6.3. LITERATURE REVIEW METHODOLOGY

MPE aimed at conducting a literature review of the minimum requirements, as well as the incentives and disincentives, for the conduction of myeloma clinical trials in Central Eastern European countries.

The first search script developed to answer the initial review question was the following: Myeloma AND ("European Union" OR "Central Eastern Europe") AND (("clinical studies as topic") OR ("drug development")). As it yielded only one hit on PubMed, the research scope was broadened geographically from Europe to worldwide, as well as from myeloma to "oncology or immunoproliferative disorders or hematologic diseases or rare diseases".

Table 24: Summary of literature review protocol

Review question	What are the minimum requirements, as well as the incentives and disincentives, to conduct of clinical trials in EU and non-EU Western and Central Eastern European countries?
Literature review type	Narrative review
Data sources	
Databases	• PubMed • Scopus • Lens.org • OpenGrey Between January 1, 2015 and January 31, 2020
Conference abstracts	• American Society for Hematology (ASH) • European Society for Hematology (EHA) Between January 1, 2018 and January 31, 2020
Additional sources	Additional Internet search • Myeloma trial analytics report, October 2020 (Consilium Scientific) • Global Data (data and analytics provider, to which Alcimed subscribes) • Applicable legislation, policies and administrative standards, including: ° The EU clinical trial regulation (Regulation EU No 536/2014, replacing former Directive 2001/20/EC of April 4, 2001) ° Examples of specific national legislation in response to the EU Clinical Trial Regulation in EU countries ° International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) ° Good Clinical Practice (GCP) recommendations (binding and non-binding guidelines) • European Clinical Research Infrastructure Network (ECRIN) • European Myeloma Network • Cancer Core Europe

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Selection of eligible studies sources	
Publication characteristics	Full-text articles (books and documents, meta-analyses, reviews and systematic reviews); Conference abstracts, institutional documentation, medical societies'/networks' publications (congress and working groups proceedings, recommendations)
Population	Patients with cancer, immunoproliferative disorders, haematologic diseases or rare diseases
Language	English
Geographical scope	Global
Key topics	• Funding and financial incentives • Institutional support • Country and site infrastructure attractiveness: equipment and specialised staff (investigators, nurses, clinical laboratory staff, radiology staff, pharmacists, legal and finance staff) • Trial set up (excessive complexity, poorly planned, design, relevance, schedule) • Site experience • Site performance in terms of data collection and reporting • Administrative burden ° Ethical reviews and committees' requirements ° Rules and strategies for data management ° Clinical trial approval time ° First patient in recruitment time • Role of patient organisations
Exclusion criteria	• Comments, position and opinion papers not issued from reference medical societies • Languages other than English Papers whose main topic is: • Other diseases than cancer, immunoproliferative disorders, haematologic diseases or rare diseases • Health interventions, which are not curative medicines, e.g. imaging, radiotherapy, surgery, screening, early detection, supportive care, medical devices, vaccines and prevention • Efficacy, safety and quality of life/patient reported outcomes of trialed or approved medicines • Coverage and access to approved medicines • Technical review/discussion of health technologies, e.g. mechanisms of action, biological pathway, pathophysiology, genomic analysis, molecular pathogenesis, tumor profiling, next generation sequencing • Care management and clinical practice optimisation • Health disparities from a clinical perspective only

6.3.2. SEARCH STRATEGY DEVELOPMENT

The search script was built through an iterative process on Pubmed, starting with an initial four-keyword search script (Clinical Studies as Topic, Neoplasms, Barriers and Facilitators). Search results highlighted additional relevant keywords to flesh out the script (see Figure 6).

