EU HTA Regulation for oncology medicines: Learnings from a simulation on the impact of proposed EUnetHTA21 methods

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Executive Summary

The European Union (EU) HTA Regulation (Regulation (EU) 2021/2282) was adopted in December 2021 with the main aims to improve the availability of innovative health technologies for patients across the EU, ensure an efficient use of resources and strengthen the quality of HTAs. The Regulation will start to apply in less than 12 months' time, on 12 January 2025, following a three-year implementation period.

The Regulation applies across all 27 Member States (MS) of the EU and introduces a Joint Clinical Assessment (JCA) of relative effectiveness of the relevant product as a key pillar, with new oncology therapies and advanced therapy medicinal products (ATMPs) the first health technologies to go through the system in January 2025. However, the product value rating and subsequent reimbursement and pricing decisions will remain within the remit of individual MS. As methods of assessment differ across MS, EUnetHTA21, a consortium of 13 European HTA bodies, was contracted by the European Commission (EC) to propose methodological and process guidelines for the future process. As of September 2023, the responsibility of overseeing the future joint EU HTA work has transitioned to the HTA Coordination Group (HTACG) of Member States. The HTACG is expected to complete the final methodological guidelines for the future JCA system by the end of 2024.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) Oncology Platform (EOP) brings together a group of health technology developers (HTDs) in the oncology area to undertake work on oncology specific policy issues. The EOP group conducted a simulation to assess the potential impact of the methods proposed by EUnetHTA21 guidelines for JCAs and have applied these to three currently approved and reimbursed oncology treatments (including an ATMP) based on the data package available at the time of their marketing authorisation.

This paper offers learnings and proposes recommendations to the EC and MS representatives as the final procedures, methods and process guidelines are defined for upcoming JCAs in oncology.

Method

The approach included a simulation of the scoping process to predict populations, the intervention, comparators, and outcomes (PICOs) based on EUnetHTA21 scoping proposal (v1.1); secondly, an analysis of the evidence available against the EUnetHTA21 proposed JCA methodological guidelines; and, thirdly, a simulation of likely JCA report findings relating to the underlying methods used and validity of evidence.

The three products selected are oncology treatments authorised by the EMA between 2017 and 2021 and broadly representative of oncology therapies expected to undergo a JCA. Additional selection criteria included availability of HTA reports in France, Germany, Italy and Spain, and EFPIA members' permission for inclusion. The selected products include a mix of orphan/non-orphan therapies, ATMP/non-ATMP, haematological/solid cancers and technologies with randomised clinical trials (RCT) or single arm trials (SAT). Throughout the analysis the identity of the products was known to the study team; for the purpose of this report all products have been anonymised.

Key findings

The simulation of the scoping process resulted in a large number of potential PICOs being identified for each product, ranging from 16 for product X to 22 for product Y, and up to 57 PICOs for product Z. Following a consolidation exercise (removing single country comparator requests), the number of PICOs decreased to 7, 6, and 23 for products X, Y and Z, respectively. It should be noted that both products X and Y are orphan designated and only seven countries were considered in the scoping simulation, therefore overestimating the consolidation possible.

To address the anticipated PICOs for a JCA, all three technologies would require the use of indirect treatment comparisons (ITC) or network meta-analyses (NMA). This includes product Z, where although an RCT was available, the direct evidence only addressed one of the many potential comparators in an evolving treatment environment. Furthermore, real-world evidence (RWE) informed the comparative effectiveness analysis in two of the three products, signalling the importance of observational data in future JCAs. Although the evidence package of all three technologies included overall survival (OS) as a pre-specified endpoint which eventually became available, in most

of the cases analysed, mature survival data was not available at the time of EMA approval; the regulatory and national HTA assessments were based on other oncology-relevant endpoints (ORE) such as progression-free-survival (PFS), patient-reported outcomes (PROs) and adverse events (AEs). First line treatments, like Product Z in a chronic setting, struggle to meet median OS as quickly as later line treatments, and survival may be confounded by the impact of subsequent treatments or cross-over.

Learnings and implications of EUnetHTA21's proposed methods for cancer therapies:

The large number of PICOs resulting from the simulation reflects the highly dynamic therapy area of oncology and the EUnetHTA21 scoping approach. Although the underlying evidence robustness is considered, oncology clinical guidelines often do not make specific treatment recommendations and instead, suggest a range of equally positioned options. This means that many equally positioned comparators may emerge across 27 MS resulting in a large number of PICOs in the majority of oncology JCAs. This will create a significant analytical burden and increase the risk that a HTD may not be able to fulfil the scope requirements, to a high-quality standard, within the short time available.

The high unmet clinical need, including limited treatment options for some diseases as well as poor prognosis of cancer, and the corresponding speed of scientific innovation and knowledge, present unique challenges in clinical development programs for cancer technologies which should be taken into consideration when assessing the evidence provided for a JCA. In the analysis, the available evidence that would inform a JCA would come from either single arm studies with external controls, or from RCTs with direct evidence, but in all scenarios there would be a challenge in meeting EUnetHTA21's proposals for data acceptability and comparisons. The use of indirect evidence, including RWE, to inform external controls is expected to be common in oncology JCAs. In the example of Product Z, where an RCT was available, rapid changes in the treatment landscape led to the comparator deemed appropriate at the time of patient recruitment in the clinical trial no longer being the standard of care at the time of the EMA marketing authorisation application. Given the likely broad range of PICOs and clinical development pathways in oncology, a wide range of evidence synthesis approaches, including NMA and state of the art ITC, in addition to any direct data, will be essential to conduct comprehensive JCAs.

Finally, in oncology, outcomes such as OS often take time to mature and long-term data collection may extend beyond the date of the regulatory approval and JCA submission. Our analysis shows that there is not one single measure which captures all the important outcomes in oncology, and no single measure is without limitations. It will be important that the JCA assessors consider the totality of endpoints available at the time of submission.

Recommendations for a robust and workable JCA process

Meaningful and timely involvement of HTD, clinical experts and patients

The HTD should propose an evidence-based base-case PICO(s) for the JCA based on objective, verifiable data on which patient(s) is most likely to receive the new technology. This can be used to propose relevant comparators that reflect the main standards of care used across the EU. The evidence-based HTD base-case PICO, and contextual background, can be used by JCA assessors as a starting point to enable more transparent and efficient scoping.

Scoping meeting should involve HTD, clinical experts and patients. The scoping meeting should involve the HTACG assessors, the HTD, patient and clinical experts. Involving patient and clinical experts in the scoping can ensure the most representative European treatment practices and relevant patient outcomes are reflected in the final scope. HTDs can add value by providing information on the clinical data in context of the disease, clinical practice evolution through the development program, available evidence within and outside of trials, and regulatory strategy and timelines. An inclusive scoping meeting is an integral enabler of an efficient JCA, which would ensure high quality dossiers, minimise incomplete submissions and result in timely JCA reports with increased uptake nationally.

Optimised evidence-based scoping process

Methodological guidelines on population and comparator selection would improve HTA method harmonisation, transparency and predictability of the scoping process, and make EU HTA more impactful. Guidelines supporting an evidence-based PICO approach to inform national policy questions will help MS complete the survey and create

a transparent scoping process that is predictable for all stakeholders thus resulting in an efficient JCA. A clear PICO consolidation approach, ensuring transparency and reproducibility is recommended. From the analysis, removing the comparators requested by only one MS was effective in consolidating the number of PICO while maintaining a European focus and should be considered as a consolidation method, and should be extended to populations as well.

Comprehensive and flexible advice is critical to accommodate the dynamic treatment landscape in oncology

Scientific advice with HTA bodies is welcomed by HTDs, but it is recommended that capacity be increased so that Joint Scientific Consultations (JSC) are available for all new technologies. Scientific advice with HTA bodies provides HTDs with an opportunity to explore important elements and decisions across clinical development plans. The proposed selection criteria and HTACG's anticipated restricted capacity for JSCs will mean that scientific advice is the exception rather than the norm, diluting the EU's voice in global HTD decision making and potentially resulting in clinical data not being optimised for decision makers across the EU.

The scope of the advice provided within a JSC should be extended providing the opportunity to address issues beyond the pivotal trial design to the overall evidence package, including the best approaches for RWD generation, evidence synthesis techniques and post-registration evidence development plans.

Follow-up scientific advice should be introduced to manage the rapidly evolving oncology treatment landscape, to ensure the evidence package submitted meets the need of the JCA assessors. Ongoing scientific advice is currently offered by EMA and pre-submission HTA dossier advice is offered in Germany; a similar option from the HTACG for European assessments would be highly valuable.

Leverage state-of-the-art methodology and all available evidence

JCA assessors should consider the totality of data submitted, including real-world data and leverage state-of-the-art data synthesis techniques. Based on the simulations, the use of NMAs, ITCs and real-world data (RWD) is likely be the norm rather than exception in oncology due to the scoping approach, likely non-alignment on a single comparator for trials, diversity in oncology treatments, evolving treatment paradigms and variable supporting evidence of historic treatments. Such evidence and methods should be regarded in the context of reducing uncertainty compared to naïve techniques or not using the evidence. As EU JCAs will rely on state-of-the-art HTA methodologies, up-to-date guidelines, adequate capacity, and relevant expertise should be built into the system to ensure high quality JCAs.

