from 13 January 2030.

[2] European Union. 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. Off J Eur Union 2021;L458/1:1–32 (http://data.europa.eu/eli/reg/2021/2282/oj).

[3] Chantzaras A, Margetis A, Kani C, Koutsiouris V, Bacopoulou F. Health technology assessment of medicinal products in Greece: a 5-year (2018–2023) review of timelines and productivity. International Journal of Technology Assessment in Health Care. 2024;40(1):e40.

[4] Kristensen FB, Lampe K, Wild C, Cerbo M, Goettsch W, Becla L. The HTA Core Model®—10 years of developing an international framework to share multidimensional value assessment. Value in Health. 2017 Feb 1;20(2):244-50.

Member States will also participate in Joint Scientific Consultations (JSC), aimed at providing guidance to technology developers on the design of clinical studies to ensure the generation of robust and relevant evidence to inform future JCAs. In addition, "horizon scanning" activities will be undertaken to identify promising health technologies at an early stage. These efforts, carried out under the Emerging Health Technologies workstream, are intended to enhance the preparedness of health systems for the timely adoption of innovative interventions.



1.2 Aim and scope of the guide

This publication aims to establish a comprehensive methodological framework to guide the HTA activities in Greece, with a particular focus on the systematic assessment and reassessment of medicinal products to inform coverage decisions and clinical practice. This methods guide should be read in parallel with the accompanying process guide, which delineates the operational procedures of the HTA process and collectively, these documents will form the foundational national framework for HTA in Greece and ensured alignment with the EU HTAR.

The implementation of Regulation EU 2021/2282 on HTA (EU HTAR), which came into force on 12 January 2025, represents a major milestone for Greece and all EU Member States. In response, Greece has been updating its HTA governance structures, legislative framework, and institutional capacity to ensure full alignment with the requirements set forth by the EU HTAR.

This guide reflects these developments, building upon the HTA framework established in 2018. It supports Greece's alignment with the EU HTAR and contributes to the advancement of HTA and reimbursement decisions that are transparent, methodologically robust, and grounded in high-quality evidence.

This guidance currently encompasses the HTA for medicinal products for two distinct scenarios: (1) where complete national HTAs need to be conducted as well as (2) when JCAs will be available for the clinical assessment and only the economic and other considerations need to be conducted at the national level.

1.3 Target audience

This guide is intended for stakeholders engaged in health technology assessment in Greece, including health technology developers (HTD), clinical professionals, patient representatives, and decision-makers. It is particularly relevant for those national decision-makers responsible for conducting or using HTA to inform pricing and reimbursement decisions and procurement of medicinal products.

1.4 How this guide was developed

This Methods Guide was developed through an iterative, collaborative process led by the Greek Ministry of Health, the Greek HTA Committee, in close cooperation with the WHO Regional Office for Europe, through the European Commission's Technical Support Instrument (SG REFORM). The evaluation of a health technology may be conceptualized as comprising five distinct steps. This guide addresses the first two methodological components, while the remaining steps are detailed in the accompanying process guide.

- Scoping or problem definition
- Analysis of the evidence (assessment)
- Appraisal
- Decision making
- Implementation and monitoring

The HTA Coordinating Group has issued HTA methodological guidance for the clinical assessment for JCAs which may be consulted as reference. However, this document is specifically designed to also address key local needs and requirements, ensuring its relevance to the Greek healthcare system.

The development process began with a comprehensive Situation Analysis of Greece's HTA landscape, aimed at identifying gaps, capacity needs, and challenges in aligning with the new EU Regulation. This phase involved an extensive literature review, in-depth stakeholder interviews, and targeted consultations, and a detailed examination of the HTAR documents.

Building on the insights from the Situation Analysis, the second phase focused on developing updated draft methodological and process guidance (National HTA framework for Greece) was initiated. This effort drew on international best practices and expert input from leading HTA agencies in France (HAS), Italy (AIFA), Portugal (INFARMED), and the United Kingdom (NICE) and the WHO Collaborating Centre for Pharmaceutical Policy and Regulation at the University of

Utrecht, The Kingdom of the Netherlands. A combination of virtual engagements and in-person site visits facilitated the identification of effective approaches and their adaptation to the specific needs and context of the Greek healthcare system.

Robust stakeholder engagement has been a cornerstone of the development process, ensuring transparency, inclusivity, and shared ownership in the effort of strengthening Greece's HTA system. Key stakeholders involved in the development of this guide include the Greek Ministry of Health, the HTA Committee, EOPYY, healthcare professionals, academia, a Scientific Advisory Group, industry representatives, and critically, patient groups who are also part of the high-level steering committee. Ensuring patient voices are heard remains a core principle of the HTA process.

This guide is conceived as a living document, subject to ongoing refinement and enhancement. Its content will be iteratively updated based on insights gained through the pilot implementation involving the assessment of a selected medicinal product, thereby ensuring its continued relevance, practicality, and responsiveness to real-world application as well as on a regular basis to incorporate new developments in the HTA methodology.

2 Defining the assessment scope using PICO

HTA begins with the clear definition of the assessment scope or decision problem, typically structured using the PICO framework: Population, Intervention, Comparator, and Outcome. PICO elements form the foundation of the assessment, shaping the data requirements for HTDs and informing the structure of the overall assessment dossier. PICO provides a standardized and systematic approach for formulating, both, clinical and economic questions, guiding literature reviews, evidence synthesis, economic modelling and other key components of the assessment process.

The HTA Coordinating Group has issued HTA methodological guidance on the scoping process that could be valuable for HTA member states even when the HTAs are being conducted outside of the JCA process (e.g. complete national level HTAs). Under the EU Regulation 2021/2282, JCAs use PICO to reflect the policy needs of EU Member States. These PICO elements are defined at the European level but must be inclusive of Member States' needs and cover the PICO(s) requested by Member States. Thus, PICO(s) relevant to Greek context should be defined even where the JCA process is being followed, and the relationship of PICO(s) relevant to Greece to those used for the JCA should be clarified as part of the discussions. PICO, as defined for Greece, should be rooted in standard care within the country, and should reflect the epidemiology, demographics and other characteristics of the Greek context.

Guidance on the JCA scoping process and PICO definition and details are available through JCA documentation.[5]

[5] HTA CG. Guidance on the scoping process. 13 November 2024. (https://health.ec.europa.eu/document/download/7be11d76-9a78-426c-8e32-79d30a115a64_en?filename=hta_jca_scoping-process_en.pdf).

While JCAs support cross-country collaboration, this Methods Guide sets out how to define PICO for national HTA in Greece, ensuring alignment with EU practices while addressing local priorities and decision-making needs. In addition, PICOs can reflect the local clinical guidelines and therapeutic protocols per indication. Information received early through horizon scanning reports can be helpful in supporting the development of PICOS.

2.1 Patient population

The patient population should include all patients relevant to the therapeutic indication being assessed in the Greek setting, encompassing both the overall target group and any clinically meaningful subgroups that may respond differently to the intervention.
When defining the population, health technology developers should:

- Describe the patient group likely to receive the intervention, including:
  - Epidemiological and clinical characteristics (e.g. average age, gender, disease severity/stage) in Greece;
  - Relevant diagnostic criteria or biomarkers used to define eligibility.
- Identify and justify (providing the clinical or pharmaceutical rationale for) any subgroups, such as those expected to experience different treatment effects due to comorbidities, disease progression, or other clinical or demographic factors.
- Include quantitative data, such as estimated population size, and, if dosing is weight- or surface area–based, provide average weight or surface area values.
- Cite all data sources, such as clinical trial data, Greek registries, or Greek epidemiological databases. Where national data sources are not available, the use of other data sources should be justified.

2.2 Intervention: description of the pharmaceutical and therapeutic area

The intervention in the PICO should reflect the intervention to be assessed in the indication for which the HTA submission is made by the health technology developer (HTD). The intervention should include only the intervention under assessment and should not include other products that are not part of the indication of interest. However, if the technology under assessment is to be used in combination with other technologies, these should be part of the definition of the intervention.

Details regarding what is within scope for a medicinal product subject to JCA is provided by the JCA guidance[6].

[6] HTA CG. Scientific specifications of medicinal products subject to joint clinical assessments. 10 June 2024. (https://health.ec.europa.eu/document/download/48974c78-1c37-4cf9-9fc9-a630fee9baac_en?filename=hta_mp_jca_sc-specifications_en.pdf).

2.2.1 Defining the intervention

The intervention under assessment may consist of a single medicinal product administered as monotherapy, or it may involve a combination of therapies. Additionally, the intervention may be delivered alongside best supportive care or any other background treatments that are part of the standard management of the condition in Greece. These background therapies may include pharmacological or non-pharmacological interventions and should be clearly specified where relevant.

The details of the intervention should include only the intervention under assessment and should not include other products that are not part of the indication of interest. However, if the technology under assessment is to be used in combination with other technologies, these should be part of the definition of the intervention.