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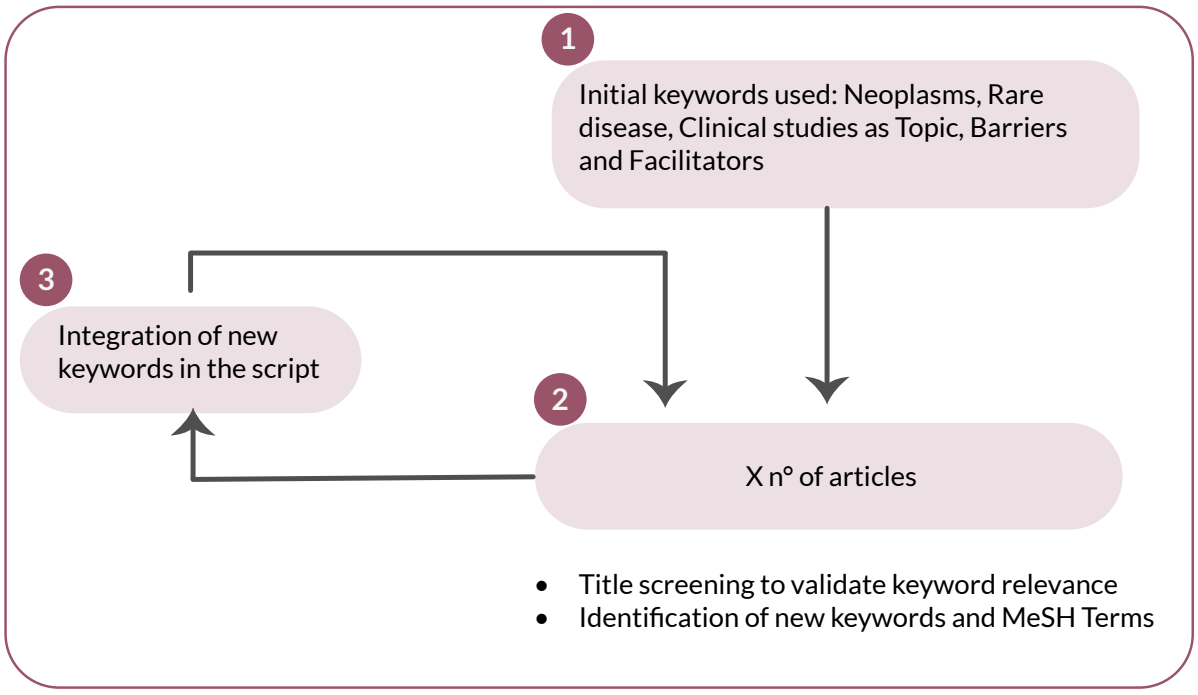
Figure 6: Search script development process on Pubmed



Process repeated by two independent reviewers until the script could no longer be optimised

Once tested and validated on PubMed, the search script was run on Scopus and Lens.org to complement the list of articles identified on Pubmed. MeshTerms used on PubMed were not used on Scopus because this classification doesn't exist on Scopus. On Scopus, the ALL filter was used so as not to limit the search. ABS was only used from "barriers" to "enablers", since the search was targeting articles dealing directly with these notions and expressing it in the title, abstract or keywords. While Pubmed and Scopus databases were searched as first level database to build and run the search script, second level sources included Lens.org and a targeted webography, both for which the search script was adapted [See Table 23]. The targeted webography focused on conference abstracts and documents published between January 2018 and January 2021 by the American Society of Hematology, the European Society of Hematology, the European Clinical Research Infrastructure Network (ECRIN), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the European Myeloma Network (EMN).

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Table 25: Search scripts used with 1st level databases Pubmed and Scopus