Totality of oncology-relevant endpoints should be considered in the EU JCA

JCA assessors should consider all oncology-relevant endpoints (ORE) not just overall survival (OS). As presented above, a variety of important endpoints, beyond OS, are routinely collected and should be considered as they capture different aspects of a treatment on patient lives, as well as downstream relevance for patient-clinician decision-making. For example, PFS is routinely accepted as a relevant clinical endpoint by regulators and clinical societies and may be preferred in measuring treatment efficacy in specific oncology indications. The measurement of OS in oncology has limitations as it can take several years to capture or be confounded by later lines of treatment or cross-over effect. JCA, and in particular the scoping process, should consider all available ORE beyond OS at the time of submission to inform the comparative effectiveness of the technology.

Call to action:

This project is unique as it considered methodologies beyond scoping, simulating a JCA, to understand the implications of EUnetHTA21's proposed methodologies on future JCAs in oncology. In this last year of the implementation of the HTA Regulation, the EOP hopes the outlined recommendations are considered by the EC and HTACG in the finalisation of implementing activities and guidelines, so that the first JCAs are workable for oncology medicines, Member States and ultimately benefit European patients.

1. Introduction

On December 15, 2021, the EU adopted a new regulation on health technology assessment (Regulation (EU) 2021/2282). The objectives of the EU HTA Regulation are to *"…improve availability of innovative health technologies for EU patients, ensure an efficient use of resources and strengthen the quality of HTA. Further the HTAR aims to reduce duplication of efforts for national HTA authorities and industry, facilitate business predictability and ensure the long-term sustainability of EU HTA cooperation." (EC, 2021, Regulation (EU) 2021/2282).* The regulation applies across all 27 MS of the EU.

The EU HTA Regulation establishes four areas of cooperation: EU wide horizon scanning, JSC on clinical study design aspects, voluntary cooperation on non-clinical aspects of HTAs, and, importantly, and probably of greatest impact, the establishment of a JCA of relative effectiveness. The product value appraisal and subsequent reimbursement and pricing decisions remain the remit of individual MS. Analyses already submitted as part of the JCA cannot be requested again by MS. However, MS can request additional analyses for the purposes of their national appraisal and decision making. Oncology medicines and ATMPs will be the first products subject to the JCA from January 2025, with other groups of medicines phased in thereafter.

The EC contracted a consortium of 13 HTA bodies (known as "EUnetHTA21") to assist the HTACG of MS and EC to prepare for the implementation of the regulation. The HTACG is comprised of representatives from MS (mainly from HTA authorities and bodies) and supported the EC, as secretariat. Throughout 2022, EUnetHTA21 coordinated a series of consultations on the proposed methods, followed by the publication of methodological guidelines applicable across all therapeutic areas.

The final procedures will be set by the EC-led implementing acts covering the JCA and JSC processes, interactions of HTACG and EMA and conflicts of interest. These implementing acts are scheduled to be finalised by the end of 2024. Although they will provide the final procedural steps, the HTA methodology for assessments is the responsibility of the HTACG, which is anticipated to adapt the EUnetHTA21 guidelines into final methods.

A major output of the regulation, the EU JCA is a mandatory clinical assessment which will be conducted jointly by MS. *"The JCA constitute a scientific analysis of the relative effects of the health technology on the health outcomes against the chosen parameters which are based on the assessment scope. The scientific analysis will further include consideration on the degree of certainty of the relative effects, taking into account the strengths and limitations of the available evidence" (Official Journal of the EU, 2021, Regulation (EU) 2021/2282).*

The EFPIA Oncology Platform brings together a group of HTDs in the oncology area to undertake joint work on important policy issues. The objective of this report is to explore the potential implications and impacts of the proposed JCA methodologies and approaches on future oncology medicines based on a simulation of EUnetHTA21's proposed methods on three currently approved and reimbursed oncology treatments, including one ATMP. Based on the learnings from the simulation, the report recommends changes to ensure that patients with cancer across the EU have access to innovative new treatments.

1.1 Objectives

1. To explore the impact of the EUnetHTA21 proposed methods for JCAs including PICO scoping, data synthesis and use of RWD on three currently approved oncology products, including an ATMP.
2. To propose recommendations to improve the efficiency of the JCA process and ensure the aims of the EU HTA Regulation are achieved.
3. To identify calls to action for stakeholders to ensure that JCAs support MS decision making relating to innovative oncology medicines.

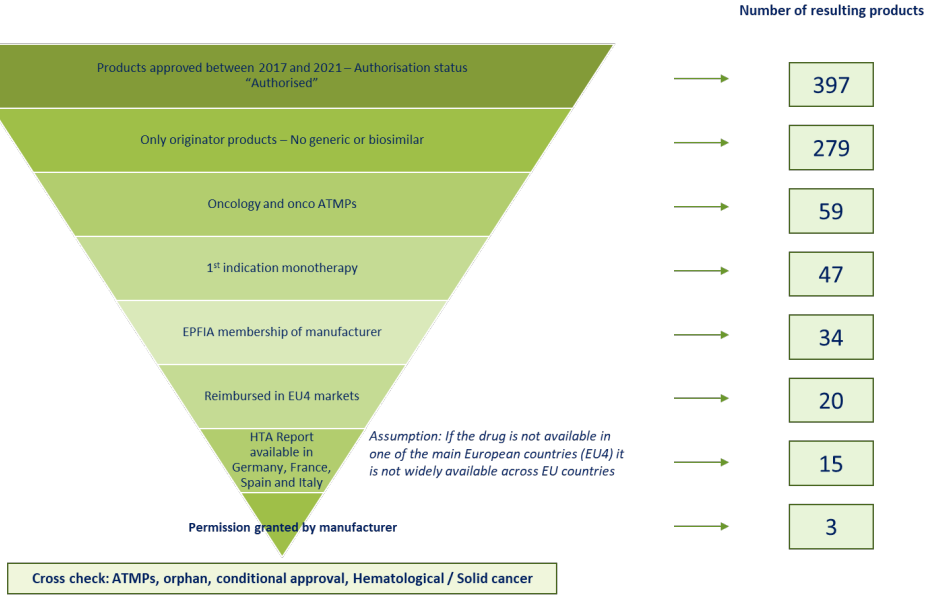
2. Methods

The analysis included three phases: firstly, simulation of the scoping process in terms of PICO and consolidation, secondly, analysis of evidence available against the methodological requirements of the JCA, and thirdly, simulation of likely JCA report findings. Following completion of the analysis, the technologies selected were anonymised for the development of this review paper.

2.1. Product Selection Process

Oncology products authorised by the EMA between January 2017 and the end of December 2021 were identified. Filters were then applied to focus on representative therapies that would undergo a JCA, using the following selection criteria: originator medicinal products, initial marketing authorisation for monotherapy, reimbursement across EU, HTA report availability in a selection of EU HTA archetypes (France, Germany, Italy and Spain), EFPIA membership of manufacturers, and manufacturer's permission for inclusion. The selection was also cross-checked to ensure a range of technical challenges were captured and included orphan/non-orphan, ATMP/non-ATMP, haematological/solid cancers and trials with RCT or SAT. Figure 1 shows the step-by-step product selection process.

Figure 1. Approach to product selection



2.2. Simulation of the Scoping Process

Figure 2. Simulation of the scoping process

a. A product profile (PP) was developed based on the European Public Assessment Report (EPAR) and publicly available data.
b. EU clinical guidelines at the time of EMA marketing authorisation were analysed to identify the potential and most likely comparators based on SoC at the time.
c. PICOs were created based on all the information collected.
d. Local clinical guidelines in France, Germany, Italy, Spain, Romania, Ireland, Sweden and Poland at the publication of the EPAR plus HTA reports for each case study were analysed to identify the potential comparators based on local SoC at the time of MA. These countries were selected in order to have a representative sample of EU MS

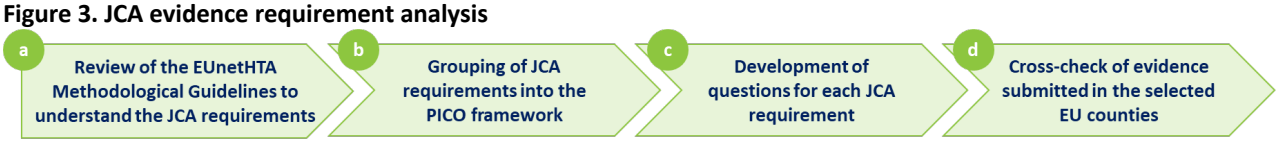
in terms of HTA archetype, size of country and geographic location. If relevant local guidelines were not available, the EU PICO table was used as a proxy for the proposed country PICO survey.

e. PICO consolidation was simulated, by removing duplicates and comparators mentioned by single markets to identify a likely set of PICOs that could specify the scope of the JCA and the data requirements for the HTD.

f. Based on the content of EUnetHTA Scoping Guideline (v1.1) and lack of transparency to methods applied in the EUnetHTA21 scoping pilots, it was not possible to further consolidate beyond removing single country requests.

2.3. JCA Evidence Requirements Analysis

Figure 3. JCA evidence requirement analysis



a. EUnetHTA21 methodological guidelines were reviewed to identify the proposed JCA requirements and key issues. The EUnetHTA21 guidelines reviewed included:
   - Practical Guideline D4.2 Scoping Process (EUnetHTA21, 2022),
   - Practical Guideline D4.3.1 Direct and Indirect Comparisons (EUnetHTA21, 2022),
   - Methodological Guideline D4.3.2 Direct and Indirect Comparisons (EUnetHTA21, 2022),
   - Practical Guideline D4.4 Outcomes (EUnetHTA21, 2023),
   - D4.5 Applicability of Evidence-practical guideline on multiplicity, subgroup, sensitivity and post hoc analyses (EUnetHTA21, 2022),
   - Practical Guideline D4.6 Validity of Clinical Studies (EUnetHTA21, 2022).