The following characteristics of the medicinal product should be reported:

- Regulatory status (e.g., conditional/accelerated approval, orphan designation, ATMP);
- SPC alignment (whether proposed Greek use fully matches EMA-approved label);
- Mechanism of action;
- Pharmacotherapeutic class (ATC codes);
- Mode of administration;
- Dosage (e.g. average daily dosage, loading and maintenance doses; based on weight; duration of therapy);
- Treatment plan, including whether treatment with the pharmaceutical includes combination therapy or any pre-treatments;
- Packaging type, size, durability, strengths and description of any device required, if relevant;
- Handling requirements of the pharmaceutical that may affect usability;
- Monitoring (for example the need for blood samples, biomarker measuring, scans);
- The expected position of the new pharmaceutical in existing Greek clinical practice; and
- Any other details about the intervention that are relevant and important for the assessment.

2.3 Comparators

A comparator defines the treatment(s) against which the health technology under assessment should be compared. Comparators are all therapeutic alternatives commonly used in clinical practice in Greece to treat the indication for which the medicinal product under assessment has a marketing authorisation, should be included.

The selection of a given intervention as a comparator does not translate into a judgement on its efficacy, the only inclusion criterion being its usual use in clinical practice in Greece. Therefore, the relevant comparators should not be constrained by the comparators used for the control group in clinical trials of the medicinal product under assessment.

Comparators can include one or more treatments (licensed or not), specific products, classes, or non-drug interventions. For an off-label comparator to be considered, they need to be widely used in clinical practice in Greece and no licensed options should be available. They can include pharmacotherapy, non-pharmacotherapeutic options (e.g. medical devices, surgery, diagnostics, psychotherapy, physiotherapy, radiation, prophylaxis, best supportive care or standard of care, or watchful waiting). When a comparator is used in both the intervention and comparator arms, this should be specified. At the national level, the dosage and regimen with which the comparator is used should also be specified. All therapeutic sequences (if used as second-line or further lines, if applicable and permitted by its marketing authorization) should be highlighted.

Within one population, different comparator scenarios can apply, potentially requiring the definition of multiple PICOS. These can be unique comparators and/ or individualized treatment options as appropriate. If one treatment suits all patients in the population, one PICO with that comparator should be defined. When there are multiple comparators, each treatment should be separately assessed, leading to distinct PICOS. Where multiple treatments are combined into one comparator, these can be combined into one PICO.

In cases where there is no standard treatment that works for all patients in the population and guidelines recommend several options, they can be bundled as an “individualised treatment” comparator. In this case, effect estimates should be given against the bundle, and where feasible each option separately. This should be used only when the population cannot be split into clear subpopulations with their own comparators.

Greece will justify the inclusion or exclusion of comparators based on national clinical practice and other relevant evidenced-based references within the health system context. The relevance of comparators to the local setting is critical for decision making.

2.4 Outcome measures

2.4.1 Defining outcomes

Outcomes represent the concepts used to estimate treatment effectiveness and safety, such as mortality, functional capacity, or life expectancy, including remission, disease control, function, adverse effects, and health-related quality of life (HRQoL). The measure of an outcome defines precisely how that outcome is assessed as a specific variable – while outcomes refer to what is measured in a study, outcome *measures* correspond to how the outcome is assessed at a patient-level. Effect measures are statistical comparisons of these outcome estimates between different groups.

Efficacy outcomes should include objective outcomes (including hard endpoints) such as mortality where relevant as well as outcomes determining morbidity (symptoms and complications), duration of illness, HRQoL. Safety outcomes should include total dropouts, total adverse events, serious adverse events, discontinuation due to adverse events as well as specific safety outcomes that are relevant for the particular intervention and condition. Other outcome measures, such as healthcare resource use, or hospitalizations should also be considered.

It can be useful to classify outcomes according to the main source of information via which they are collected keeping in mind that categories for classifying outcomes are not mutually exclusive, as some measurement instruments for some outcomes require the collection of elements from multiple sources.

- Clinician-reported outcomes: Assessments by healthcare professionals based on clinical exams and judgments of observable signs or biomarker data.
- Performance outcomes: Require patients to complete standardized tasks evaluated by clinicians (e.g., walking tests).
- Patient-reported outcomes: Direct reports from patients about their health, symptoms, or quality of life, often via questionnaires.
- Observer-reported outcomes: Reports by non-clinical observers (e.g., caregivers) on patient behaviors or events, especially when patients cannot self-report.
- Digital outcomes: Data collected via health technologies or devices, which may represent any of the above outcomes, but require careful validation before use.

Further guidance and details on outcomes are available through the JCA guidance.[7]

2.4.2 Clinical relevance

A set of outcome measures relevant to the Greek context should be proposed, related to the efficacy and safety of the intervention. The submission should specify how Greek relevance was determined (e.g. inclusion of Greek/comparable population, or adaptation of study findings using any validated tools). These measures should allow for a comprehensive view of the effect of treatment and should include measures relevant to the patient such as HRQoL.

Clinical effect measures, including outcomes relating to benefit and safety should be assigned critical importance (critical or important) when being assessed.

A surrogate outcome is a substitute for a direct outcome of interest in clinical studies when direct measurement isn't feasible. It can be a biomarker or an intermediate outcome that indirectly reflects the effect of a treatment. Biomarkers, specifically, are objective indicators of biological

[7] HTA CG. Guidance on outcomes for joint clinical assessments. 10 June 2024. (https://health.ec.europa.eu/publications/guidance-outcomes-joint-clinical-assessments_en).

processes, disease progression, or responses to therapy. Surrogate outcomes may also be used with justification for their relevance, highlighting whether they are validated surrogate markers, reasonably likely surrogate markers or candidate surrogate markers to support local decision-making. Surrogate outcomes should be supported by biological plausibility, consistent clinical evidence, and regulatory acceptance (e.g., EMA or FDA). The HTA Committee may also consider conditional acceptance of reasonably likely surrogate markers, especially when supported by real-world evidence. However, they will likely be assessed as not critical (important) where direct outcomes are available.

Composite outcomes combine two or more related clinical events (e.g., death, stroke, myocardial infarction) into a single measure to increase statistical power, especially when individual events are rare. They help reduce issues with multiple comparisons and can reflect a broader treatment effect. The selection of components should be clinically coherent, expected to respond similarly to treatment and reflect real-world disease burden. For appropriate interpretation, results and analysis of individual components should be presented separately as well, to ensure consistency and relevance. Any deviations from the study protocol regarding components must be justified. Composite outcomes may also be used with justification for their relevance but will likely be assessed as not critical (important) where direct outcomes are available.

Further guidance and details on outcomes are available through the JCA guidance.[6]

Safety

The terms “safety” and “adverse event” must be used consistently, avoiding terms implying causality. Safety reporting should follow standardized reporting methodology such as Medical Dictionary for Regulatory Activities (MedDRA) terminology. Safety outcomes can be noted for their seriousness including being graded for severity using standardised severity grading (e.g., Common Terminology Criteria for Adverse Events [CTCAE] for interventional studies in oncology) as well as, through deaths, treatment discontinuations, and interruptions. All adverse events must be reported regardless of causality.

2.4.3 Validity, reliability, and interpretability of outcomes measurement instruments

Outcome measurement instruments are tools used in clinical studies to quantify specific outcomes (e.g., HRQoL, response rate). These instruments consist of items (questions or tasks) and follow a conceptual framework and measurement model to generate scores or profiles. They are measurement models that convert item responses into scores (single or multiple domains).

The perspective of measurement for the same outcome can differ depending on whether information comes from healthcare professionals, medical technology, or patients. Correct interpretation therefore requires access to the full instrument text, instructions, and supporting validation literature. Outcome measurement instruments must demonstrate validity (the degree to which an instrument measures what it is intended to measure; poor validity can lead to

indirectness or bias) and reliability (the consistency and reproducibility of measurements under stable conditions; reflects freedom from random errors), assessed through dedicated, well-designed studies using appropriate statistical methods.

Common types of such instruments include PROMs (Patient-Reported Outcome Measures), OBsROs (Observer-Reported Outcome Measures), ClinROs (Clinician-Reported Outcome Measures), and Performance Measures (e.g., walking distance). They can be generic instruments that are broadly applicable across conditions (e.g., SF-36, EQ-5D-5L) and disease or condition specific instruments that are tailored to particular diseases or populations (e.g., EORTC QLQ-C30 for cancer).

These properties are complex, not binary, and their adequacy depends on the intended use. The COSMIN taxonomy[8] provides a taxonomy and tools for evaluating measurement properties and risk of bias of such instruments. These instruments such as PROMs require careful cross-cultural adaptation when translated to preserve validity, and studies validating the instruments in the languages used should be documented. It should be considered that even valid and reliable instruments do not always guarantee high certainty in treatment effect estimates and the study design and statistical analysis also determine appropriateness.

Interpretability refers to how clearly and meaningfully outcome scores can be understood and for better interpretability, it may be useful to consider "responders" (patients showing improvement), as a responder definition can help enhance interpretability. These definitions can be based on various perspectives and should complement, not replace, continuous outcome measures.

3 Clinical Assessment

Detailed guidance for JCAs on the validity of clinical studies, reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analyses as well as quantitative evidence synthesis for direct and indirect comparisons are available through JCA guidance documentation and can also act as guidance for the clinical assessment of national HTAs.[9][10][11][12]

[8] A consensus taxonomy of the measurement properties of outcomes measurement instruments has been developed by the international Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) group.

