HTA315

The Elusive PICO: Assessing Prediction in Joint Clinical Assessments (JCA)

A Case Study in Soft Tissue Sarcoma (STS)

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BACKGROUND

JCA is a new, mandatory procedure under the European Union (EU) Health Technology Assessment Regulation (HTAR).

- The goal of JCA is to harmonize the robust clinical assessment of new technologies across EU member states (MSs) to ensure quicker and more equitable access to effective, innovative technologies.[1]
- The JCA standardizes the clinical review of new medicines across EU MSs by requiring drug developers to submit a single dossier of clinical and safety data. This process, which runs in parallel with the European Medicines Agency marketing authorization, aims to reduce repetitive work and promote consistency and efficiency in HTAs.

The JCA process is built around the PICO (Population, Intervention, Comparator[s], and Outcomes) framework, which the JCA identifies and consolidates on the basis of input from the 27 EU MSs.[2]

To align with JCA requirements, health technology developers (HTDs) submit a comprehensive dossier that addresses the scope, PICO framework, and technical specifications outlined by the JCA.

The timeline for dossier development allows **a maximum of 100 days (60 days under accelerated procedure)** from scope finalization (and HTD receipt of the PICO) to submission (**Figure 1**).

It is important to evaluate JCA guidance for heterogenous conditions, such as STS, which are marked by a lack of clear standard of care (SOC).

- STS is a rare cancer of the soft tissues (e.g., fat, muscle, nerves, tendons, ligaments, and blood vessels) characterized by disease subtype heterogeneity and multiple treatment options. Any new treatments for STS that launch in Europe will be required to be submitted to the JCA.

OBJECTIVE

- To assess the process of defining PICO elements ahead of JCA, focusing on STS.

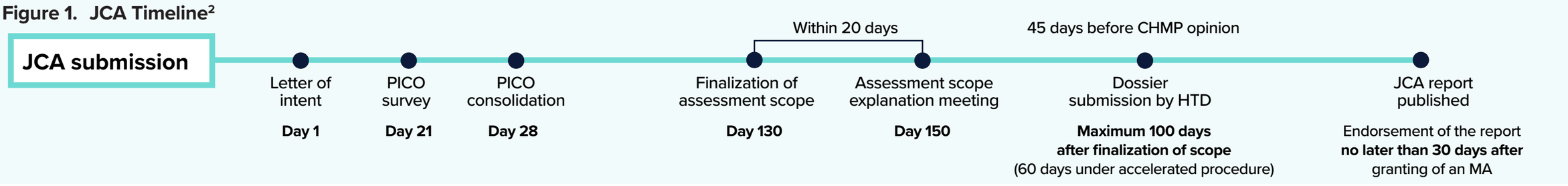
METHODS

A targeted literature review informed PICO assessment across the 27 EU MSs, based on guidelines, HTAs, and clinical studies (both randomized controlled trials [RCTs] and real-world evidence [RWE]).

A structured search using Nested Knowledge was used to identify and summarize populations, treatments, and outcomes in published clinical studies.

Country-specific PICOs were summarized and, where feasible, were consolidated on the basis of clinical justification and the HTA Coordination Group (HTA CG) guidance.

Figure 1. JCA Timeline[2]



CHMP = Committee for Medicinal Products for Human Use; MA = marketing authorisation.

RESULTS

- Results of the literature search are summarized in **Table 1**. Identified articles, guidelines, and HTAs were largely from the EU4 (France, Germany, Italy, and Spain), with fewer reports from other MSs.
- Guidelines and HTAs from non-EU countries also were included to provide additional insights on treatment patterns.
- Based on the frequently reported outcomes in the RCTs and RWE studies of metastatic STS (mSTS) and the PICO exercises published by the HTA CG, the outcomes most likely to be in JCA scope for mSTS are presented in **Figure 2**.

Table 1. Results of the Pragmatic Searches to Identify Broad PICOs Across All EU MSs

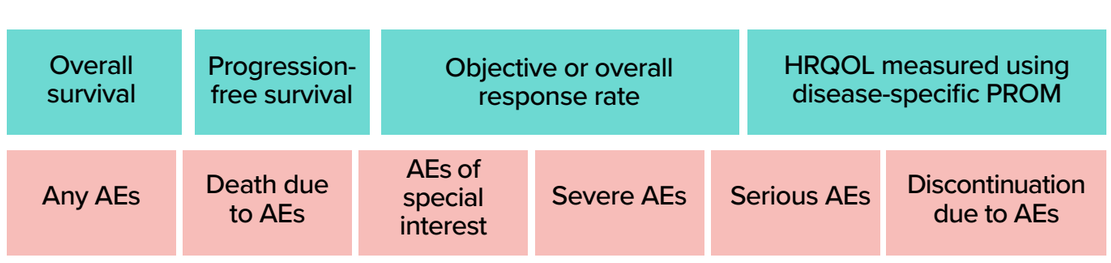
Methods	Results
Nested Knowledge	**Published clinical studies search:** 222 RCTs and 1,050 RWE studies or guidelines provided possible PICOs based on the identified studies
Published guidelines	**European guidelines:** ESMO; SELNET **Country-specific guidelines:** UK STS, German GGPO, Spanish SEOM-GEIS, US NCCN *Note: No guidelines were identified for France, Italy, the Nordic countries,[a] Benelux,[b] or any remaining EU MSs.*
Review of interventions, SOC, and recommendations	**24 HTA reports in STS** **EU:** AEMPS (Spain), G-BA (Germany), HAS (France), INFARMED (Portugal) **Non-EU:** PBAC (Australia), CDA-AMC (Canada), NICE (England and Wales), SMC (Scotland) *Note: No relevant HTAs were identified for other EU MSs.*