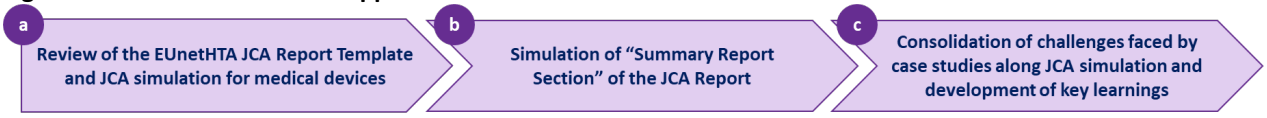
b. A framework was created to capture the data available from the pivotal study against final PICOs and proposed JCA methodological guidelines for each selected oncology treatment. The JCA requirements were expressed across a modified PICO framework including population, intervention, comparator, outcomes, study design, real world evidence, and applicability of evidence.

c. Questions were developed for each JCA requirement to aid exploration of data availability and feasibility of analysis to address the JCA requirements and analysis questions for the case studies.

d. The evidence submitted for EMA approval was captured and any challenges of meeting JCA requirements were identified and local publicly available HTA appraisals were reviewed.

2.4. JCA Simulation

Figure 4. Simulation of the JCA appraisal



a. The EUnetHTA21 guidelines for the JCA Report Template and the JCA Pilots (EUnetHTA21 June 2023, EUnetHTA21 July 2023) for medical devices were reviewed to understand the evidence and methodological aspects that could emerge in future JCAs.

b. To simulate how JCAs will be conducted only the evidence available at time of EMA marketing authorisation was considered. This is important as in each case significant additional data have been generated since MA. Any data available after the MA were not considered.

c. The outcomes from the JCA evidence requirement analysis were presented in the JCA Summary Report Template for each case study. Aspects highlighted included a recap of the consolidated assessment scope, evidence available to fulfil the proposed PICOs, and potential uncertainties.

d. The challenges faced in the JCA simulation were consolidated and key learnings developed based on the most frequent observed gaps.

3. Results

The table below provides an on overview of the case studies including orphan drug designation status, ATMP status, target tumour and data package. All technologies included in the simulation have been anonymised in the report but were known by the study team who had access to full publicly available data on the technologies.

Table 1. Overview of the three selected case studies

Product	EMA approval	EMA Orphan Drug Designation	ATMP	Target tumour	Data Package
Product X	Full	Yes	No	Solid tumour in a metastatic stage	Phase 2, open label, single arm trial, external control arm and RWD
Product Y	Full	Yes	Yes	Haematological tumour in late-line setting	Phase 2, single arm trial, RWD study
Product Z	Full	No	No	Haematological tumour in 1L setting	Phase 3, open label, randomised controlled trial, systematic literature review

Abbreviations: 1L: First line, RWD: Real world data

3.1. Simulation of the PICO scoping process

Multiple potential PICOs were identified for each product including, in one case, comparators without a marketing authorisation for the indication. The table below identifies the PICOs that could be requested as the scope of each JCA based on the EU and local treatment guidelines at the time. The PICO identification process considered each population and the respective comparator and population as a single PICO, whilst outcomes did not contribute to the PICO number.

Table 2. Simulation of the PICO scoping process for the three case studies

Category	Product X Orphan therapy for solid tumour in a metastatic stage	Product Y Orphan ATMP for haematological tumour in 3L+ setting	Product Z Haematological tumour in 1L+ setting
Population	2 populations	10 populations	10 populations
Comparator	16 PICOs made up for 2 populations and 15 unique comparators • 14 comparators for patients with metastatic disease in 1L • 2 comparators for patients with metastatic disease in 2L+	22 PICOs made up of 10 populations and 8 unique comparators • 14 comparators for patients eligible for transplant (across 3 populations) • 8 comparators for patients not eligible for transplant (across 7 populations)	57 PICOs made up of 6 populations and 23 unique comparators • 8 comparators for patients with mutation “a” • 15 comparators for patients with mutation “b” • 10 comparators for patients with mutation “c” • 6 comparators for patients with mutation “d”

Category	Product X Orphan therapy for solid tumour in a metastatic stage	Product Y Orphan ATMP for haematological tumour in 3L+ setting	Product Z Haematological tumour in 1L+ setting
			• 13 comparators for patients with mutation "e" • 5 comparators for patients with mutation "f"
Outcomes	5 outcome categories*	7 outcome categories*	5 outcome categories*
Resulting number of PICOs	16 PICOs	22 PICOs	57 PICOs
Consolidated PICOs (if comparators with single country responses removed)	7 PICOs	6 PICOs	23 PICOs
Observations	At the time of assessment, 14 treatment options are mentioned for 1L, but none have national or EMA approval in 1L	At the time of assessment, European and local guidelines recommend specific treatments for patients (mainly palliative care and ASCT)	At time of launch few European or local guidelines recommended targeted treatment (just chemotherapy). Updated local and ESMO guidelines at time of HTA assessment added additional set of PICOs

Abbreviations: 1L: First line, 1L+: First line or more, 2L+: Second line or more, ASCT: Allogeneic stem cell transplantation, EMA: European Medicines Agency, ESMO: European society for medical oncology, HTA: Health technology assessment, PICOs: Population, intervention, comparator, and outcomes

*Please note that safety and patient reported outcomes (PROs) have been included as a single outcome category. However, in the EUnetHTA21 Submission Dossier Template several safety outcomes and PROs outcomes are required. Outcomes mentioned in the table are likely underestimated as based on analysis of clinical guidelines and HTA reports of the three case studies that might not reflect the totality of the endpoints considered for the evaluation of the three products at the time of assessment.

3.2. Evidence requirement analysis for the JCA Report

Table 3 shows the JCA requirements based on the EUnetHTA21 methodological guidelines listed in Section 3.3. The generated evidence to support JCA requirements, includes the data that would have been available at the time of regulatory assessment and does not include later data readouts.

Table 3. Evidence requirement analysis for the JCA report for Product X

Question category	JCA Requirement	Analysis questions	Generated evidence to support JCA requirements
Population	D4.2 (Scoping) HTD provides evidence for all the populations provided by the members states in the PICOs	Would the HTD have been able to submit evidence for all populations predicted in the PICOs? Were representative European geographies included in the pivotal clinical trial?	Yes (1L and 2L+) 7 countries, 4 of them EU (FR, DE, IT, ES)

Question category	JCA Requirement	Analysis questions	Generated evidence to support JCA requirements
Comparator	D4.2 (scoping) HTD provides evidence for all comparators provided by MS in the PICOs D4.3 (comparators and comparisons) If HTD does not provide evidence for all comparators provided in the PICOs, ITC can be conducted but needs to meet JCA method requirements*	Would the HTD have been able to submit evidence, either direct or indirect for each comparator predicted in the PICOs using acceptable methods? Did the trial comparator match the current SOC?	Single arm study with no direct comparison to placebo or active molecule Multicentre, multi-country, retrospective, observational study provides naïve indirect comparison to chemotherapy.
Outcomes	D4.2 HTD provides evidence for all outcomes provided by MS in the PICOs D4.4 HTD recommends use patients centered outcome measures and use of validated surrogate measures only if necessary. Evidence for a patient-centered outcome such as morbidity, overall mortality and health related quality of life e.g. SF-36, EQ-5D should be requested during the scoping process.	Are the endpoints that correspond to predicted PICO outcomes aligned with JCA methods?	Outcomes represent main ones tested for oncology orphan therapies (ORR, DOR, OS, PFS). Primary endpoints ORR and DRR are surrogate endpoints.
Study design	D4.6 HTD trial data is from adequate RCT which is considered gold standard with low risk of bias The certainty of effectiveness results is determined by three concepts: internal validity, applicability and statistical precision. Cochrane ROB 2 assessment needs to be provided in JCA and could be impacted by non-RCT and open label design	Would there have been challenges related to the study design?	RoB would be deemed to be high due to the single arm study design and the Cochrane ROB 2 was not completed or requested at the time of submission.
Real world data	D4.6 If RWD is used, HTD should give details on the validity and reliability of RWD for adequately answering a given research question, especially the potential use of proxy variables, the risk of attrition bias, and the adequate measurement of endpoints.	If RWD was submitted, did the HTD demonstrate validity and reliability of the RWD submitted for the specific PICO(s)?	Multicentre, multi-country, retrospective, observational study provides naïve indirect comparison to chemotherapy and outcomes for 1L and 2L+ therapy. Divergences in terms of ORR in registry and clinical experience Geographic difference shows lack of consensus. Different baseline patient characteristics e.g., stage of disease/age

Question category	JCA Requirement	Analysis questions	Generated evidence to support JCA requirements
Applicability of evidence	D4.5 HTD need to meet general JCA reporting requirements for multiple hypothesis testing and subgroup analysis in JCA.	Were the subgroups and outcomes defined clearly in the pivotal trial?	Population, subgroups and endpoints clearly defined in protocol. Subgroups not powered for subgroup analysis. Immaturity of patient centred results e.g. OS and interim analysis in patient subgroups (1L).