[9] HTA CG. Guidance on the validity of clinical studies for joint clinical assessments. 19 September 2024. (https://health.ec.europa.eu/publications/guidance-validity-clinical-studies-joint-clinical-assessments_en).

[10] HTA CG. Guidance on reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analyses in joint clinical assessments. 13 June 2024. (https://health.ec.europa.eu/publications/guidance-reporting-requirements-multiplicity-issues-and-subgroup-sensitivity-and-post-hoc-analyses_en).

[11] HTA CG. Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. 8 March 2024. (https://health.ec.europa.eu/publications/methodological-guideline-quantitative-evidence-synthesis-direct-and-indirect-comparisons_en).

[12] HTA CG. Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. 8 March 2024. (https://health.ec.europa.eu/publications/practical-guideline-quantitative-evidence-synthesis-direct-and-indirect-comparisons_en).

3.1 Systematic review and sources of evidence

All relevant studies of the best available methodological quality should be considered. The systematic review is a methodological process that is used to identify, select and critically assess the available studies on a clearly formulated question. It is fundamental to the assessment process that the evidence base considered is comprehensive and complete. The systematic review should be transparent and objective in order to reduce bias and ensure that the most valid answer is obtained.

Thus, the scientific evidence to be considered to inform the assessment and determine the comparative efficacy of treatment includes secondary studies, namely systematic review of clinical trials on the intervention under analysis, and primary studies. The preferred source of evidence for primary studies for medicinal products would be high-quality randomized controlled trials (RCTs). RCTs provide the highest standard of evidence regarding the comparative efficacy of a treatment and should be preferred whenever possible. RCTs that compare directly the intervention with one or more relevant comparator(s) are preferred and still considered as the gold standard. RCTs that examine indirect comparisons are accepted in addition to RCTs, if they are available, or in the absence of direct RCTs.

Non-randomised and qualitative studies can be included in the evidence submission as additional evidence with detailed justification of the uncertainties they may reduce and/or specifying how additional information they bring is relevant to the stated decision problem e.g., for specific outcomes or population sub-groups. This is because they are prone to confounding and can therefore require adjustment methods. Unlike comparative clinical trials, uncontrolled trials, when they are the only source of data submitted as evidence, do not allow relative effectiveness assessment but can be considered as appropriate for example for rare conditions (see further guidance in Section 3.1.1).

3.1.1 Real-world evidence (RWE)

Real-world studies help capture how health products are used in routine clinical practice, including variations in prescribing patterns, adherence, and patient populations. This contextual understanding complements clinical trial data and informs regulatory and reimbursement decisions. RWE assesses the actual effectiveness and safety of health products outside controlled trial settings. They provide insights into long-term outcomes, rare adverse events, and performance across diverse patient groups, enhancing the relevance of evaluations.

Utility scores derived from real-world data reflect patients' HRQoL and apart from informing clinical benefit are also essential for economic evaluations. RWE can also be used to quantify healthcare resource use such as hospitalizations, consultations, and treatments associated with a health product. These studies also evaluate how health products affect healthcare delivery systems, including workflow, staffing, and infrastructure. Understanding organizational implications

helps anticipate implementation challenges and supports strategic planning. The choice of the RWE study design cohort, case-control, registry-based, or pragmatic trial must align with the research objectives. Leveraging existing routine data sources including electronic health records, and established registers enhances feasibility and efficiency. These databases offer comprehensive, longitudinal data suitable for real-world evaluations.

The use of real-world data is permitted as supplementary material for all submissions but maybe considered most useful for rare/ ultra rare conditions. The Haute Autorité de Santé (HAS) - or French National Authority for Health have developed detailed guidance on real world studies and their use for HTA and can be used for further information.[13] Guidance is also available from other HTA agencies such as NICE from the UK.[14] RWE should ideally be from the Greek context, but where such data is not available, data from other relevant countries with a similar context, healthcare system can be provided instead. RWE collected post-launch can also used to re-assess both clinical and economic value and for conditional or revised reimbursement decisions.

3.2 Evidence Literature search and selection

The health technology developer should perform its literature search in accordance with the international principles and with a systematic and transparent approach to formulating focused questions defined by PICO as a systematic review. This refers to established standards for systematic reviews, namely those defined by PRISMA (Preferred Reporting Items for Systematic Reviews) and MOOSE (Meta-analysis of Observational Studies) consensuses, including justifications for excluded studies. As a minimum, the HTD should perform the literature search in at least two databases such as MEDLINE[15] and CENTRAL,[16] a justification for the selected time period for the searches (start date of the search) with it being not more than within one year prior to the submission of the dossier or if 18-24 months prior only accepted with justifications provide by the HTD.

The research strategy must be provided, and be reproducible, established in line with the agreed and final PICO(S) and should include the pivotal trials used for the marketing authorization. Literature selection should be based on explicit inclusion and exclusion criteria, using standardized and recognized methodologies. Ineligible studies should be listed, along with the justification for

[13] HAS. Real-world studies for the assessment of medicinal products and medical devices Methodology guide - Posted on Jun 30 2021 - Updated on Sep 02 2021. https://www.has-sante.fr/jcms/p_3284524/en/real-world-studies-for-the-assessment-of-medicinal-products-and-medical-devices
[14] NICE. NICE real-world evidence framework. Corporate document. Reference number: ECD9. 23 June 2022. https://www.nice.org.uk/corporate/ecd9/chapter/overview

[15] The National Library of Medicine's (NLM) National Center for Biotechnology Information (NCBI). MEDLINE: https://www.nlm.nih.gov/medline/medline_home.html
[16] Cochrane. Cochrane Library: Cochrane Central Register of Controlled Trials (CENTRAL): https://www.cochranelibrary.com/central/about-central

their exclusion and a flow chart summarizing this information. Every effort should be made to include all relevant evidence, regardless of language.

With regard to the sources of information to be searched, a wide range of bibliographic databases should be included to ensure the identification of all relevant studies for the topic under assessment. The existence of completed or ongoing clinical trials of relevance to the intervention under assessment should also be systematically searched and reported. For different aspects of the assessment, sources of information other than published literature, such as registers and other forms of real-world evidence, may also be considered, as appropriate for example for rare or ultra rare conditions (see Section 3.1.1).

3.2.1 Presentation of included studies

The HTD should present all relevant information on all the studies included in its application, including elements such as the study design, the intervention and comparator, the follow-up period, the number of randomised patients, inclusion and exclusion criteria for patients, the outcomes of the study (primary, secondary and exploratory), including their definition, documentation of validity, and clinical relevance, baseline characteristics of patients included broken down by treatment groups, any relevant sub-groups, and whether they were pre-defined in the study and any other relevant information for the assessment.

The HTD should discuss the internal and external validity of each study included and present the most important variables that are prognostic factors and effect-modifiers that may impact the effect of treatments at an individual level following the PRISMA and MOOSE checklists and principles as well as details are available through the EU-level guidance on the validity of clinical studies[8] as noted above in sections 3 and 3.1. All effect estimates should be accompanied by an estimate of the uncertainty when possible and a description of the analysis method applied.

In addition, for the safety data, the application should include safety data from the same studies and reports used to document the effects of both the intervention and the comparator(s). In cases where there is data from a safety population that is significantly larger than the one included in the studies of clinical effect, then this data should be used instead.

3.3 Evidence synthesis and methods of comparison

The clinical assessment for the HTA evaluates the additional benefit of an intervention in relation to comparators of interest. For this purpose, it uses different methods of comparison. RCTs summarized in a meta-analysis (conventional or network) are preferred for estimating comparative effects of the intervention under study and its comparators. Non-randomized evidence may be accepted in specific situations, which should be adequately justified (see section 3.1).

As noted in section 3, quantitative evidence synthesis for direct and indirect comparisons is available through JCA guidance documentation and can also act as guidance for the clinical assessment of national HTAs (references 9 and 10).[9-10]

3.3.1 Direct comparisons and conventional meta-analysis

Direct comparison between two specific treatments is understood as the comparison in a study of these two treatments. When the available evidence includes several studies that compare treatments directly, sometimes the results of these studies are combined using meta-analytic techniques to generate a pooled estimate of the relative efficacy of the two treatments. This allows to generate a combined estimate (meta-analysis estimate) of the relative effect of the two treatments across all the studies. This methodology of synthesis and quantitative analysis of the evidence base follows naturally from a systematic review and is usually its last phase.

All quantitative evidence synthesis methods are built on the foundational assumption of exchangeability, which ensures that the studies being compared are sufficiently similar to yield meaningful conclusions. This assumption encompasses three key elements: similarity, homogeneity, and consistency. Similarity refers to the comparability of patient populations and interventions across studies, ensuring that the groups being analyzed are alike in relevant clinical aspects. Homogeneity implies that the treatment effects observed in different studies are consistent and not significantly variable. Consistency involves the alignment between direct evidence (from head-to-head trials) and indirect evidence (from comparisons across a network of studies). If any of these assumptions are violated, the resulting synthesis may be biased or unreliable, potentially leading to incorrect conclusions about the relative effectiveness of interventions (see further details in section 3.3.2 for indirect and mixed treatment comparisons).

