How to Manage Multiple PICOs and Challenging Timelines in Systematic Reviews for JCA Submissions

HTA320

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Background

- The variability in healthcare systems and standards of care across the 28 member states of the EU poses significant challenges when conducting the mandatory systematic literature reviews (SLRs) of efficacy and safety evidence needed to inform Joint Clinical Assessment (JCA) submissions. Specifically, each member state has its own priorities in terms of populations and interventions, and this will be reflected in the customised population, intervention, comparison, and outcome (PICO) criteria needed to define the data of relevance to that particular state. Therefore, SLRs conducted for JCA admissions must address multiple sets of PICO criteria. The situation is further complicated by the fact that the JCA process requires up-to-date SLR evidence and yet the PICO criteria are often not finalised until late in the JCA process.
- To meet the tight deadlines required for JCA submissions, an SLR approach capable of efficiently managing multiple PICO criteria is essential. This includes having Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-aligned search results for the overall JCA scope while also providing study lists specific to each PICO set. Moreover, the approach must be able to accommodate late-stage changes in country-specific PICO criteria, ensuring the process remains responsive and keeps the SLR evidence up-to-date throughout the submission timeline.

Objectives

- To develop and evaluate practical methods for addressing the challenges of managing multiple PICO criteria while meeting JCA submission requirements and timelines.

Methods

- We simulated and explored solutions to potential challenges associated with conducting a JCA-compliant SLR of clinical trials of treatments for multiple myeloma. For this, we used a previously completed comprehensive SLR on this topic (hereafter known as the "global SLR") and developed five distinct hypothetical sets of country-specific PICO criteria to represent the kind of differences in population and treatment combinations that might occur in the scope of a JCA submission (**Table 1**).

Table 1. Simulated Country-specific PICO Criteria

	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5
Population	Overall MM	NDMM (low-risk)	NDMM (high-risk)	R/R MM	R/R MM
Intervention/ Comparator	MD, VRD, VCD, VTD, KRD	MD, VTD, VRD	MD, KRD	MD, VRD, VCD, VTD	MD, KRD
Outcomes	Survival Response HRQoL Safety	Survival Response HRQoL Safety	Survival Response HRQoL Safety	Survival Response HRQoL Safety	Survival Response HRQoL Safety

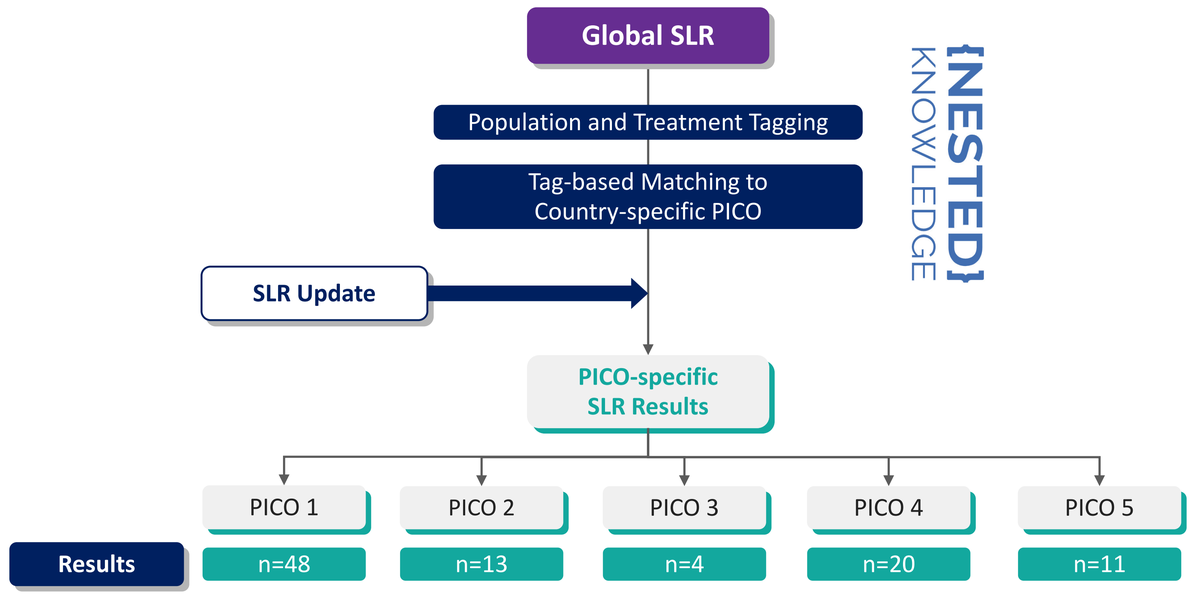
Abbreviations: HRQoL = health-related quality of life; KRD = carfilzomib, lenalidomide, dexamethasone; MD = manufacturer's drug; MM = multiple myeloma; NDMM = newly diagnosed multiple myeloma; PICO = population, intervention, comparison, outcome; R/R = relapsed/refractory; VCD = bortezomib, cyclophosphamide, dexamethasone; VRD = bortezomib, lenalidomide, dexamethasone; VTD = bortezomib, thalidomide, dexamethasone

- Traditional methods would require rescreening each publication included in the global SLR to assess its eligibility for each of the hypothetical PICO sets—a lengthy, inflexible, and inefficient approach. Instead, we tested a process in which a computer-based screening tool was used to manage screening the records and 'tag' (i.e., electronically mark) those recognised as being potentially relevant to one or more PICO sets.
- The screening tool was Nested Knowledge (NK), in which all screened records are catalogued in a 'nest'—a folder that contains all citations listed together with the screening decisions. NK allows reviewers to tag records that include pre-specified key words, at each screening phase. For this analysis, NK was set up to enable screening of all publications included in the global SLR and application of the following populations and interventions tags:
  - Population tags to capture patient status regarding previous treatments (newly diagnosed vs. relapsed/refractory) and risk group (low risk vs. high risk)
  - Intervention tags to capture the treatment modalities assessed in each study.
- In total, four population tags and five intervention tags were created.
- One of the scenarios explored deliberately was a situation where the overall scope for JCA was much narrower than that of the global SLR in terms of population and interventions of interest (PICO 3). In this case, we tested an approach for producing a customised PRISMA diagram to show how tagged studies relevant for PICO 3 would be identified through an SLR that used much more restrictive PICO criteria than those of the global SLR.