Abbreviations: 1L: First line, 2L+: Second line or more, , DE: Germany, DOR: Duration of response, ES: Spain, FR: France, HRQoL: Health related quality of life, HTD: Health technology developer, IT: Italy, ITC: Indirect treatment comparison, JCA: Joint clinical assessment, NMA: Network meta-analysis, ORR: Overall response rate, OS: Overall survival, PFS: Progression free survival, PICO (s): Population, intervention, comparator and outcomes, ROB: Risk of bias, RWD: Real world data, SF-36: 36 Item Short Form Survey

Table 4. Evidence requirement analysis for the JCA report for Product Y

Question category	JCA Requirement	Analysis questions	Generated evidence to support JCA requirements
Population	D4.2 (Scoping) HTD provides evidence for all the populations provided by the members states in the PICOs	Would the HTD have been able to submit evidence for all populations predicted in the PICOs? Were representative European geographies included in the pivotal clinical trial?	Yes 3 European countries (FR, DE, NL)
Comparator	D4.2 (scoping) HTD provides evidence for all comparators provided by MS in the PICOs. D4.3 (comparators and comparisons) If HTD does not provide evidence for all comparators provided in the PICOs, ITC can be conducted but needs to meet JCA method requirements*.	Would the HTD have been able to submit evidence, either direct or indirect for each comparator predicted in the PICOs using acceptable methods? Did the trial comparator match the current SOC?	Single arm study with no direct comparison to placebo or active molecule. Indirect comparison between data from phase II and retrospective analysis of pooled historical data of patients with aggressive refractory haematological tumour.
Outcomes	D4.2 HTD provides evidence for all outcomes provided by MS in the PICOs. D4.4 HTD recommends use patients centered outcome measures and use of validated surrogate measures only if necessary. Evidence for a patient-centered outcome such as morbidity, overall mortality and HRQoL e.g. SF-36, EQ-5D should be requested during the scoping process.	Are the endpoints that correspond to predicted PICO outcomes aligned with JCA methods?	Outcomes represent main one's tested for oncology orphan therapies (ORR, DOR, OS, PFS, CR) Relevant efficacy data achieved in short term for CR and OS in life-threatening clinical situations. Lack of analysis of PFS, CR due to single-arm study design. Additionally, the analysis of PFS did not consider the symptoms perceived by the patient and only considered morphological, imaging features of the tumor extent or growth.

Question category	JCA Requirement	Analysis questions	Generated evidence to support JCA requirements
Study design	D4.6 HTD trial data is from adequate RCT which is considered gold standard with low risk of bias The certainty of effectiveness results is determined by three concepts: internal validity, applicability and statistical precision. Cochrane ROB 2 assessment needs to be provided in JCA and could be impacted by non-RCT and open label design	Would there have been challenges related to the study design?	Risk of bias would be deemed to be high due to the single arm study design and the Cochrane ROB 2 was not completed or requested at the time of submission.
Real world data	D4.6 If RWD is used, HTD should give details on the validity and reliability of RWD for adequately answering a given research question, especially the potential use of proxy variables, the risk of attrition bias, and the adequate measurement of endpoints.	If RWD was submitted, did the HTD demonstrate validity and reliability of the RWD submitted for the specific PICO(s)?	Patient pooled retrospective analysis with integrated data from 2 randomised phase 3 studies and 2 observational studies. Data provided context for interpreting the clinical results and an ITC. ITC highlighted the heterogeneity between patient populations and missing patient characteristics data. Issues with interpreting outcomes results and uncertainty of relative effect
Applicability of evidence	D4.5 HTD need to meet general JCA reporting requirements for multiple hypothesis testing and subgroup analysis in JCA.	Were the subgroups and outcomes defined clearly in the pivotal trial?	Population, subgroups, and endpoints clearly defined in protocol. Robust results for OS at 24 months

Abbreviations: CR: Complete response, DE: Germany, DOR: Duration of response, FR: France, HRQoL: Health related quality of life, HTD: Health technology developer, ITC: Indirect treatment comparison, JCA: Joint clinical assessment, NL: Netherlands, NMA: Network meta-analysis, ORR: Overall response rate, OS: Overall survival, PFS: Progression free survival, PICO (s): Population, intervention, comparator and outcomes, ROB: Risk of bias, RWD: Real world data, SF-36: 36 Item Short Form Survey

Table 5. Evidence requirement analysis for the JCA report for Product Z

Question category	JCA Requirement	Analysis questions	Generated evidence to support JCA requirements
Population	D4.2 (Scoping) HTD provides evidence for all the populations provided by the members states in the PICOs.	Would the HTD have been able to submit evidence for all populations predicted in the PICOs? Were representative European geographies included in the pivotal clinical trial?	Partially for two of the six mutations. North America, Western Europe, Other.

Question category	JCA Requirement	Analysis questions	Generated evidence to support JCA requirements
Comparator	D4.2 (scoping) HTD provides evidence for all comparators provided by MS in the PICOs. D4.3 (comparators and comparisons) If HTD does not provide evidence for all comparators provided in the PICOs, ITC can be conducted but needs to meet JCA method requirements*.	Would the HTD have been able to submit evidence, either direct or indirect for each comparator predicted in the PICOs using acceptable methods? Did the trial comparator match the current SOC?	Direct comparison against chemo-immunotherapy comparator identified in PICOs. Other identified comparators are not included for the different sub-populations. ITC via NMA included nine comparative studies in 1L was uncertain because of several reasons such as: study heterogeneity, uncertainty in rationale of selected comparators, exhaustiveness of the chosen studies, different study definitions and measurement of PFS, etc.
Outcomes	D4.2 HTD provides evidence for all outcomes provided by MS in the PICOs D4.4 HTD recommends use patients centered outcome measures and use of validated surrogate measures only if necessary. Evidence for a patient-centered outcome such as morbidity, overall mortality and health related quality of life e.g. SF-36, EQ-5D should be requested during the scoping process.	Are the endpoints that correspond to predicted PICO outcomes aligned with JCA methods?	Outcomes represent main ones tested for oncology therapies (OS, PFS, ORR, TTNT, HRQoL, safety). For HTA bodies requiring evidence of surrogacy for a patient centred outcome, clinical outcomes, such as PFS, will require additional supportive information.
Study design	D4.6 HTD trial data is from adequate RCT which is considered gold standard with low risk of bias The certainty of effectiveness results is determined by three concepts: internal validity, applicability and statistical precision. Cochrane ROB 2 assessment needs to be provided in JCA and could be impacted by non-RCT and open label design.	Would there have been challenges related to the study design?	Open label nature of phase 3 RCT could introduce follow up bias for HRQoL endpoints, PFS and safety. RoB 2 was not completed or requested at the time of the original submission for the systematic review and NMA.
Real world data	D4.6 If RWD is used, HTD should give details on the validity and reliability of RWD for adequately answering a given research question, especially the potential use of proxy variables, the risk of attrition bias, and the adequate measurement of endpoints.	If RWD was submitted, did the HTD demonstrate validity and reliability of the RWD submitted for the specific PICO(s)?	No real or observational studies submitted but indirect evidence submitted from NMA based on the outcomes of a comprehensive systematic literature review.

Question category	JCA Requirement	Analysis questions	Generated evidence to support JCA requirements
Applicability of evidence	D4.5 HTD need to meet general JCA reporting requirements for multiple hypothesis testing and subgroup analysis in JCA.	Were the subgroups and outcomes defined clearly in the pivotal trial?	Population, subgroups and endpoints clearly defined in the clinical trial protocol. PFS difference was statistically significant but was not reached at 28 months. OS data was immature. PROs may be reviewed as being subject to bias due to the open label design of the trial.

Abbreviations: 1L: First line, HRQoL: Health related quality of life, HTD: Health technology developer, ITC: Indirect treatment comparison, JCA: Joint clinical assessment, NMA: Network meta-analysis, ORR: Overall response rate, OS: Overall survival, PFS: Progression free survival, PICO (s): Population, intervention, comparator and outcomes, ROB: Risk of bias, RWD: Real world data, SF-36: 36 Item Short Form Survey, TTNT: Time to next treatment

3.3. Discussion of the results and key challenges

PICO scoping challenge: significant number of PICOs were identified due to the application of the proposed additive approach to a highly dynamic landscape of oncology and treatments.

Numerous PICOs were identified for each case study, due to diversity in standards of care and recommendations in local clinical guidelines across the EU. Furthermore, although an evidence-based approach is considered in clinical guidelines, equal positioning of treatment options is also frequently encountered in oncology clinical guidelines and can be anticipated to create significant variations in clinical practice, including when there is no clear SoC. The challenge this creates for compiling the evidence required for a JCA submission, either directly from the pivotal trial(s) or through ITCs/NMAs, is clearly demonstrated in our case studies. For example, in the case of Product Z (a first line treatment setting for a haematological tumour with a number of subpopulations), the availability of multiple alternate treatment options, including targeted therapies and other chemotherapy regimens, led to the generation of 57 potential PICOs when combining subpopulations and comparator options. Additionally, HTDs are increasingly creating new treatment options in later lines across different tumours, in settings where treatment options are limited, and clinical need is extremely high. In these cases, a variety of earlier lines of equally positioned therapy options could be considered as additional, different populations with different relevant comparators, further complicating the challenge of predicting PICOs to inform pivotal clinical trial designs and at a late point, the JCA dossier submission. This was demonstrated by Product Y, an ATMP in a later line setting for a haematological tumour, for which 22 PICOs were generated, due to multiple prior treatment pathways resulting in multiple different patient populations, subpopulations (10 subpopulations were identified) and comparator options prior to consolidation. Considering the strength of evidence supporting different treatment options (i.e. NCCN evidence blocks) and the proportion of usage across the European Union could be options to minimise the number of PICO while ensuring the most relevant comparators are considered.