In the context of direct comparisons between health interventions, several statistical approaches are commonly employed to synthesize evidence. Frequentist methods are widely used and include techniques such as inverse variance for analyzing continuous data and the Mantel-Haenszel method for binary outcomes. These methods rely on observed data without incorporating prior beliefs. In contrast, Bayesian methods are particularly useful when data are sparse or limited, as they allow for the integration of prior information into the analysis. However, the use of Bayesian approaches requires careful justification of the chosen prior distributions to ensure transparency and credibility.

- The fixed-effect model assumes that all studies included in a meta-analysis are estimating the same true effect of an intervention in the target population. Any differences observed between study results are attributed solely to random variation due to sampling.
- In contrast, the random-effects model recognizes that there may be genuine differences in the intervention effects across studies, beyond just random variation. It assumes that each study estimates a true effect specific to its own population, and that these true effects follow a distribution—typically a normal (Gaussian) one. This approach uses a hierarchical framework with two levels: one for the individual studies and another for the distribution

of true effects across studies. Essentially, the studies are viewed as a random sample from a broader theoretical population of studies addressing the same research question.

Regardless of the statistical framework, random-effects models are generally preferred, especially when there is heterogeneity across studies. These models account for variability in treatment effects and provide more robust estimates in diverse clinical settings. The HTD should justify the statistical approach considered for the meta-analysis.

3.3.2 Indirect, mixed treatment comparisons and network meta-analyses

Indirect comparison is the estimate of the relative efficacy between two or more treatments in the absence of studies that directly compare them. Mixed treatment comparison is defined as estimating the relative efficacy of 3 or more treatments using both direct and indirect comparisons simultaneously. The term network meta-analysis encompasses direct, indirect and mixed comparisons.

Therefore, when there is insufficient data to reliably estimate the relative efficacy of two treatments or there may be a need to compare more than two treatments simultaneously, in which case it is necessary to use multiple treatment comparison methods, for example network meta-analysis. Thus, multiple treatment comparison methods can be used to infer the relative efficacy of two or more treatments in the absence of studies comparing them directly or by combining direct and indirect comparisons.

Several methods are available for conducting indirect comparisons when direct randomized evidence is lacking or insufficient.

- Bucher's method is a straightforward anchored approach that enables indirect comparisons by leveraging a common comparator across studies. It requires a connected evidence network and maintains the integrity of randomization.
- For more complex scenarios involving multiple treatments, Network Meta-Analysis (NMA) is employed. NMA allows for the simultaneous comparison of several interventions and can be implemented using frequentist or Bayesian statistical frameworks, as well as models tailored for time-to-event data.

When the assumption of similarity between studies is violated, and individual patient data (IPD) are available, population-adjusted methods become necessary. These include Simulated Treatment Comparison (STC), Matching-Adjusted Indirect Comparison (MAIC), and Multilevel Network Meta-Regression (ML-NMR). These techniques adjust for differences in patient characteristics across studies, enhancing the validity of indirect comparisons in the presence of heterogeneity. Further details on these methods are available through the JCA guidance documentation references 9 and 10 on direct and indirect comparisons.

For these more complex methods, having access to specialized software for the HTA assessors to check the data and analyses is needed, so they have the same tools as available to the HTDs for the

dossier development. The most commonly used software is STATA[17] and those that are actively coding themselves can also use R[18] but this requires specialized expertise and training, whereas STATA is more easy to .

3.3.3 Comparisons based on non-randomized evidence

The use of non-randomised evidence maybe needed in situations where RCTs are not available in particular for rare and ultra rare conditions. In such cases, evidence must be drawn from observational studies, which inherently carry a higher risk of bias. This makes it essential to carefully assess potential confounding factors and the overall methodological quality of the studies being considered. One of the primary tools for addressing confounding in observational data is the use of propensity score methods. These statistical techniques aim to balance treatment groups based on observed characteristics and include approaches such as matching, stratification, and weighting. While these methods can help reduce bias and improve the reliability of comparisons, they do not offer the same level of rigor as randomized studies. Therefore, their application must be well-justified by the HTD, and the results should be interpreted with caution to avoid drawing misleading conclusions.

3.3.4 Multiplicity issues and subgroup, sensitivity and post hoc analyses

Multiplicity in hypothesis testing refers to the increased risk of false-positive findings when multiple hypotheses are evaluated within a single study or across related analyses. This issue arises because each additional test raises the chance of detecting a statistically significant result purely by chance. To address this issue, the importance of transparency and rigor in how these multiple analyses are planned, conducted, and reported is essential. Multiplicity can occur when there are multiple data cuts, interim analyses, multiple treatment groups, and multiple outcomes. For instance, analyzing data at different time points or across various subgroups can introduce bias if not pre-specified. Similarly, conducting interim analyses (where data is reviewed before the study concludes) can inflate the risk of type I errors unless properly adjusted. When studies involve several treatment arms or measure numerous outcomes, the potential for selective reporting increases. To mitigate these risks, pre-specification and justification of all planned analyses should be made by the HTDs as noted in a protocol or statistical analysis plan.

Subgroup analyses are a critical component of clinical research, used to explore how treatment effects may vary across specific patient subpopulations. These analyses can provide valuable insights into differential responses based on characteristics such as age, sex, disease severity, genetic markers, or comorbidities. However, to ensure scientific validity and avoid misleading conclusions, subgroup analyses must be clearly defined and pre-specified by the HTDs in the study protocol or statistical analysis plan. This means that the rationale for selecting subgroups, the statistical methods to be used, and the expected direction of effects should be outlined before

[17] STATA: statistical software, https://www.stata.com/.
[18] R: The R project for statistical computing: https://www.r-project.org/.

data collection begins. When subgroup analyses are conducted post hoc that is, after the data has been examined, they carry a higher risk of spurious findings due to chance alone. Such exploratory analyses should be interpreted with caution and must be transparently labeled as post hoc to distinguish them from pre-planned evaluations. The HTDs should provide statistical justification, including appropriate adjustments for multiple comparisons, to maintain the integrity of the findings.

Sensitivity analyses are an essential part of clinical and statistical research, designed to assess the robustness and reliability of study findings under varying assumptions or analytical approaches. These analyses help determine whether the main results hold true when alternative methods, data handling procedures, or model specifications are applied. For example, researchers might test how results change when missing data is imputed differently, when certain covariates are included or excluded, or when different statistical models are used. This process helps identify potential vulnerabilities in the analysis and provides greater confidence in the conclusions drawn. To ensure their credibility, sensitivity analyses should be pre-planned and methodologically sound, with a clear rationale for each approach. This includes specifying the assumptions being tested and the reasons for choosing particular alternative methods. The impact of each sensitivity analysis must be transparently reported by HTDs, showing how the results compare to the primary analysis and discussing any discrepancies.

Post-hoc analyses are exploratory evaluations conducted after the initial inspection of study data. Unlike pre-specified analyses, which are planned before data collection begins, post-hoc analyses are often driven by observations or unexpected findings that emerge during or after the main analysis. These can be useful for generating new hypotheses or uncovering patterns that were not initially considered. However, because they are not pre-planned, they carry a higher risk of bias and false-positive results, making their interpretation more uncertain.
To maintain scientific integrity, post-hoc analyses must be clearly distinguished from pre-specified analyses in all reporting by the HTDs. Moreover, such analyses should be interpreted with caution and not used to support primary conclusions unless they are subsequently validated in independent datasets or studies. While post-hoc analyses can offer valuable insights, they should be presented as hypothesis-generating rather than confirmatory, and their limitations must be openly acknowledged.

Further details on these methods are available through the JCA guidance documentation reference 8 on reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analyses.

3.4 Assessment of quality of evidence

The assessment of the quality of the evidence will be done in accordance with the internationally recognized best practices and principles and in line with the methodological guidance for the JCAs at the European level but keeping the Greek context in mind.

3.4.1 Assessment of quality of evidence (certainty of evidence) for conventional meta-analysis

The quality of evidence for both the efficacy and safety outcomes for a convention al meta-analysis will be conducted using the GRADE framework (Grading of Recommendations Assessment, Development and Evaluation), which provides a structured and transparent approach to rating the certainty of evidence by the HTA body. The assessment of the quality of evidence will begin by evaluating the risk of bias for each of the studies included in the assessment. Six domains are used to assess the risk of bias for each study: lack of random sequence generation, lack of allocation concealment, lack of blinding (participants, investigators and adjudicators of outcome measures), incomplete accounting of patients and outcome events, selective reporting of outcome measures and other sources of bias (e.g. stopping early for benefit, use of unvalidated outcome measures, carryover effects in crossover trial). Assessing the risk of bias for non-randomized studies is highly complex and is most appropriately assessed using ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) and further details are available from the risk of bias tools.[19] The GRADE assessment includes five core domains: Risk of Bias, Inconsistency, Imprecision, Indirectness, and Publication Bias and further details are available from the GRADE book.[20]

3.4.2 Assessment of quality for NMAs

Assessing the quality of evidence derived from a network meta-analysis requires specialized methodologies due to the complexity of its structure. Unlike traditional meta-analyses, NMAs combine both direct and indirect comparisons across multiple interventions, which means that the final estimates for each treatment pair are influenced by a web of interconnected studies. This complexity necessitates tools that can account for the mixed nature of the evidence and the varying influence of individual studies. These approaches evaluate how each study contributes to the overall network and help determine the confidence in the results. Notably, the quality of a study does not always correlate with its influence on the final estimates, some high-quality studies may have minimal impact, while others with limitations might disproportionately affect outcomes. Two key methods used for this purpose are:

- **CiNeMA (Confidence in Network Meta-Analysis)**[21] assesses six criteria: within-study bias, selective outcome reporting bias, indirectness, inaccuracy, heterogeneity, and incoherence/inconsistency. It also uses a contributions matrix to quantify how much each study informs the network, aiding in semi-automated bias assessments. Unlike GRADE, CiNeMA does not use categorical ratings for imprecision, heterogeneity, or inconsistency; instead, it evaluates their clinical impact.
- **Threshold Analysis** evaluates how robust the results are to potential changes in the underlying evidence. It quantifies how much the evidence would need to change due to factors like bias adjustments or sampling variation before it would alter the treatment recommendation. If the evidence remains within the calculated thresholds, the results are

[19] Risk of Bias tools. (https://www.riskofbias.info/welcome).
[20] Neumann I, Schünemann H (Editors). [list the section editors] (Section Editors). The GRADE Book version 1.0 (updated September 2024). The GRADE Working Group. (https://book.gradepro.orhttps://book.gradepro.org/).
[21] CINeMA (Confidence in Network Meta-Analysis). (https://cinema.ispm.unibe.ch/).

considered stable; if it falls outside, the conclusions may shift, indicating sensitivity to changes. This analysis is applied to each study in the meta-analysis and to each relative effect estimated. A key strength of threshold analysis is its ability to identify studies that could potentially change the recommendation. These studies should be examined closely, considering their risk of bias and relevance to the target population. The focus is typically on comparisons between the technology under assessment and its current comparators, with detailed inspection of thresholds for these specific comparisons. This helps decision-makers understand the plausibility of changes in effect estimates and the stability of the network's conclusions.

3.4.3 Determination of added clinical benefit and therapeutic value

The assessment of a medicinal product used to treat a given indication includes, firstly, the assessment of the additional benefit of that intervention compared to therapeutic alternatives commonly used in clinical practice to treat that same indication. If actual clinical benefit is demonstrated, the product is also then considered through the lens of whether it provides added therapeutic or clinical value. The **Added Therapeutic Value** (ATV) can be considered to determine the reimbursement level.

The criteria considered for determining the **Actual Clinical Benefit** are:

- Severity of the disease/condition and its impact on morbidity/mortality
- Clinical efficacy/effectiveness
- Safety (adverse effects, toxicity, tolerability)
- Intended role in the therapeutic strategy in comparison with other available therapies
- Aim of the therapy and whether this is preventive, symptomatic or curative
- Impact in terms of public health and associated benefits (burden of disease, health impact at community level, transposability of clinical trial results)

The different products can then be categorized in the following classes:

- **Sufficient actual clinical benefit:** a favourable opinion and recommended for inclusion onto the list of reimbursable medicines by the HTA Committee, with 3 resulting levels of substantial, moderate and low.
- **Insufficient actual clinical benefit**: an unfavourable opinion and not recommended for inclusion onto the list of reimbursable medicines by the HTA Committee for inclusion onto the list of reimbursable medicines.

The European Society for Medical Oncology–Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a validated, structured tool developed by the European Society for Medical Oncology to grade the clinical benefit of cancer medicines in a transparent and evidence-based manner. Introduced in 2015, it supports clinicians, policymakers, and patients by providing a consistent framework to evaluate the value of anti-cancer therapies across solid tumours and since 2023, hematological malignancies, using a rational and reproducible methodology that minimizes bias. The scale

informs health policy, clinical guidelines, and treatment decision-making by clearly communicating the magnitude of therapeutic benefit, helping guide prioritization of high-value cancer treatments within resource-constrained healthcare systems and can therefore be a helpful validated tool for the assessment of cancer medicines.[22]

Additionally, the medicinal product should provide ATV to the existing available treatments/appropriate comparators with good quality of evidence as assessed in 3.4.1 or 3.4.2. to determine the comparative efficacy and safety with regards to available treatments. A medicinal product, having no ATV, can only be included onto the list of medicines for reimbursement if it offers savings in terms of treatment cost.

The categories considered for **Added Therapeutic Value** for medicinal products, when compared with existing therapeutic interventions, are the following and can be used for pricing negotiations:

- I: major
- II: substantial/ important
- III: moderate
- IV: minor
- V: no improvement

For categories I-IV, ATV needs to be demonstrated through a superiority trial design.

The categorization of the ATV should follow the suggestions from the table below similar to those seen in France.[23]

Category of ATV	Description of the category
I: major	A major therapeutic improvement may be recognized for drugs with a new mechanism of action, demonstrated with a high level of evidence and a superiority associated with a clinically relevant effect in terms of mortality or morbidity, compared to the clinically relevant comparator, in the context of an under-covered medical need for a serious disease.
II: substantial/ important	Important therapeutic progress may be recognized for drugs that have demonstrated superiority associated with clinical efficacy in terms of mortality or morbidity in the context of an under-covered

[22] ESMO-Magnitude of Clinical Benefit Scale. Available from: https://www.esmo.org/guidelines/esmo-mcbs

[23] Boucaud-Maitre D, Berdaï D, Salvo F. Added therapeutic value of medicinal products for French and German health technology assessment organizations: a systematic comparison. Value in Health. 2021 Mar 1;24(3):346-52.

Category of ATV	Description of the category
	medical need. The value of this efficacy can be positively modulated by a substantial gain in quality of life and/or safety.
III: moderate	Moderate therapeutic progress may be recognized for drugs that have demonstrated superiority associated with clinical efficacy in terms of mortality or morbidity in the context of an under-covered medical need. The value of this efficacy can be positively modulated by a substantial gain in quality of life and/or safety.
IV: minor	Small progress compared to the existing therapeutic/preventive/diagnosis procedures. It reflects a demonstration and/or quantity of effect (efficacy, quality of life, tolerance) that is not optimal in view of the medical context. It may be a drug that has demonstrated relevant efficacy with a slight and acceptable reduction in quality of life or safety. Conversely, it may be a drug with little additional efficacy or demonstrated nonoptimal efficacy but associated with a gain in terms of quality of life or tolerance. It may also be a major improvement in conditions of care demonstrated or expected.
V: no improvement	A demonstration based on a non-inferiority study, a generic or a biosimilar medicinal product. In the absence of a therapeutic alternative or when alternatives are limited, it may also reflect a deficiency or uncertainty related to the choice of comparator, the quality of the proof of effect, the quantity of effect, or its clinical relevance. A suspected or established loss of opportunity for patients with respect to clinically relevant comparators.

Ranking of new medicinal products based on the categories above will take into account the evidence summarized within the table above keeping the clinical evidence itself, the clinical pertinence/relevance, and size of the effect. The size of the effect can also be adapted from the German methodology as per the table below as a guide.[19][24]

	Comment	Outcome category		
Category		All cause mortality	Serious or severe adverse effects as well as HRQoL#	Non-serious or non-severe adverse effects
I Major	Large effect (e.g., large reduction in risk mortality) or large	0.5-0.85	0.70 and risk ≥ 5%*	Not applicable

[24] IQWiG. General Methods. The English translation of the German document Allgemeine Methoden (Version 7.0) of 19 September 2023.

	Comment	Outcome category		
	improvement in HRQoL			
II Moderate	Moderate effect seen	0.85	0.75 and risk ≥ 5%*	Not applicable
III Considerable	Considerable effect seen	0.95	0.90	0.80
IV - Minor	Small or minor reduction in risk of non-serious adverse effects	1.00	1.00	0.90

#pre-condition for HRQoL is a use of a validated instrument and appropriate response criterion and should show improvements in HRQoL

* risk must be at least 5% for at least 1 of the 2 groups compared

4 Economic assessment

This section details methods for assembling, synthesising and analysing economic evidence on the medicinal product in an economic or cost-effectiveness evaluation. A full cost-effectiveness evaluation will only be needed when a medicinal product will be deemed to have major, substantial, moderate, or minor added therapeutic value at the clinical assessment stage. This is to ensure that the new medicinal product's relative clinical effectiveness provides good value for money for the Greek healthcare system.

When a medicinal product offers no added therapeutic value, a cost minimization may be employed to ensure efficient resource allocation. In such cases, the analysis should focus exclusively on comparing costs, aiming to identify the least expensive option among therapeutically similar alternatives. This approach simplifies decision-making by excluding effectiveness measures, assuming that health outcomes are essentially the same but should ensure that there are robust noninferiority trials with clearly defined margins based on minimal clinically important differences. This supports price parity for therapeutically equivalent treatments, ensuring that public funds are not spent on more expensive options without added value. This is a pragmatic tool that reduces the time and resource burden associated with full cost-effectiveness models and supports deliberative decision-making, when no added therapeutic value is established. Products with no added therapeutic value may have the potential to offer cost savings (e.g., administration route, monitoring), therefore this can be presented by the HTD along with the relevant justifications. HTDs can choose to submit a full cost-effectiveness evaluation in advance of the ATV clinical assessment decision, if they so choose.