Script used on Pubmed	Script used on Scopus	Script used on Lens
((neoplasms[MeSH Terms]) OR ("immunoproliferative disorders"[MeSH Terms]) OR ("hematologic diseases"[MeSH Terms]) OR ("rare diseases"[MeSH Terms])) AND (("clinical studies as topic"[MeSH Terms]) OR ("drug development"[MeSH Terms])) AND (barriers[Title/Abstract] OR barrier[Title/Abstract] OR obstacle[Title/Abstract] OR obstacles[Title/Abstract] OR facilitators[Title/Abstract] OR facilitator[Title/Abstract] OR facilitate[Title/Abstract] OR facilitating[Title/Abstract] OR enhance[Title/Abstract] OR enhancing[Title/Abstract] OR enhancement[Title/Abstract] OR engage[Title/Abstract] OR engaging[Title/Abstract] OR engagement[Title/Abstract] OR equal[Title/Abstract] OR equality[Title/Abstract] OR accrual[Title/abstract] OR disparity[Title/Abstract] OR disparities[Title/Abstract] OR feasibility[Title/Abstract] OR enable[Title/Abstract] OR enabled[Title/Abstract] OR enablers[Title/Abstract]) AND (((access[All Fields]) OR (participation[All Fields]) OR (participate[All Fields]) OR (participated[All Fields]) OR ("health services accessibility"[MeSH Terms])) OR (communication[MeSH Terms]) OR ("Delivery of health care"[MeSH Terms]) OR (("cost of illness"[MeSH Terms]) OR ("health care costs"[MeSH Terms])) OR ((infrastructure[All Fields]) OR (equipment[All Fields]) OR ("research personnel"[MeSH Terms]) OR ("research support as topic"[MeSH Terms])) OR ("Research Design"[MeSH Terms]))	((ALL (((neoplasms) OR ("immunoproliferative disorders") OR ("hematologic diseases") OR ("rare diseases"))) AND ALL ((("clinical studies as topic") OR ("drug development"))) AND ABS (((barriers) OR (barrier) OR (obstacle) OR (obstacles) OR (facilitators) OR (facilitator) OR (facilitate) OR (facilitating) OR (enhance) OR (enhancing) OR (enhancement) OR (engage) OR (engaging) OR (engagement) OR (equal) OR (equality) OR (accrual) OR (disparity) OR (disparities) OR (feasibility) OR (enable) OR (enabled) OR (enablers))) AND ALL (((access) OR (participation) OR (participate) OR (participated) OR ("health services accessibility") OR (communication) OR ("Delivery of health care") OR ("cost of illness") OR ("health care costs") OR (infrastructure) OR (equipment) OR ("research personnel") OR ("research support as topic") OR ("Research Design"))))	((neoplasms) OR (immunoproliferative disorders) OR (hematologic diseases) OR (rare diseases)) AND ((clinical studies as topic) OR (drug development)) AND ((barriers) OR (barrier) OR (obstacle) OR (obstacles) OR (facilitators) OR (facilitator) OR (facilitate) OR (facilitating) OR (enhance) OR (enhancing) OR (enhancement) OR (engage) OR (engaging) OR (engagement) OR (equal) OR (equality) OR (accrual) OR (disparity) OR (disparities) OR (feasibility) OR (enable) OR (enabled) OR (enablers)) AND ((access) OR (participation) OR (participate) OR (participated) OR (health services accessibility) OR (communication) OR (Delivery of health care) OR (cost of illness) OR (health care costs) OR (infrastructure) OR (equipment) OR (research personnel) OR (research support as topic) OR (Research Design))

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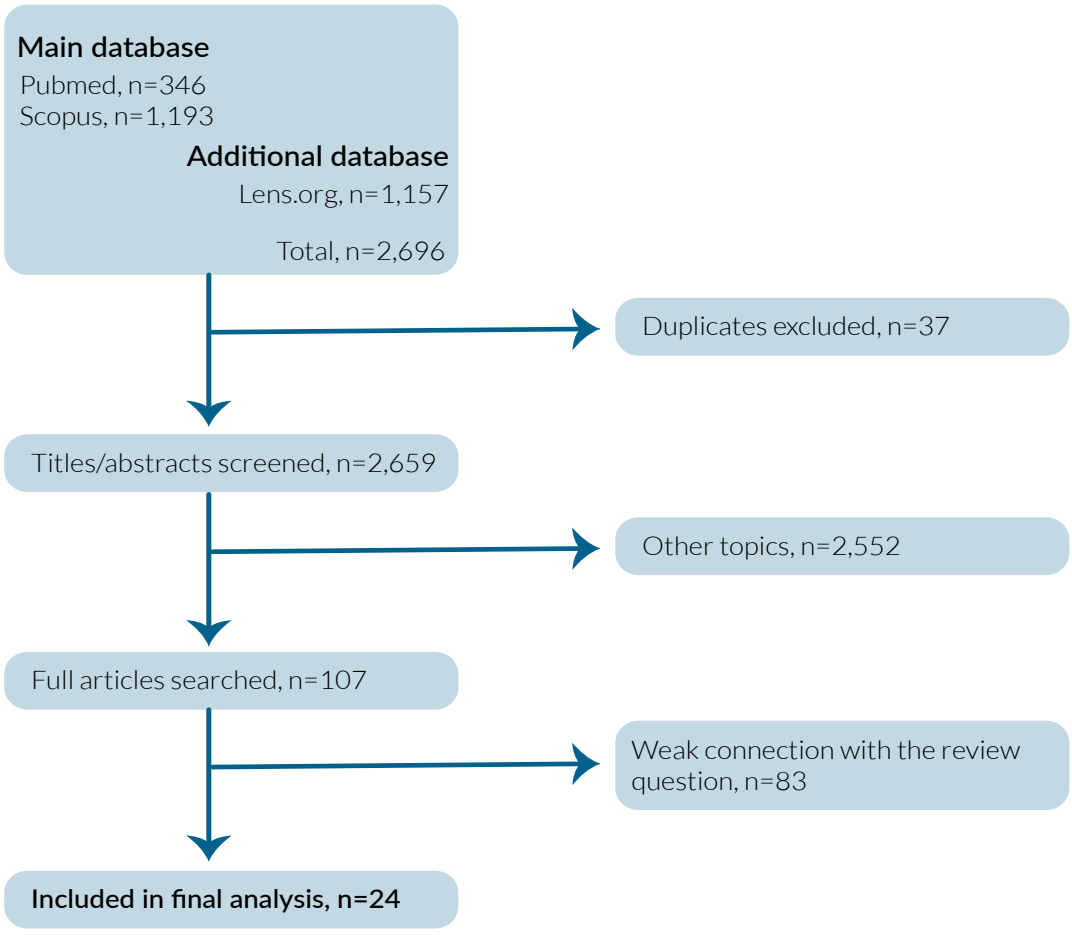
6.3.3. SELECTION PROCESS