Product X, a treatment for a rare tumour in the metastatic stage, highlights another practical challenge for HTDs and researchers relating to the proposal to include off-label treatment options as potential comparators within a JCA. In this case, no appropriate comparator was identified by regulatory bodies as there was no clear SoC in clinical practice due to lack of treatment options. Despite the regulator deeming there is no clear SoC, applying EUnetHTA21's recommended approach yielded 14 potential off-label comparators for patients with metastatic disease in 1L. The conflicting position between regulatory bodies and the EUnetHTA21 proposed scoping guidelines and consequently comparative effectiveness requirements creates significant challenges for HTDs. In such circumstances, use of a comparator in line with clinical guidelines with a poor evidence base would not be requested by regulators; but by not developing the evidence, will impact HTA assessment and consequently patient access. Such zero-sum situations are extremely difficult for HTDs to navigate and can be anticipated frequently in oncology especially as new

treatments target increasingly later lines of therapy, where there may be no approved treatment and no clinical consensus. It can also be expected that undertaking indirect comparisons against off-label treatments with a likely poor evidence base will be extremely challenging. Therefore, the opportunity to seek advice through a JSC on the clinical program but also for evidence generation plans outside of the trial would be very valuable. As these challenges are likely to be common in oncology, it is imperative there is enough JSC capacity and expertise on evidence synthesis available within the advice procedure.

The impact of fast-paced development of oncology is evident in the case of Product Z where at the time of regulatory registration, very few European guidelines recommended targeted treatments. However, at the time of its launch, an updated version of the ESMO guideline had been published along with updated national guidelines which added an additional set of comparators to the existing PICOs. Although a direct comparison versus one comparator was possible from the clinical trial data, the ITC provided the overwhelming comparative data for the remaining PICOs required to inform the appraisal by HTA bodies across the EU.

The final number of PICOs in the JCA scope is expected to be highly influenced by any consolidation step; it is currently unclear how PICOs consolidation will be done, though a specific methodology may be developed by the HTACG. A clear, harmonised, evidence-based approach to inform national policy questions when selecting populations and comparators, with a focus on prioritising the most impactful PICOs (e.g. most patients covered by the PICOs, and/or most commonly used comparators) during the consolidation process will be essential to manage the potentially large number of PICOs within the timeframe and with the available resources. Without a clear consolidation process and methodology, assessors could potentially reach their own subjective and arbitrary decisions when consolidating PICOs. This would result in a lack of transparency and introduce inconsistency between JCAs. Likewise, there is a need for methodological guidelines on scoping to ensure MSs are applying an evidence-based and consistent approach in setting national policy and subsequent PICO requirements. The current lack of clarity also makes it hard for HTDs to anticipate the likely JCA scope, which will compromise HTDs ability to inform decisions on the clinical development program and ability to develop appropriate evidence packages, resulting in unnecessary upfront resource use and decreased efficiency. Transparent PICO consolidation and harmonisation across all MS of a single PICO would enable the EU to have a strong voice within global clinical development program decisions and a clear focus of the evidence generation needs for the EU. This would require early engagement with HTDs to explore the optimal PICO. Persistence with the non-harmonised scoping approach and the resulting inefficiencies introduced by a lack of transparency and predictability in scoping and its consolidation, are in contradiction to the objectives of the HTA Regulation which aims to improve existing inefficiencies, minimise divergences in national methodologies of assessments (Article 6), and in turn, may lead to a lack of business predictability, higher costs and, in the long run, negative effects on innovation (Article 13) (Regulation (EU) 2021/2282).

Across all case studies, a consolidation approach was undertaken where comparators with a request from a single country were removed, reducing the number of potential PICOs significantly. This led to a reduction of PICOs from 16 to 7 for Product X, 22 to 6 for Product Y and 57 to 23 for Product Z. This is an example of just one consolidation approach, which could be taken and has shown to be effective at reducing the number of PICOs. It should be noted, however, that this research was only based on eight MS and when rolled out to all 27 MS, this approach may be less effective. The concept of eliminating single MS requests could also be extended to subpopulations. More evidence-based approaches to scope consolidation will be required focussing on either the most relevant comparators for the majority of patients, and populations that are clinically relevant in current clinical practice.

Dynamic nature of oncology development and variable treatment influencing trial design and conduct will impact the feasibility of meeting all the requirements of the proposed JCA methods.

Within the Regulation (Article 35) (Regulation (EU) 2021/2282) and JCA methods there is a preference for RCTs which the EUnetHTA21 guidelines consider to be the gold standard. Ideally, evidence should be developed based on well-designed and conducted RCTs comparing an investigational treatment to a widely agreed SoC. However, as we have already discussed, in many instances in oncology, due to the rapid advances in scientific knowledge, there is no "widely agreed SoC". Therefore, there are many practical challenges when designing and conducting RCTs in oncology such as identifying a comparator that will reflect the current SoC globally and that will still be relevant at the time of marketing authorisation. Furthermore, conducting RCTs in oncology often involves a thoughtful balance between

developing the required clinical data and the time required to do this, especially in areas of high unmet medical need, frequently requiring complex trade-off decisions. Cancer treatment is moving towards more targeted therapies as fundamental molecular pathways are identified along with new specific targets potentially common to multiple cancer types. Increasing use of targeted therapies is changing which patients and cancers may benefit based on specific biomarkers and genetic profiles. Adaptive trial designs are becoming more common, allowing opening and closing of cohorts quickly based on surrogate endpoints to efficiently explore activity and efficacy on different subgroups of patients. Adjuvant and neoadjuvant therapies are becoming increasingly common in oncology prolonging survival either through curing the disease or by slowing its recurrence and reducing cancer-related symptoms. Such therapies can complicate the design of trials for therapies used before or after the intervention especially when considering the relative contribution of each therapy to efficacy and safety outcomes.

Regulatory approvals based on evidence from single-arm trials in oncology have occurred where there is a high unmet clinical need due to a lack of alternate potential active comparator treatments and where the natural course of the cancer and scientific advances regarding the mechanism of action is well understood with high response rates (the latter often requires confirmatory RCT data by the EMA). In such instances and given the lack of active comparator, beyond supportive care, in disease areas outside of cancer, a placebo-controlled study might be preferable.

However, the use of single arm trials in oncology becomes the only realistic option for HTDs when facing ethical challenges like in case of randomisation to an off-label treatment in the comparator arm with limited robust information, randomisation to a treatment that is now known to have less benefit than new ones, or randomisation to best supportive care (BSC) which could lead to poor prognosis whereas the new treatment has evidence of activity. In addition, it should be considered that conditional approvals based on single arm trials often require confirmatory data in many oncology cases. These practical and ethical challenges were highlighted in our analysis of Products X and Y both of which were approved by regulators on the basis of phase 2 single arm trials (SAT).

In cases of rare diseases, identifying and recruiting sufficient patients to take part in a RCT can be very challenging. In the absence of highly specialist clinical centres “concentrating” patients into a manageable number of potential research centres, recruitment requires engagement of many sites with small numbers of potential participants and possibly few resources to conduct complex oncology trials. Due to monitoring of cancer progression and tolerability management, oncology studies frequently require far more study visits than typical non-oncology studies, placing resource pressures on smaller sites limiting their participation. Oncology studies are increasing involving precision medicine treatment options. This means that patients are eligible to participate only if they have the specific molecular profile or tumour type. Due to these requirements, such trials typically recruit a very small proportion of those screened, adding to the operational challenges of conducting RCTs. These practical challenges are typified through the example of Product X, a treatment for a rare solid tumour in the metastatic disease setting, approved based on a phase 2 SAT. In this instance both the rarity of the disease and the very high unmet clinical need meant that recruiting sufficient patients to take part in a RCT would have been highly challenging resulting in a very lengthy delay in bringing a highly effective treatment in a very challenging setting, to patients. In situations such as these the EMA (EMA/CHMP/564424/2021, 2023) and FDA (JAMA Oncol, 2023) are accepting of the use of SATs.

Product Y, an ATMP for a rare haematological tumour in a late-line setting, highlights similar challenges in the feasibility of conducting an RCT. The treatment was unconditionally approved by the EMA on the basis of a SAT for patients who relapse after two or more lines of therapy, a setting in which there is a lack of alternate treatments and where the natural course of the disease is well understood in terms of mortality. Again, undertaking an RCT in this setting where the SoC comparator is BSC and not a licensed active treatment, would be extremely challenging from an ethical perspective.

Looking to the future, as ATMPs likely become the SoC in several settings, conducting comparative RCTs will become difficult for additional operational reasons. Firstly, RCTs comparing a one-off ATMP to a chronic treatment or a course of chemotherapy will be potentially difficult in terms of blinding, patient inclusion criteria and treatment randomisation (e.g., a CAR-T therapies are developed for individual patients and having a true control is challenging). In the case of conducting comparative RCTs of one ATMP to another further challenges may occur due to the nature of the manufacture of the treatments requiring the cooperation of a second HTD to manufacture the comparator.