The cost-effectiveness model will be one of the tools considered for pricing and reimbursement decisions by the payer in Greece. The cost-effectiveness assessment will provide the HTA

perspective and guidance for these negotiations. Broader expenditure control mechanisms, such as claw backs and rebates, will operate independently alongside the HTA process.

4.1 Scope of the evaluation

4.1.1 Reference case

As the Greek HTA body and HTA Committee will have to make decisions across different medicinal products and disease areas it is crucial that analyses done to inform the economic evaluation are consistent and robust. Economic evaluation as part of HTA is useful and informative only if appropriate methods are used, and the results reported with clarity and accuracy. A cornerstone of a robust set of methods is a reference case (RC), a way of standardizing methods so that both the analytical approaches and presentation of results are more consistent. Not only can the use of an RC improve the quality of assessments, but it can also enable the results of multiple assessments to be more easily understood and compared. A reference case not only describes expectations based on best practice with respect to purely technical issues (such as the preferred approach to assessing uncertainty) but can also incorporate issues that are essentially value judgements (such as equity positions), and that are likely to be more context-specific.

A reference case specifies the preferred approach for the standard or base case analysis. However, it does not prevent additional analyses being presented when one or more aspects of methods differ from the reference case. However, these must be justified and clearly distinguished from the reference case by the HTD.

For the purposes of HTA in Greek, a reference case has been developed, informed by the format of the reference case from other European countries in particular Portugal's INFARMED as well as the approach of the iDSI Reference Case[25] but using the Greek context and data.

Component of the economic evaluation	Reference case (standard analysis)	Sub-section for details
Type of economic evaluation	Cost-utility analysis when a full analysis of costs and health benefits is needed. A cost-comparison analysis is sufficient when similar or greater health benefits at similar or lower cost than the	Section 4.1.2

[25] iDSI Reference Case for Economic Evaluation: https://www.idsihealth.org/resource-items/idsi-reference-case-for-economic-evaluation/

	relevant comparator(s) is expected.	
Scope and PICO	The economic evaluation should assess the medicinal product in the entire target population and in relevant subgroups, with all relevant comparators, for all relevant health effects as defined in the scope.	Section 2
Analysis perspective	The Greek health system with the pharmaceutical budget in the healthcare system and the full healthcare perspective for the broader consideration.	Section 4.2.3
Time horizon	Long enough to reflect all important differences in costs or outcomes between the intervention and comparators being compared	Section 4.3.1
Synthesis of evidence on health effects	Based on systematic review of the evidence	Section 3
Measurement and valuation of health effects	Health effects should be expressed as health-related quality of life (HRQoL) and validated quality-adjusted life years (QALYs) instruments such as are preferred e.g. EQ-5D-5L for adults. The QALY values of patients will be considered and only where appropriate those of carers.	Section 4.3.2
Identification, measurement and valuation of costs	Costs should relate to Greek health system resources and should be valued using the prices relevant for the national health system. Sources can be taken from diagnosis-related group (DRG) costs, reimbursement costs for medical exams and other costs within the Greek health system.	Section 4.3.3

Threshold	Academic evidence using an empirical econometric approach, suggests a base threshold of €27 117 per QALY gained, and the HTD should calculate the opportunity costs using cost-effectiveness threshold ranges between 10,000 EUR per QALY and 100,000 EUR per QALY.	Section 4.3.4
Discounting	Greece currently does not have an officially published national guideline specifying a standard discount rate for health economic evaluations but one is currently being considered through an academic publication and with evidence and through international comparisons 3.5% would likely be appropriate as the base case.	Section 4.3.5
Methods of addressing uncertainty, validation and sensitivity analysis	Probabilistic sensitivity analysis and relevant deterministic sensitivity analyses.	Section 4.4

4.2 Type of analysis

In cases where the HTD finds that the new medicinal product has an effect that is equal or similar to the current comparator, the HTD can choose to carry out a cost-comparison or cost-minimization analysis. For medicinal products where added therapeutic value has been established a full cost-utility analysis should be submitted.

4.2.1 Cost-comparison analysis

For the Greek context, a cost-comparison analysis should be used to evaluate the costs and resource use of a medicinal product relative to its relevant comparator(s), when similar health outcomes have been established in the clinical assessment in section 3.

This approach is therefore only suitable when the medicinal product is expected to offer equivalent clinical benefits at a comparable or lower cost. Relevant cost differences such as those from

adverse events or care pathway impacts should be included and justified. Where applicable, data sources should align with those used in prior HTA assessments in Greece for consistency.

4.2.2 Cost-utility analysis

For the Greek context, a cost-utility analysis should be used to assess whether differences in costs between medicinal products are justified by differences in expected health outcomes, measured in quality-adjusted life years (QALYs).

This approach supports efficient resource allocation within a constrained healthcare budget. Analyses should follow standard decision rules, including an incremental cost-effectiveness ratio (ICER) and net health benefits, and consider alternative measures only when QALY assumptions are inappropriate.

$$ICER = \frac{\Delta \text{ Costs}}{\Delta \text{ QALY}} = \frac{\text{Costs}_{\text{new medicinal product}} - \text{Costs}_{\text{comparator}}}{\text{QALY}_{\text{new medicinal product}} - \text{QALY}_{\text{comparator}}}$$

4.2.3 Analysis perspective

The reference-case perspective for economic evaluations should include all relevant health effects for patients and, only where when applicable or appropriate, for carers. Costs should be considered from the perspective of the pharmaceutical budget and for the broader perspective the national healthcare system, (both first excluding productivity costs and then including it in the sensitivity analyses). Indirect benefits from healthcare delivery such as improved diagnosis or patient convenience should be quantified when possible and provided as supplementary information. The rationale and sources for all costs must be clearly documented. Effects on life expectancy and HRQoL should always be included.

4.3 Economic model and model specifications

In the majority of applications, it is necessary to use a health economic model to conduct the health economic analysis. Health economic models allow for a synthesis of relevant evidence from several sources to estimate cost-effectiveness. The HTDs should prepare models in Microsoft Excel. The model should be intuitive and easy to understand, which can be aided by a technical description of the model aligned with the international standards for reporting such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS). The model may not be locked or have any hidden elements. All inputs in the model should be fully manipulable, and automatically update all the results, sensitivity analyses, etc.

The HTDs may use and adapt international models if they are appropriately adapted to a Greek context in relation to clinical practice, patient characteristics, health effects, costs and discounting,

etc. In such cases, the adaptation of the model to Greek conditions and the sources used should be documented.

The HTDs should justify the choice and structure of health economic models, ensuring alignment with disease progression and local clinical practice. All assumptions, data sources, and parameter estimates must be clearly explained, with both deterministic and probabilistic results reported. The cycle length of the model should reflect the clinical course of the disease and treatment intervals (for example as indicated by survival curves for partition survival models with as appropriate extrapolation if needed and justification for the methods of extrapolation used), and any use of a half-cycle correction should be justified. If surrogate outcomes are used, their link to final endpoints must be validated and analyzed for uncertainty, and individual components should be reported.

The economic evaluation will be critically assessed using international standards such as the Drummond checklist, that considers the following 10 domains: 1) the research question; 2) the description of the study/intervention; 3) the study design; 4) the identification, 5) measurement, and 6) valuation of costs and consequences; 7) whether discounting was carried out; 8) incremental analysis; 9) presentation of results with uncertainty and sensitivity analyses; and 10) discussion of results in the context of policy relevance and existing literature,[26] based upon the older guidance for the BMJ.[27] The appropriate access to the software used for the model (e.g. Microsoft Excel) should be made available to the HTA assessors as well as the proposed HTA body should ensure continued training for the HTA assessors in economic modelling.

4.3.1 Time horizon

The time horizon used in the cost-effectiveness model should be sufficiently long to include all important differences in costs and consequences of all technologies under comparison, including any intended and unintended effects related to the treatment or the condition. In general, a lifetime time horizon is the most appropriate approach not only for chronic diseases but also for acute conditions where there may be effects over mortality or long-term disability. The time horizon must be identical for costs and consequences, so that equal weight is given to each dimension.

It will often be necessary to extrapolate effects in order to achieve the relevant time horizon in the health economic analysis. When extrapolating effects beyond the study period, the HTD should describe and justify the assumptions made. This description should contain detailed information on the software used to carry out the extrapolation. When extrapolating clinical effects, the company should present graphs of observed data or Kaplan-Meier plots with the fitted extrapolation curves as well as any external data the company has used for validation.

[26] Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programs. Oxford: Oxford University Press; 2005.

[27] Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996 Aug 3;313(7052):275-83.

4.3.2 Measurement and valuation of health effects

In the Greek context, for the cost-effectiveness analyses health effects should be expressed in Quality Adjusted Life Years (QALYs). A QALY combines both quality of life (in the form of a utility value) and life expectancy into a single index. In the base case, the measurement of changes in health-related quality of life should be reported directly from patients and the utility (valuation) of these changes should be based on public preferences using a choice-based method (for example, time trade-off). The EQ-5D is the preferred measure of health-related quality of life in adults.

Cost-effectiveness studies that are carried out with the consequences expressed as Quality-Adjusted Life Years (QALYs) are preferred because they: (I) incorporate HRQoL; (ii) account for the patients' perspective and society's preferences; (iii) allow the comparison of different treatments for different diseases; and (iv) have been widely adopted by most national health technology assessment agencies.