Two independent reviewers selected articles/documents at title, abstract and full-text levels to ensure consistent data collection and reduce subjective selection. The same two reviewers extracted data from the selected studies using a predefined table based on the clinical trial decision-making framework described above. Any differences between reviewers about compliance of studies with the inclusion criteria and data extraction were resolved by discussion and consensus. Data from the included studies were extracted and summarised. Data extraction and inclusion grids in Excel format were agreed in consultation with MPE to ensure that the review was focused on the appropriate criteria of interest. Of the 2,696 articles extracted from the databases, 24 were eventually selected [see Figure 7].

Figure 7: Literature review flowchart



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6.3.4. LIST OF SELECTED STUDIES

- Ahaghotu C, T. R. (2016). African American Participation in Oncology Clinical Trials-Focus on Prostate Cancer: Implications, Barriers, and Potential Solutions. Clin Genitourin Cancer. , Apr;14(2):105-16.
- Arai RJ, G. R. (2019). Personalizing Precision Oncology Clinical Trials in Latin America: An Expert Panel on Challenges and Opportunities. Oncologist., Aug;24(8):e709-e719.
- Babiker HM, D. L. (2019). A Multidisciplinary Evaluation of Barriers to Enrolling Cancer Patients into Early Phase Clinical Trials: Challenges and Patient-centric Recommendations. Expert Opin Investig Drugs. , Aug;28(8):675-686.
- Barrios CH, R. T. (2018). Global Breast Cancer Research: Moving Forward. Am Soc Clin Oncol Educ Book., May 23; 38:441-450.
- Byrne M, D. N. (2017). Making inroads to the cure: Barriers to clinical trial enrollment in hematopoietic cell transplantation. Clin Transplant., May;31(5).
- Cartmell KB, B. H. (2020). Patient barriers to cancer clinical trial participation and navigator activities to assist. Adv Cancer Res. , 146:139-166.
- Chan A.Y.L., C. V. (2020). Access and Unmet Needs of Orphan Drugs in 194 Countries and 6 Areas: A Global Policy Review With Content Analysis. Value Health. , Dec;23(12):1580-1591.
- Chino F, Z. S. (2019). Financial Toxicity and Equitable Access to Clinical Trials. Am Soc Clin Oncol Educ Book. , Jan;39:11-18.
- Djurisic S, R. A. (2017). Barriers to the conduct of randomised clinical trials within all disease areas. . Trials, Aug 1;18(1):360.
- Ellis S, G. M. (2019). Development, acceptability, appropriateness and appeal of a cancer clinical trials implementation intervention for rural- and minority-serving urology practices. Trials. , Oct 7;20(1):578.
- Gammie T., L. C.-D. (2015). Access to orphan drugs: A comprehensive review of legislations, regulations and policies in 35 countries. PLoS One. Oct 9;10(10):e0140002.
- Haddad RI, C. A. (2015). Barriers to clinical trial recruitment in head and neck cancer. Oral Oncol. , Mar;51(3):203-11.
- Napoles A, C. E. (2017). Applying a Conceptual Framework to Maximize the Participation of Diverse Populations in Cancer Clinical Trials. Adv Cancer Res. , 133:77-94.
- Nielsen ZE, B. C. (2019). Cancer patients' perceptions of factors influencing their decisions on participation in clinical drug trials: A qualitative meta-synthesis. J Clin Nurs. , Jul;28(13-14):2443-2461.
- Nipp RD, H. K. (2019). Overcoming Barriers to clinical trial enrollment. Am Soc Clin Oncol Educ Book , Jan;39:105-114.
- Nipp RD, L. H. (2019). Addressing the Financial Burden of Cancer Clinical Trial Participation: Longitudinal Effects of an Equity Intervention. Oncologist. Aug;24(8):1048-1055.
- Rath A, S. V. (2017). A systematic literature review of evidence-based clinical practice for rare diseases: what are the perceived and real barriers for improving the evidence and how can they be overcome? Trials. Nov 22;18(1):556.
- Rivers D, P. T. (2019). A community-academic partnership to explore informational needs of African American women as a primer for cancer clinical trial recruitment. Ethn Health., Aug;24(6):679-693.