Given the challenges highlighted, it will be important that JCA assessors and co-assessors consider that, in oncology, evidence beyond RCTs need to be used for JCAs to address PICOs and the guidelines should enable flexibility to accept all evidence provided. Although RCTs are the gold standard, data from other types of studies can help mitigate uncertainty and help MS decision making. As our case studies demonstrate, failure to do so will potentially deny patients in the EU access to effective new oncology treatments.

All relevant oncology endpoints need to be considered. OS for example often takes time to mature and long-term data collection may extend beyond the date of the JCA report publication.

In oncology, outcomes are impacted by the time of assessment and require different time frames to generate mature results in clinical trials (which are often event, rather than timeline driven). For this reason, outcomes like OS, which takes time to mature, are commonly secondary endpoints in cancer studies. Typically, a trend can be observed where, for the purposes of the regulatory assessment, it is sufficient to indicate no downstream harm is caused to patients. First line treatments, like Product Z, struggle to meet median PFS or OS as quickly as later line treatments. At the follow up of 28 months, the OS data was immature with only 6% of OS events observed and insufficient to estimate the magnitude of the OS benefit, whilst the statistically significant PFS results (improvement at 30-month landmark PFS of approximately 50% vs comparator, median PFS not reached for Product Z) were used to demonstrate a reliable estimate of efficacy. Whilst in the case of Product Y, where treatment options are exhausted, outcomes are related to the severity of the disease.

ITCs and RWE will be very important in reducing uncertainties of comparisons against multiple comparators, but these methods must be tailored to maximise the ability to reduce uncertainty and support decision making.

Meta-analysis and ITCs will be critical to meet the evidence development requirements of likely multiple PICOs outlined in a JCA scope, especially in oncology for the reasons already outlined. In addition, creation of the counterfactual through a historical control arm (external comparator) mirroring the trial population using data from previous trials, evidence from routine clinical care e.g., via registries, or health claims and electronic health records will be important approaches in circumstances where NMAs and ITCs are not possible or no published evidence of the comparator is available, recognising potential selection bias issues.

To address the likely range of comparators that may be stipulated in the PICO scope of a JCA, ITCs (including the use of historical control arms and RWD) will be the norm, rather than the exception, for JCA for oncology products. However, conducting an ITC is not always feasible due to the limited available data for comparators and the preferred JCA ITC methodologies may not be possible given the evidence available. Off label comparators may be requested to be part of a JCA submission irrespective of the level of evidence available to support their use, likely limiting their ability to be included as direct or indirect comparators.

Our case studies highlight the challenges of meeting rigid methodological guidelines. The ability to use state-of-the art statistical approaches for evidence synthesis is crucial in oncology. In the case of Product Y, an indirect treatment comparison (ITC) was conducted against a patient pooled historical control. This was developed as a companion study alongside the single arm pivotal trial to provide further context. In this case, the ITC was criticised on the basis of patient heterogeneity, lack of systematic analysis of biases involved, and for the lack of consideration of prognostic factors. However, the importance of the context and changing dynamic of the treatment pathway were recognised and considered in the appraisal of the medicine and supporting ITC results by the MS HTA bodies. Our case study with Product Z also demonstrates this recognition of potential uncertainty and its subsequent management. In this case the HTD submitted evidence via an NMA involving nine comparative studies in the first line treatment setting. Although this analysis was also associated with elements of uncertainty created through use of the available data with heterogeneity across studies in respect to comparators, and different measures of response that may have evolved over time. These were taken into consideration during the analysis and consequent MS decision making ensuring patients had access to the treatment.

To support the SAT for Product X, two observational studies were conducted focused on the efficacy of a variety of chemotherapy options in the first- and second-line settings, providing a naïve indirect comparison to the potential SoC. This novel approach to the use of RWD was widely welcomed by MS HTA bodies in the absence of the possibility of generating data by other approaches. It is unclear from the proposed JCA methodology whether such data would

be considered appropriate, given that the results were aggregated for all chemotherapy regimens as naïve comparisons are prone to bias due to confounding. HTDs are unlikely to have access to individual patient data for competitor products due to competition and privacy laws. Methods of comparison using aggregate data exist and should be utilised if this is the only option.

Given the heterogeneity of studies and data commonly encountered across and within different oncological diseases, it will be essential that JCA assessors and co-assessors are able to fully consider the specific circumstances, limitations, and rationale for the evidence package developed by HTDs. Our case studies clearly demonstrate that whilst uncertainties in certain types of data should be identified and acknowledged, they should not preclude consideration to generate the most useful report possible to inform MS decision making.

Attrition bias, ITT and ICH E9 (R1) Addendum on Estimands and Sensitivity Analyses

The EUnetHTA21 D4.6 guideline states that *"The use of ROB-2 does not exclude the possibility of assessing evidence with an analysis strategy that corresponds best to a given PICO question (e.g., for addressing the issue of the adequate management of intercurrent events and missing data), as defined according to the principles of the estimand framework outlined in ICH E9 and its addendum (E9(R1))"*

However, this statement is fundamentally flawed, since the PICO framework does not allow the specification of the intercurrent events, nor of the strategies for addressing them, as reflected in the estimands framework. Furthermore, the ROB-2 tool does not reflect the potential strategies for addressing intercurrent events as described in the ICH E9(R1) Addendum.

The methodological guidelines that the HTACG will issue should recognise that the assessment of the RoB for RCTs, however important, needs to be seen in the context of the trial objectives, thus recognising that strategies that depart from the ITT principle (or treatment policy strategy) may in some cases be more relevant to address the research question of interest.

For example, clinical trials in oncology are often characterised, for ethical reasons, by the possibility of participants to switch to alternative treatments than those they were initially randomised to, e.g., upon disease progression. The estimate of treatment effects in these trials, particularly of long-term outcomes such as OS, has often been analysed using the ITT approach, comparing patient groups based on the treatment they had been randomised to, irrespective of whether treatment switching occurred and whether any subsequent therapy was received. However, an ITT strategy in this context will generate a clinically meaningful comparison of two treatment arms only if subsequent therapies reflect clinical practice in the MS (thus, reflecting the use of the treatment in a real-world context) (Maitz J. et al, 2022). However, in most cases, adjusting for the confounding effects of treatment switching or other intercurrent events on OS will be important to determine an estimate of the "true" survival benefit associated with the new treatment, via established statistical methods (Latimer N.R. et al, 2015).

In summary, strategies that depart from a treatment policy (ITT principle) may be more pertinent and appropriate to answer the research question of interest in oncology trials where treatment switching (or use of rescue medication post-disease progression) takes place. Such strategies would allow estimates of treatment effects in the hypothetical scenarios where treatment switching had not occurred, in other words, adjusting for cross-over.

Sensitivity analyses, as highlighted in the D4.5 guideline, will be important to assess the robustness of the estimate. Consequently, the assessment of the validity of RCTs requires an in-depth understanding of the trial objectives, trial design, data collection, and methods of analysis which should be adequately reported in the JCA report.

When assessing the validity of clinical trials for the purpose of the JCA, no strategy for intercurrent events should, a priori, be seen as only acceptable for supplementary analysis for hypothesis generation or sensitivity analysis in special situations. Against this context, the parallel JSC will be particularly important to reflect the perspectives of different critical stakeholders regarding the relevant estimand strategies, specifically Regulatory Authorities (such as the EMA) and the HTACG.

4. EFPIA Oncology Platform recommendations to predict and mitigate risks identified in the JCA process

The EOP group have provided recommendations for the future JCA process, to address the key challenges/risks identified in the case studies which fall under five key categories:

- Meaningful and timely involvement of HTD, clinical experts and patients.
- Optimised evidence-based scoping process.
- Comprehensive and flexible advice is critical to accommodate for dynamic oncology treatment landscape.
- Leverage state-of-the-art methodology and all available evidence.
- Totality of oncology-relevant endpoints should be considered in EU JCA.

4.1. Meaningful and timely involvement of HTD, clinical experts and patients

HTD to propose evidence-based base-case PICO(s) for the JCA based on objective, verifiable data on which patient population(s) is most likely to receive the new technology. For example, HTDs could use physician research on patients most likely to receive treatment and data on what those patients are currently treated with. The HTD would use these data to propose relevant comparators that reflects the main SoC used across the EU healthcare systems. Information from EU clinical guidelines (e.g. ESMO) may also provide objective, verifiable context and evidence on robustness of supporting data on each comparator's use.

The EU HTA Regulation mandates that the HTACG should adopt methodological guidance on joint work following international standards of evidence-based medicines (Article 7). EFPIA believes that defining the scope of an assessment should also follow the principles of evidence-based medicines. MS define their national PICOs using a policy driven approach, but such policy has to be informed by evidence on actual clinical practice and clinical relevance of populations and epidemiology – the same evidence that HTD would use to provide the base-case PICO(s). Any PICO(s) that are not based on evidence compromise their relevance and may result in additional work for all stakeholders (especially the HTD and assessors/co-assessors) that are not relevant for final decision makers.

The HTD base-case PICO, together with the contextual background evidence, would be used by the JCA assessors and MS for the purpose of the PICO survey. It is therefore a justified input to the scoping process. As such, the survey can be accelerated and would be more effective enabling MS to confirm or amend the base-case PICO, rather than start from scratch. The proposed assessor-led PICO(s) sent to MS should also be shared with the HTD at the same time, increasing transparency and allowing for predictability on likely analyses to be requested.