HTDs should summarize health effects using QALYs that combine life years and quality of life, calculated by multiplying the time spent in a health state by its utility value. Utility values are derived through a two-step process: patients describe their health using a generic tooland values are assigned based on population preference weights. These weights should ideally reflect the Greek population to ensure relevance and accuracy.

Health effects should be expressed as health-related quality of life (HRQoL) and validated quality-adjusted life years (QALYs) instruments such as are preferred e.g. EQ-5D-5L for adults. EQ-5D-5L is a generic validated instrument used for many patient populations and in many countries. It is composed of five questions covering five dimensions of health-related quality of life: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Currently, Greece does not have a published, nationally validated EQ-5D-5L value set. However, the EQ-5D-3L value set for Greece has been validated and is available for use and the crosswalk method (i.e. mapping), which maps EQ-5D-5L responses to the existing EQ-5D-3L value set and should be considered until a validated EQ-5D-5L value set is available. In some cases, disease-specific instruments that can be mapped to predict EQ-5D-5L may be available. If this can be done by using validated methods, then the HTD can also use these instruments. If there are both generic and disease-specific instruments that the company can map to EQ-5D-5L, then the company should use the generic instrument. The company can then use the disease-specific instrument in a sensitivity analysis. [28] Therefore the utilities used within the model should come from published literature and where possible mapped onto the Greek population. If the EQ-5D-5L value set of another country is used, then it should be clearly stated which population is considered and the

[28]van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012 Jul-Aug;15(5):708-15. EuroQoL Value sets: https://euroqol.org/information-and-support/resources/value-sets/

justification included, why that country's dataset was used. In the future a Greek validated EQ-5D-5L value set, would be helpful to support local economic evaluations once it becomes available.

The HTDs should clearly describe all health states and adverse effects relevant to the patient population and treatments. They must explain how utility values (or dis-utility values) are calculated and integrated into the analysis, including data on quality-of-life reporting, handling of missing data, and statistical models used. Differences in baseline utility between treatment groups should be addressed, and sensitivity analyses should explore potential biases, especially those related to missing data methods. This ensures transparency and robustness in QALY estimation. The QALY values of patients will be considered and only where appropriate that of carers.

Identifying minimally clinically important differences (MCIDs) in quality-of-life and utility values should be through established thresholds reported in the published literature, often derived using anchor-based or distribution-based methods and should be reported as such with references by HTDs. When such evidence is unavailable, clinical experts and patient representatives play a crucial role in defining meaningful changes by providing context on what constitutes a perceptible and important improvement or decline. HTDs can therefore complement the literature based MCID with real-world input from clinical and patient experts from Greece.

While QALYs are considered the most appropriate generic measure of health benefit to be used in the Greek setting, it is understood that under certain circumstances assumptions underpinning the QALY and other factors (such as adequate data availability) may make its use open to question. This can often be the case for rare and ultra rare conditions. In such situations, evidence to this effect must be produced and analyses using alternative patient reported outcome measures that may be presented as additional non-reference case analyses. QALYs implicitly incorporate value judgments such as the additivity of health and ability to compare health across populations and conditions. Such judgments and assumptions should be borne in mind when conducting and reporting analyses using QALYs.

4.3.3 Identification, measurement and valuation of costs

In order to identify and compare the costs, the HTDs should identify, quantify and value direct and derived resource consumption for each medicinal product included in the analysis. As far as possible, the company should divide all costs into two elements and report them separately: consumed quantities and related unit costs. In the health economic analysis submitted, it should be possible to distinguish between any regional costs, municipality costs and if included other indirect costs associated with transport and the time spent by patients and carers. As far as is possible, the HTD should use market prices as estimates for calculating unit prices and costs, as well as Greek unit costs. The HTD should justify any deviation from this.

In the event that the HTD uses foreign costs, they should be adjusted using relevant purchasing power parities. Resource consumption and the costs of treatment for the same patient group may vary significantly from country to country. Costs based on foreign data may have limited relevance

for the Greek context due to differences in clinical practice, differences in health service capacity and organization, as well as differences in the subsidies/reimbursement systems.

If international models are used, the company should replace the cost data with Greek data to adapt the analysis to the Greek conditions. If foreign information on quantities is used, the HTD should separately argue the relevance of using this data and whether the estimate is representative of Greek clinical practice.

The costs of the intervention should be clearly identified, and this should include any administration costs and any related costs as well as those for the comparator(s). The costs of treating any side effects should be identified and similarly for those related to comparator side-effects. Any potential cost-savings in terms of background disease costs relative to comparator should be identified as well as costs associated with added years of life as relevant. The HTD should document all costs included with references, including expert sources if relevant and only when no other source is available. A detailed and thorough description of how costs are calculated should always be provided. The HTD should describe and justify any assumptions and methods used to calculate costs. In cases where there is uncertainty regarding cost estimates, as far as possible, the HTD should quantify the uncertainty.

Some helpful resources are listed below:

- List of reimbursed procedures and their reimbursement rates https://eopyyfiles.blob.core.windows.net/eopyysite/ServiceCategories/2662827f-1a8f-4121-9b78-9d15483105fa.pdf
- Available from Approved EOPYY Products, Medical Specialties, Providers, and Therapists (Αναζήτηση Εγκεκριμένων Προϊόντων ΕΟΠΥΥ, Ιατρικές Ειδικότητες, Πάροχοι και Θεραπευτές https://eservices.eopyy.gov.gr/eSearchAllMaterial/) and within provided medical procedures αποδιδόμενες ιατρικές πράξεις).
- Greek Ministry of Health: https://www.moh.gov.gr/articles/times-farmakwn

4.3.4 Threshold rate

Cost-effectiveness thresholds play a critical role in healthcare decision-making by providing a benchmark for determining whether a health intervention offers good value for money. They represent the maximum amount a health system is willing to pay for one additional QALY. These thresholds help guide resource allocation, ensuring that limited healthcare budgets are used efficiently to maximize population health. While some countries have explicit thresholds, others use them implicitly or derive them from economic indicators like gross domestic product (GDP) per capita. The WHO-CHOICE framework' new methods have shifted toward a generalized cost-effectiveness analysis model that compares all interventions to a null scenario (i.e., no intervention) to assess allocative efficiency across disease areas. This allows for cross-programme comparisons and supports strategic priority setting but does not prescribe any fixed thresholds for

country-level decision-making, which was previously recommended to be considered along GDP criteria.[29]

A Greek academic study estimated a cost-effectiveness threshold for the Greek healthcare system by analyzing the relationship between public health spending and quality-adjusted life expectancy over 30 years. Using regression methods, it calculated the cost per QALY gained from a permanent increase in per capita health expenditure, providing a data-driven benchmark for healthcare decision-making. Their calculations estimated that for most cases/ a base case cost-effectiveness threshold of €27,117 per QALY gained for the Greek healthcare system, from a third-party payer perspective would be appropriate, ranging from €23 612 to €36 086 for alternative specifications.[30] Further research based upon the willingness to pay (WTP) for different scenarios and types of health technologies including ATMPs, orphan and ultra orphan drugs as well as for conditions with high-unmet need, would be helpful to have for Greece. So further local research on this area for Greece is recommended for future updates of the Threshold rate in the country as appropriate.

To support contract negotiations, all analyses submitted by the HTD must calculate the opportunity costs using cost-effectiveness threshold ranges between 10,000 EUR per QALY and 100,000 EUR per QALY.

4.3.5 Discount rate

A discount rate is needed in economic evaluations because future costs and health outcomes are valued less than those occurring today, reflecting societal time preference, opportunity cost of capital, and uncertainty about the future. A consistent discount rate ensures comparability across interventions by converting future costs and benefits into their present value, which is essential for informing long-term healthcare investment decisions. Cost-effectiveness results should reflect the present value of the stream of costs and benefits accruing over the time horizon of the analysis. For the reference case, the same annual discount rate should be used for both costs and benefits.

Greece currently does not have an officially published national guideline specifying a standard discount rate for health economic evaluations but one is currently being considered through an academic publication currently still in development. It has estimated a country-specific threshold for Greece based on an extended form of the Ramsey formula and a set of parameters that were derived from national datasets on mortality, taxation, GDP growth, and demographic trends, at 3.42%.[31]

[29] Bertram MY, Edejer TT. Introduction to the Special Issue on" The World Health Organization Choosing Interventions That Are Cost-Effective (WHO-CHOICE) Update". International Journal of Health Policy and Management. 2021 Sep 19;10(11):670.

[30] Athanasakis K, Agorastos G, Kyriopoulos I. Estimating a cost-effectiveness threshold for healthcare decision-making in the Greek NHS. Health Policy and Technology. 2024 Aug 1;13(3):100882.

[31] Athanasakis K, Loupas MK, Kryiopoulos I. A discount rate for economic evaluations for Health Technology Assessment in Greece. Health Policy and Technology. 2026 Jan (in Press https://doi.org/10.1016/j.hlpt.2026.101169).