AEMPS = Spanish Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios); CDA-AMC = Canada's Drug Agency; ESMO = European Society for Medical Oncology; G-BA = German Federal Joint Committee (Gemeinsamer Bundesausschuss); GGPO = German Guideline Program in Oncology; HAS = French National Authority for Health (Haute Autorité de Santé); INFARMED = Portuguese Medicines Agency (Autoridade Nacional do Medicamento e Produtos de Saúde); NCCN = National Comprehensive Cancer Network; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SELNET = Sarcoma European and LatinAmerican NETwork; SEOM-GEIS = Spanish Society of Medical Oncology, Spanish Group for Sarcoma; SMC = Scottish Medicines Consortium; UK = United Kingdom; US = United States.

[a] Iceland, Denmark, Sweden, Finland, and Norway, along with the Faroe Islands, Greenland, and Åland Islands.

[b] Belgium, Luxembourg, and the Netherlands.

Figure 2. Potential Outcomes Anticipated in the JCA Scope



- Searches identified key themes, including:
  - Therapies used in the first line (1L) and later lines
  - Subpopulations with different treatment recommendations resulting in separate PICOs
- The ESMO guidelines provide multiple treatment recommendations in both lines of therapy and therefore support multiple PICOs, whereas unique comparators identified in country guidelines and HTAs were more limited (**Table 2**). RWE was largely from the EU4 and demonstrated use of more established treatment regimens.

Table 2. 1L Comparators Identified in EU Guidelines and RWE

Comparators	Recommending bodies
Doxorubicin; ifosfamide + doxorubicin	ESMO; SELNET; GGPO; SEOM-GEIS
Doxorubicin + dacarbazine	ESMO; SELNET; GGPO
Pazopanib; doxorubicin + trabectedin	SEOM-GEIS (pazopanib in older adults)
Liposomal doxorubicin ± ifosfamide	GGPO
Chemotherapy[a]	RWE studies
Epirubicin ± ifosfamide; dacarbazine ± ifosfamide	RWE studies
Taxanes	SEOM-GEIS

[a] Various guidelines recommend chemotherapy, but regimens vary.

- **Although there were clear SOC therapies in 1L STS, 13 potential PICOs were identified following consolidation due to differing clinical recommendations and practices in different countries.**
  - **10 were in a broad STS population, and 3 were in subtypes (leiomyosarcoma [LMS] or angiosarcoma [AS]).**
    - Doxorubicin is a standard therapy for STS, either as monotherapy or as a combination with alkylating agents (such as ifosfamide or dacarbazine) or other chemotherapy agents.
    - Several different chemotherapy combinations are recommended by different guidelines.
- **In third-line (3L) therapy, there was no clear SOC and 11 possible consolidated PICOs were identified.**
  - **8 were in a broad STS population, and 3 were in subtypes (liposarcoma [LPS], AS, LMS).**
  - Subsequent lines of therapy were based on many of the same agents recommended at 1L, but treatment varied depending on the regimens previously used and subtype of STS.
  - Monotherapy (with alkylating agents, including trabectedin or ifosfamide) was widely recommended if there had been no prior exposure.
  - Other chemotherapy agents also were recommended by ESMO and country-specific guidelines.

DISCUSSION AND CONCLUSIONS

- JCA provides a harmonized, scientific, rigorous assessment of clinical evidence that requires proactive efforts to anticipate and assess potential PICOs to inform indirect treatment comparisons (ITCs).
- Heterogeneous conditions such as STS are characterized by many possible treatments and a lack of clear, country-specific guidelines.
- This leads to varying treatment patterns both within and across countries, multiple comparators and potential PICOs, with limited data to support selected subpopulations and comparisons and inform ITCs.
- Furthermore, it may not be possible to conduct ITCs for all identified outcomes if definitions or timings of assessments vary, populations are small subgroups and/or heterogeneous, or reporting differs between trials.
- Because the HTDs will have only 100 days from receipt of the JCA scope to submit the dossier, it is important that they plan early to identify PICOs and develop data generation strategies.
- HTDs must also consider the differing requirements of JCA versus national HTAs in terms of systematic literature reviews (e.g., databases and registries required, the need to update 3 months prior to submission) and ITCs of multiple outcomes for each PICO.
- The HTA CG can facilitate the development of robust, fit-for-purpose submissions by providing additional guidance on PICO consolidation and working with companies and the MSs to ensure proposed comparators and outcomes align with treatment guidelines and data availability and minimize redundancy.

REFERENCES

1. European Commission. 9 Jan 2025. https://ec.europa.eu/commission/presscorner/detail/en/ip_25_226.
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