Scoping meeting should involve HTD, clinical experts and patients. The scoping meeting should involve the assessors, JCA subgroup, the HTD, and relevant patient and clinical experts. Involving patient and clinical experts in the scoping can ensure the most representative European treatment practices and relevant patient outcomes are reflected in the final scope. HTDs can add value by providing information on the clinical data in the context of the disease, clinical practice evolution through the development program, available evidence within and outside of trials, and regulatory strategy and timelines.

The scoping meeting should take place face-to-face and be sufficiently long to allow for meaningful discussions to take place (EUnetHTA JA3 experience showed that scoping meetings should be a minimum of 3 hours long).

Broad expertise from HTDs from various functions (i.e. clinical development, outcomes research) can also provide meaningful insights around treatment practice across MS, objective data on which patient(s) is most likely to receive the new technology and where the new technology is likely to fit into clinical practice and development of endpoints.

An inclusive scoping meeting is an integral enabler of an efficient JCA process, which would ensure high quality dossiers, minimise incomplete submissions and result in timely JCA reports. For HTDs with limited regulatory and market access experience in Europe, it also provides an opportunity to describe the process and what is expected and why.

4.2. Optimised evidence-based scoping process

Methodological guidelines on scoping are required to reduce variations in the process of PICO determination across MS. Guidelines will help MS complete the PICO survey and ensure a harmonised, transparent process that is predictable for all stakeholders resulting in an efficient JCA, reduced work for the assessor and co-assessor, and shorter times for PICO finalisation. In addition, a standardised approach and a unified core European PICO would help HTDs to predict and include the data needs of the European Union in clinical development, within registrational trial design, supporting timely access for patients to innovative medicines.

Scoping process should include a transparent consolidation step to manage the potentially high number of PICOs. The tight timeline envisaged by EUnetHTA21's guideline 4.2 and the relevant implementing act, between the PICO scoping publication and the dossier submission, will require the HTD to proactively prepare its dossier contents before the final scope is shared with it. Thus, a potentially a large amount of upfront analysis could be discarded if not finally required for the purposes of the JCA. Even if there is consolidation of MS PICOs so that not all are requested for the JCA, these analyses can still be requested during country-specific HTA submissions. In such cases, the HTAR is at risk of not meeting its objective of reducing the administrative burden for HTDs, and national HTA bodies. Therefore, it is important that the consolidation step is transparent, specifying what PICOs the MS have asked for (at the very latest upon HTD dossier submission), to improve predictability, manage the potentially high number of PICOs, speed up the scoping process and prepare for local submissions.

The consolidation approach should be clear and non-subjective for JCA assessors and HTD should have transparency of the process. One potential approach could be to remove comparators where there is only a request from a single country. In our analysis, this approach led to a PICO reduction from 16 to 7 for Product X, 22 to 6 for Product Y and 57 to 23 for Product Z, although this final consolidated number may be conservative as it only considered likely PICO request from 8 not the full 27 MS. Another potential approach could be to weight the PICOs based on the availability and robustness of the clinical data available, or comparators used to treat the majority of patients.

4.3. Comprehensive and flexible advice is critical to accommodate the dynamic treatment landscape in oncology

Scientific advice with HTA bodies is welcomed by HTDs, but it is recommended that capacity be increased so that Joint Scientific Consultations (JSC) are available for all new technologies. With the highly dynamic nature of development and scientific progress in oncology, there is no widely agreed SoC, and it can be challenging to identify a comparator that will satisfy this requirement globally. Clinical guidelines often recommend a wide range of therapies with equal positioning which creates significant variations in clinical practice and no clear SoC. Scientific advice from HTA bodies provides HTDs with an opportunity to explore important elements and decisions across clinical development plans. The proposed selection criteria and HTACG's anticipated limited capacity to partake in JSCs will mean that scientific advice is the exception rather than the norm. This will undermine EU's requirements being incorporated in global HTD decision making on clinical development plans and potentially resulting in clinical data not being optimised for decision makers across the EU.

The scope of the advice provided within a JSC should be extended providing the opportunity to address issues beyond the pivotal trial design to the overall evidence package, including the best approaches for RWD generation, evidence synthesis techniques, and post-registration evidence development plans.

Follow-up scientific advice should be introduced to manage the rapidly evolving oncology treatment landscape, to ensure the evidence package submitted meets the need of the JCA assessors. Ongoing scientific advice is currently offered by EMA and pre-submission HTA dossier advice is offered in Germany; a similar option from the HTACG for European assessments would be highly valuable.

4.4. Leverage state-of-the-art methodology and all available evidence

JCA assessors and co-assessors should consider the totality of the evidence including RWD and state-of-the-art data synthesis techniques to address the potentially diverse range of populations and comparators across 27 MS requested in the JCA scope. A wide range of analytical techniques, data sources, and data synthesis approaches are likely to be required. Use of NMAs, ITCs and RWD are likely be the norm rather than exception to address the JCA scope. Similarly, different challenges are likely to be encountered with respect to comparator requirements.

JCA dossier and report template should allow HTD and assessors to contextualise the evidence, explain the context of the disease (i.e., rarity of the disease, unmet medical need, burden of disease, clinical characteristics, and peculiarities of treatment) and the evolution of clinical practice and guidelines from registrational trial planning to JCA dossier submission to allow for a comprehensive analysis of the evidence developed and included in the JCA dossier. This will help ensure JCA reports are informative and valuable for local HTA bodies and decision makers. The rationale for the approach chosen for the use of ITCs and RWE to support comparative effectiveness, could be provided by HTDs, and included in the JCA report.

4.5. Totality of oncology-relevant endpoints should be considered in the EU JCA

JCA assessors should consider all oncology-relevant endpoints (ORE) not just overall survival (OS). A variety of important endpoints, beyond OS, are routinely collected in oncology and should be considered as they capture different aspects of a treatment on patient lives, as well as downstream relevance for patient-clinician decision-making. For example, PFS is routinely accepted as a relevant clinical endpoint by regulators and clinical societies and may be preferred in measuring treatment efficacy in specific oncology indications. The measurement of OS in oncology has limitations as it can take several years to capture or be confounded by later lines of treatment or cross-over effect. In addition, PROs can be measured using cancer-agnostic, cancer-specific or symptom-specific instruments. The value of OREs should be considered and evaluated, by cancer type and stage, to ensure they are fit for purpose, measuring outcomes of high importance to patients, collecting core outcome sets per treatment setting, and using standardised methodologies to collect them. The measurement of overall survival in oncology has limitations as it can take several years to capture or can be confounded by later lines of treatment or cross-over effect. Intermediate endpoints such as PFS are routinely accepted as an endpoint in regulatory processes, are valued by clinical societies and can be preferred in specific oncology indications where long post-trial survival, several post-progression lines of treatment, and treatment crossover could impact or dilute the ultimate OS benefit.

Specifically in oncology, JCA assessors and co assessors should recognise that PFS is both a patient-centred outcome and "an intermediate endpoint that is relevant in its own right", as stated in the EUnetHTA 2015 guideline on Endpoints used for Relative Effectiveness Assessment (JA1). A progression event impacts the course of current and future treatments, providing information on patient prognosis (i.e., based on length of response, refractory status) and healthcare resource utilisation, which are all important metrics on the effect of the technology, providing valuable information for health care systems, clinicians and, most importantly, patients.

The EOP recommends HTACG methods for oncology consider EMA guidelines on the evaluation of anticancer medicinal products (EMA, 2024) which specifies that acceptable primary endpoints include cure rate, OS and PFS or disease-free survival (DFS). When OS is reported as a secondary endpoint, the estimated treatment effect on OS should ensure that there are no relevant negative effects on this endpoint, in most cases by showing trends towards superiority. In situations where there is a large effect on PFS, or if there is a long-expected survival after progression, and/or a clearly favourable safety profile, precise estimates of OS may not be needed for approval. JCAs should consider all available ORE beyond OS at the time of submission to inform the comparative effectiveness of the technology.

5. Conclusions

The unique characteristics and challenges facing HTDs when developing oncology treatments, as demonstrated by the case studies of the three oncology products, should be considered when developing the final procedural and

methodological guidelines for JCAs. From the analysis conducted on the three simulations, we found that the proposed EUnetHTA21 guidelines do not offer the required flexibility and pragmatism to address the challenges of highly dynamic disease areas such as oncology. For an example, the proposed scoping process resulting in numerous PICOs will be a particular challenge in oncology given the variation in treatment availability across MS, the sometimes heterogeneous nature of clinical guidelines and the rapidly evolving treatment landscape. Given the potentially large numbers of comparators likely to be requested during a typical JCA, complex analyses using disconnected networks and ITCs will become a pivotal part of submissions and not an exception. Further, the proposed outcome guidelines emphasise the requirement for mature OS data which will likely not be available for most oncology submissions. The JCA should review the data available at the point of EMA submission and consider the value of intermediate outcomes such as PFS in oncology. Further demonstration of OS may not be possible due to treatment switching and confounding of subsequent treatments needs to be considered.

Within the proposed methods there are no explicit recognition of the challenges facing HTDs with products already in registrational studies which will not conclude until after the JCA is applied. Addressing the changed requirements mid registrational study will be especially difficult, and the JCA assessors and co-assessors should take this into consideration when assessing the first few waves of new treatments to create a fair process.