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- Sacristán. (2016). Patient involvement in clinical research: why, when and how. Patient Prefer Adherence., Apr 27;10:631-40.
- Salman A, N. C. (2015). A Review of Barriers to Minorities' Participation in Cancer Clinical Trials: Implications for Future Cancer Research. J Immigr Minor Health. , March;18(2):447-53.
- Siembida, E., Loomans-Kropp, H. A., Trivedi, N., O'Mara, A., Sung, L., TamiMaury, I., Roth, M. (2020). Systematic review of barriers and facilitators to clinical trial. Cancer, March 01; 126(5): 949–957. doi:10.1002/cncr.32675.
- Steensma D.P., B. A. (2018). Low clinical trial accrual of patients with myelodysplastic syndromes: Causes and potential solutions. Cancer. Dec 15;124(24):4601-4609.
- Tang M, J. H. (2019). Challenges of international oncology trial collaboration - a call to action. Br J Cancer., Oct;121(7):515-521.
- Unger JM, V. R. (2019). Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation. J Natl Cancer Inst. , Mar 1;111(3):245-255.
- Vuong I, W. J. (2020). Overcoming Barriers: Evidence-Based Strategies to Increase Enrolment of Underrepresented Populations in Cancer Therapeutic Clinical Trials - a Narrative Review. J Cancer Educ. Oct;35(5):841-849.

6.3.5. CHARACTERISTICS OF SELECTED ARTICLES

- Main indications investigated: All cancers, breast cancers, head and neck cancers, prostate cancers, hematological diseases and rare diseases
- Geographical representativity: USA (12), World (8), Europe (4), Latin America (1)
- Europe is often considered as a whole entity, with discrepancies in access to clinical trials between European countries not directly covered and discussed. Disparities in access to clinical trials as a topic is discussed when comparing the level of involvement of Low-Medium Income Countries (LMIC) to that of High-Income Countries (HIC)
- Key topics:
  - A limited number of articles address the difficulties of initiating clinical trials in a specific country. Greater emphasis is placed on the difficulties of initiating and conducting multi-center trials
  - Most documented topic: Barriers to patient enrolment and participation in clinical trials, including challenges in enrolling minorities (particularly in the USA)
- Type of articles: Narrative reviews were the most prevalent (16) then, systematic literature review (2), systematic-review and meta-analysis (1)

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6.3.6. LITERATURE REVIEW LIMITATIONS

A lack of references addressing specifically the issues of the access to clinical trials in MM in Central and Eastern European countries led to a broadening of the investigation scope. This meant including scientific papers for global findings not specifically refined to the situation of European countries.

Furthermore, potential biases in the methodological process could arise from the transfer of the initial script built on Pubmed (using Mesh Terms heading) to Scopus and Lens.org. The script was designed and refined on Pubmed, even though adapted to the methodological frame of Scopus and Lens.org.

The literature review confirmed the need to conduct interviews with key clinical trial stakeholders [see Appendix 6.3] to better understand specificities related to the opening and set up of myeloma clinical trials.

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