The most commonly used discount rates globally are 3% for both costs and health outcomes (used in many high-income countries) and 5% also frequently applied, especially in middle-income countries and based on a comprehensive review of official discount rates in guidelines of health economic evaluations across countries and over time, a 3.5% discount rate would be appropriate for Greece as the base case. [32] For very long-time horizons, that is over 30 years a reduced discount rate of 1.5% could be considered as per France and the UK.

4.4 Methods of addressing uncertainty: validation and sensitivity analyses

4.4.1 Validity

The HTD should discuss the model's internal and external validity in its application. The face-validity of input data and model results should be assessed in relation to the Greek context. There should be consistency between the model and the clinical documentation. For example, external validity should be assessed by comparing the predicted values from the model with external data from epidemiological studies or clinical databases. The external validation should be thorough and should be presented in a straightforward manner using both graphs and tables.

Where empirical evidence directly relevant to the Greek context is not available, expert opinion can be used to provide insight into the transferability of outcomes to the Greek context. Experts should seek to identify any significant differences between the model outcomes and what would be expected in the Greek clinical practice. Where differences are identified, uncertainties may be quantitatively elicited using a formal elicitation process. Further research on these quantities should be considered.

4.4.2 Uncertainty in health economic analyses

All health economic analyses are subject to uncertainty. It is important for the decision-making process, that the most significant uncertainties are managed systematically so that it is clear how the uncertainties affect the cost-effectiveness.

The uncertainties in the analysis should therefore always be identified, described, analyzed and discussed. There are a number of different sources of uncertainties in health economic analyses and different ways to analyze them.

There are a number of sources of uncertainty in health economic analyses:

- **Variability**: Differences in individual patient responses that cannot be reduced by more data.

[32] The systematic review included guidance from 48 countries over 30 years and 43 other international guidelines over 43 years. Khorasani, E., Davari, M., Kebriaeezadeh, A. et al. A comprehensive review of official discount rates in guidelines of health economic evaluations over time: the trends and roots. Eur J Health Econ 23, 1577–1590 (2022).

- **Heterogeneity**: Differences explained by observable factors, which can be addressed through subgroup analysis. For many medicinal products, the capacity to benefit from treatment will vary among patients with differing characteristics. This should be explored as part of the base-case analysis by providing estimates of clinical and cost effectiveness separately for each relevant subgroup of patients. The characteristics of patients in the subgroup should be clearly defined and should preferably be identified on the basis of an expectation of differential clinical or cost effectiveness because of known, biologically plausible mechanisms, social characteristics or other clearly justified factors. All relevant subgroups should have been identified at the PICO stage with consideration being given to the rationale for expecting a subgroup effect. However, this does not preclude the identification of subgroups later in the process; in particular, during the deliberations of the clinical assessment by the HTA Committee.
- **Parameter uncertainty**: Inaccuracy in model inputs due to limited data, which can be reduced by collecting more evidence.
- **Decision uncertainty**: Overall uncertainty assessed through probabilistic sensitivity analysis, indicating the likelihood that a decision (e.g., adopting a new treatment) is correct.
- **Model uncertainty or structural uncertainty**: This refers to the limitations and assumptions made when designing health economic models, which can never fully capture real-world complexity. This type of uncertainty can be explored through scenario-based sensitivity analyses and may also be included in broader decision uncertainty assessments. Addressing model uncertainty helps ensure more robust and transparent evaluations.

The HTDs should identify, analyze and discuss the most important uncertainties in the results of the health economic analysis. This should be done by submitting sensitivity analyses.

4.4.2.1 Deterministic sensitivity analyses

The HTDs should perform deterministic sensitivity analyses to test how changes in key parameters affect cost-effectiveness results. This includes varying inputs for different parameters in the model using one-way, two-way, or multi-way approaches. Results should be presented in tables and tornado diagrams. Scenario analyses such as best- and worst-case assumptions, can help explore uncertainty. The HTD should also illustrate the impact of the new medicinal product pricing on ICERs across a range of plausible prices to a price where the ICER is negative.

4.4.2.2 Probabilistic sensitivity analysis (PSA)

In the Greek context, HTDs should conduct probabilistic sensitivity analysis (PSA) to assess overall parameter uncertainty by assigning probability distributions to key model inputs. They must justify the choice of included variables and distributions, especially when empirical data is lacking. PSA can also explore uncertainty in model assumptions. Results should be presented using scatter plots and cost-effectiveness acceptability curves (CEACs) to show the likelihood of cost-effectiveness across different thresholds.

4.4.2.3 Expected value of perfect information (EVPI)

Probabilistic sensitivity analysis also forms the basis of an evaluation framework to extend the characterization of uncertainty in order to estimate the value of collecting further information and reduce the probability of making the "wrong" decision (that is, one which recommends a cost-ineffective option). Value of Information (VOI) analysis, which includes Expected Value of Perfect Information (EVPI) methods, can be used to estimate the value of eliminating all uncertainty in a model, or all uncertainty in specific parameters (such as quality of life). The former sets the upper boundary on the cost for future research. While VOI/EVPI techniques may be helpful in a broader systematic approach to identifying situations where further research is warranted, such analyses are not required as part of the reference (standard) case analysis but could be considered if the HTD is considering applying for the conditional reimbursement fund.

4.5 Budget impact

Budget impact analysis focuses on the financial consequences of adopting an intervention. In addition to the health economic analysis, the HTD should prepare a budget impact analysis that estimates the impact on Greek budget. This analysis solely focuses on the financial consequences of adopting a given intervention. However, in a context of limited public resources for health, knowing these financial consequences is crucial for budget planning and forecasting. Information received early through horizon scanning reports can be helpful in supporting the potential impact on the budget and health systems of new health technologies.

The analysis describes how budgets will be affected over a five-year period after the medicinal product is recommended. In the budget impact analysis, the HTD should present the expected number of patients and expected market share both given a recommendation and given a non-recommendation of the pharmaceutical. Relevant sources should be used to substantiate this. The company should present the budget impact as the annual cost for the first five years for a scenario where the pharmaceutical is recommended for reimbursement, and a scenario where the pharmaceutical is not recommended for reimbursement. Budget impacts should be reported for each of the five years separately. The analysis should use estimates for market take-up, prevalence and incidence. The analysis should assume that patients commence treatment at the start of each year. Health resource costs and unit costs should form main category of reporting and all relevant direct costs should be included in the analysis.

5 Other considerations

The ethical, legal, organizational, social and feasibility implications of implementing or not implementing a health technology deserve at least some exploration and evidence given their potential to bring highly contextual and relevant insights. The evidence base for these domains tends to be of an observational nature and the quality assessment is therefore considered

accordingly (see section 3.1.1). Many countries have developed their social value judgments[33][34] that guide decision-making and the appraisal process (see process guide section 5). Currently Greece does not have such a set of judgments and if and once they are developed, they should be considered and included.

The summary table outlines a framework for considering a selection of these aspects in the HTA process in Greece. Key considerations in terms of access in Greece would be relevant such cities versus rural areas, isolated islands etc. Additionally, health system capacity in service delivery for example for advanced therapeutic medicinal products (ATMPs) is also an important factor. The HTDs should provide evidence on the discussion on these aspects and the Cochrane Equity methods Group's PROGRESS-Plus framework can be considered for stratifying the analysis systematically by key characteristics, particularly for equity considerations.[35]

Domain	Aspects to consider
Ethical	What are the potential benefits and harms from adopting or not adopting the medicinal product for patients, family, health professionals, society as a whole and other groups?
Legal	Which rules and regulations may influence or be influenced, and in what way, by the implementation of the medicinal product?
Social	Are there groups of patients who currently don't have good access to similar (types of) health technologies? Are there factors – e.g., financial, cultural, socio-demographic – that could prevent a group or person from gaining access to the medicinal product?
Feasibility	What are the requirements for using the medicinal product in terms of human resources (staff mix and skills), premises, equipment and consumables, information systems and maintenance? How do these requirements differ relative to the comparator(s)? To what extent is the health technology likely to be deemed acceptable to patients, healthcare providers and society at large?
Organizational	How may implementing the medicinal product influence or be influenced by the existing healthcare delivery processes and health system structure? What healthcare management challenges and opportunities may the medicinal product bring?

The GRADE evidence to decision (EtD) framework for coverage decisions provides further guidance on other domains and further guidance is available in the process guide section 5 on Appraisal and

[33] Littlejohns P, Sharma T, Jeong K. Social values and health priority setting in England: "values" based decision making. Journal of health organization and management. 2012 Jun 15;26(3):363-71.
[34] Clark S, Weale A. Social values in health priority setting: a conceptual framework. Journal of health organization and management. 2012 Jun 15;26(3):293-316.
[35] Cochrane Methods Equity: PROGRESS-Plus: https://methods.cochrane.org/equity/projects/evidence-equity/progress-plus

1284 decision-making, as this framework allows for consideration of all forms of evidence together
1285 including values and preferences, to make draft recommendations for coverage decisions.[36]
1286

[36] Parmelli E, Amato L, Oxman AD, Alonso-Coello P, Brunetti M, Moberg J, Nonino F, Pregno S, Saitto C, Schünemann HJ, Davoli M. GRADE Evidence to Decision (EtD) framework for coverage decisions. International journal of technology assessment in health care. 2017 Jan;33(2):176-82.