Call to action

This project is unique in that it considered methodologies beyond scoping, simulating a JCA, to understand the potential implications of EUnetHTA21's proposed methodologies on future JCAs in oncology. In this last year of the implementation of the HTA Regulation, the EOP hopes the recommendations from this paper are considered by the EC and HTACG in the finalisation of the implementing procedures and methodological guidelines, so that the first JCAs are workable for oncology medicines, Member States and ultimately benefit European patients.

Limitations

The clinical trials of the three products were designed for the requirements at the time of launch and a retrospective analysis was conducted to assess how they would have been reviewed in the JCA process. In reality, the HTD would have had foresight of the JCA expectations and could prepare, although would have uncertainty on the final PICOs, thus planning for extensive analyses without further predictability. However, most of the challenges identified are fundamental to the challenges faced in oncology and would remain. In order to conduct this simulation, the researchers considered the evidence requirements and likely PICO requests from only eight EU MS. Therefore, in practice when all 27 MS are involved in JCA scoping, it is reasonable to assume that a larger number of PICO would be identified, as there is the likelihood of more than one MS asking for comparator. Finally, the simulations were done based on EUnetHTA21's proposed guidelines, however, the researchers recognise that the final procedural steps and methodological guidelines for future JCAs will be defined by implementing acts and HTACG methodological guidelines, which may differ.

APPENDICES

Appendix 1. Detailed JCA Requirements

Table 6. Detailed JCA requirements organised by adapted PICO criteria

Category	EUnetHTA21 Methodology
Population	D4.2 (Scoping) HTD provides evidence for all the populations provided by the members states in the PICOs
Comparator	D4.2 (scoping) HTD provides evidence for all comparators provided by MS in the PICOs D4.3 (comparators and comparisons) If HTD does not provide evidence for all comparators provided in the PICOs, ITC can be conducted but needs to meet JCA method requirements: • Comparators can be connected by at least one path of RCTs, and RCTs provide sufficient information to carry out assessment along connected network • Assessment of exchangeability shows properties of similarity (PICO similar for each study), homogeneity (no meaningful difference in effect estimates) and consistency. Useful models approaches for ITC include the Bucher method, the frequentist and Bayesian NMA models • If the similarity assumptions are not met, methods for population-adjusted indirect comparisons may be considered, provided the network is connected and individual patient data are available for some of the trials included.
Outcomes	D4.2 HTD provides evidence for all outcomes provided by MS in the PICOs D4.4 HTD only uses validated surrogate outcome data to replace a final patient-centered outcome of interest if absolutely necessary. Evidence for a patient-centered outcome such as morbidity, overall mortality and health related quality of life should be requested during the scoping process
Study design	D4.6 HTD trial data is from adequate RCT which is considered gold standard with low risk of bias • Individual uncontrolled studies (single arm trial, case series for example) are of limited value in the HTAR context, because they cannot allow a comparative/relative evaluation The certainty of effectiveness results is determined by three concepts: internal validity [i.e., the extent to which a study is free from bias), applicability (i.e., the extent to which study results provide a basis for generalisation to the target population); and statistical precision (i.e., the uncertainty associated with study results due to random sampling variability) Cochrane ROB 2 assessment needs to be provided in JCA and could be impacted by non-RCT and open label design
Real world data	D4.6 If RWD is used, HTD should give details on the validity and reliability of RWD for adequately answering a given research question, especially the potential use of proxy variables, the risk of attrition bias, and the adequate measurement of endpoints.
Reporting of evidence	D4.5 HTD needs to meet general JCA reporting requirements for multiple hypothesis testing and subgroup analysis in a JCA including: • Subgroup definitions in protocol and SAP • Subgroups defined a priori • Accurate and unambiguous endpoint definition (concept, main source of information, measure, timing, summary and effect measure)

Abbreviations: HTD: Health technology developer, ITC: Indirect treatment comparison, NMA: Network meta-analysis, PICOs: Population, intervention, comparator and outcomes, RCT: Randomised controlled trial

Appendix 2. Detailed blinded PICOs for each product

Table 7. Detailed blinded PICOs for each product

	Product X Orphan therapy for patients with solid tumour in a metastatic stage	Product Y Orphan ATMP for patients with haematological tumour in 3L+ setting	Product Z Therapy for patients with haematological tumour in 1L+ setting
PICOs	PICO 1: P (I) + C (a) PICO 2: P (I) + C (b) PICO 3: P (I) + C (c) PICO 4: P (I) + C (d) PICO 5: P (I) + C (e) PICO 6: P (I) + C (f) PICO 7: P (I) + C (g) PICO 8: P (I) + C (h) PICO 9: P (I) + C (i) PICO 10: P (I) + C (j) PICO 11: P (I) + C (k) PICO 12: P (I) + C (l) PICO 13: P (I) + C (m) PICO 14: P (I) + C (n) PICO 15: P (II) + C (i) PICO 16: P (II) + C (o)	PICO 1: P (I) + C (a) PICO 2: P (I) + C (b) PICO 3: P (I) + C (c) PICO 4: P (I) + C (d) PICO 5: P (II) + C (a) PICO 6: P (II) + C (b) PICO 7: P (II) + C (c) PICO 8: P (II) + C (e) PICO 9: P (II) + C (f) PICO 10: P (III) + C (a) PICO 11: P (III) + C (b) PICO 12: P (III) + C (e) PICO 13: P (III) + C (f) PICO 14: P (III) + C (g) PICO 15: P (IV) + C (h) PICO 16: P (V) + C (b) PICO 17: P (VI) + C (b) PICO 18: P (VI) + C (c) PICO 19: P (VII) + C (b) PICO 20: P (VIII) + C (b) PICO 21: P (IX) + C (b) PICO 22: P (X) + C (g)	PICO 1: P (I) + C (a) PICO 2: P (I) + C (b) PICO 3: P (I) + C (c) PICO 4: P (I) + C (d) PICO 5: P (II) + C (a) PICO 6: P (II) + C (c) PICO 7: P (II) + C (d) PICO 8: P (II) + C (e) PICO 9: P (III) + C (a) PICO 10: P (III) + C (b) PICO 11: P (III) + C (c) PICO 12: P (III) + C (d) PICO 13: P (III) + C (e) PICO 14: P (III) + C (f) PICO 15: P (III) + C (g) PICO 16: P (III) + C (h) PICO 17: P (III) + C (i) PICO 18: P (IV) + C (a) PICO 19: P (IV) + C (c) PICO 20: P (IV) + C (d) PICO 21: P (IV) + C (e) PICO 22: P (IV) + C (h) PICO 23: P (IV) + C (i) PICO 24: P (V) + C (d) PICO 25: P (V) + C (f) PICO 26: P (VI) + C (a) PICO 27: P (VI) + C (d) PICO 28: P (VI) + C (e) PICO 29: P (VI) + C (j) PICO 30: P (VI) + C (k) PICO 31: P (VI) + C (l) PICO 32: P (VI) + C (m) PICO 33: P (VI) + C (n) PICO 34: P (VII) + C (a) PICO 35: P (VII) + C (c) PICO 36: P (VII) + C (o) PICO 37: P (VII) + C (p) PICO 38: P (VII) + C (q)

	Product X Orphan therapy for patients with solid tumour in a metastatic stage	Product Y Orphan ATMP for patients with haematological tumour in 3L+ setting	Product Z Therapy for patients with haematological tumour in 1L+ setting
			PICO 39: P (VII) + C (r) PICO 40: P (VIII) + C (a) PICO 41: P (VIII) + C (o) PICO 42: P (VIII) + C (p) PICO 43: P (VIII) + C (q) PICO 44: P (VIII) + C (s) PICO 45: P (IX) + C (a) PICO 46: P (IX) + C (o) PICO 47: P (IX) + C (p) PICO 48: P (IX) + C (s) PICO 49: P (IX) + C (t) PICO 50: P (IX) + C (u) PICO 51: P (IX) + C (v) PICO 52: P (IX) + C (w) PICO 53: P (X) + C (c) PICO 54: P (X) + C (g) PICO 55: P (X) + C (h) PICO 56: P (X) + C (i) PICO 57: P (X) + C (p)

Abbreviations: ATMP: Advanced therapy medicinal product, C: Comparator P: Population

Appendix 3. Glossary of terms

AE	Adverse event
ASCT	Allogeneic stem cell transplantation
ATMP	Advanced therapy medicinal products
CR	Complete response
DE	Germany
DFS	Disease-free survival
DOR	Duration of response
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EOP	European Federation of Pharmaceutical Industries and Associations (EFPIA) Oncology Platform (EOP)
EPAR	European Public Assessment Report
EQ-5D	EuroQol-5D
ES	Spain
ESMO	European Society for Medical Oncology
EU	European Inion
EU4	France, Germany, Italy, Spain
FDA	Food and Drug Administration
FR	France
HRQoL	Health Related Quality of Life
HTA	Health technology assessment
HTAb	Health technology assessment body
HTACG	Health Technology Assessment Coordination Group
HTAR	Health Technology Assessment Regulation
HTD	Health technology developers
IT	Italy
ITC	Indirect treatment comparisons
ITT	Intention-to-treat
JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultation
MA	Marketing Authorisation
MS	Member States
NL	Netherlands
NMA	Network meta-analysis
ORE	Oncology relevant endpoint
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PICO	Population, Intervention, Comparator and Outcomes
RCT	Randomised controlled trials
RoB	Risk of bias

RWD	Real-world data
RWE	Real world evidence
SAT	Single arm trial
SF-36	36-Item Short Form Survey
SoC	Standard of care
TTNT	Time to next treatment

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