Results

- We utilised the results of the global SLR, where 2,621 records—followed by 321 full texts—were double-screened, and 48 studies met the global PICO criteria. These studies were subsequently tagged for elements varying between country-specific PICO criteria (**Figure 1**), including populations and interventions.

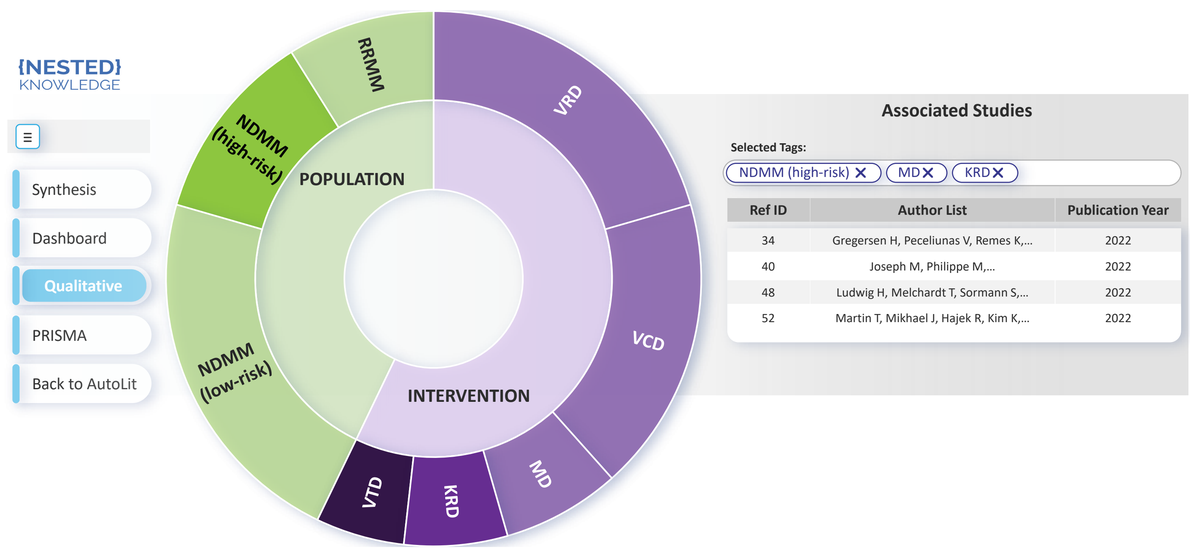
Figure 1. Overall Approach to Create PICO-specific Study Selection Results



Abbreviations: PICO = population, intervention, comparison, outcome; SLR = systematic literature review

- Once tagging was complete, the relevant studies for each of the five PICO sets were identified using tags specific to that individual PICO set. This was done by using the NK's 'Synthesis' feature, which combines relevant population and intervention tags to filter in PICO-specific screening results.
  - In the 'Synthesis' feature, studies based on specific combination of tags were selected (**Figure 2**). In the 'Associated Studies' section, a list of tagged studies per specific combination was presented. The filtering step was repeated per specific PICO combination to identify the list of PICO-relevant studies for each of the five countries envisaged in the hypothetical JCA submission.

Figure 2. Example of NK Synthesis Feature—Matching for PICO 3



Abbreviations: KRD = carfilzomib, lenalidomide, dexamethasone; MD = manufacturer drug; NDMM = newly diagnosed multiple myeloma; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RRMM = relapsed/refractory multiple myeloma; VCD = bortezomib, cyclophosphamide, dexamethasone; VRD = bortezomib, lenalidomide, dexamethasone; VTD = bortezomib, thalidomide, dexamethasone

- In the scenario that envisaged an overall JCA scope matching that of PICO 3, it would be important to appropriately represent this narrower breadth, rather than that of the global SLR. To this end, using the tagging process, we were able to quickly and successfully develop a JCA-specific PRISMA diagram. This involved copying the original screening results into a new NK subfolder—known as a 'sub-nest'—then updating the inclusion/exclusion criteria (to those of PICO 3) and finally automatically generating a PRISMA diagram for the sub-nest.
- The two-step approach, which involves tagging populations and interventions separately before matching them with the relevant PICO (instead of trying to classify each study upfront on whether it met the specific criteria for each of multiple countries), provided greater flexibility in accommodating changes to the PICO criteria in our simulated example.
- Any updates to the SLR could be quickly addressed by simply re-filtering the relevant tags, which would generate the updated PICO screening results.

Conclusions

- To address some challenges related with new submission processes to JCA, we have tested a new approach during the screening stage, which allowed us to quickly and successfully navigate to studies differentiated by populations and interventions.
- The records were screened and tagged by reviewers for multiple PICO elements concurrently, in contrast with conventional SLR techniques. By leveraging the NK tool, we streamlined the identification and tagging of studies that meet multiple JCA PICO criteria.
- This process can ensure country-specific variations are accounted for and addressed in JCA submission involving multiple PICO sets.
- This approach addresses the requirements of the JCA submission process by providing rapid, accurate, and PRISMA-aligned screening results. The flexibility of this methodology will allow for real-time adjustments to the PICO criteria, facilitating seamless updates without compromising the integrity or comprehensiveness of the conducted review.

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