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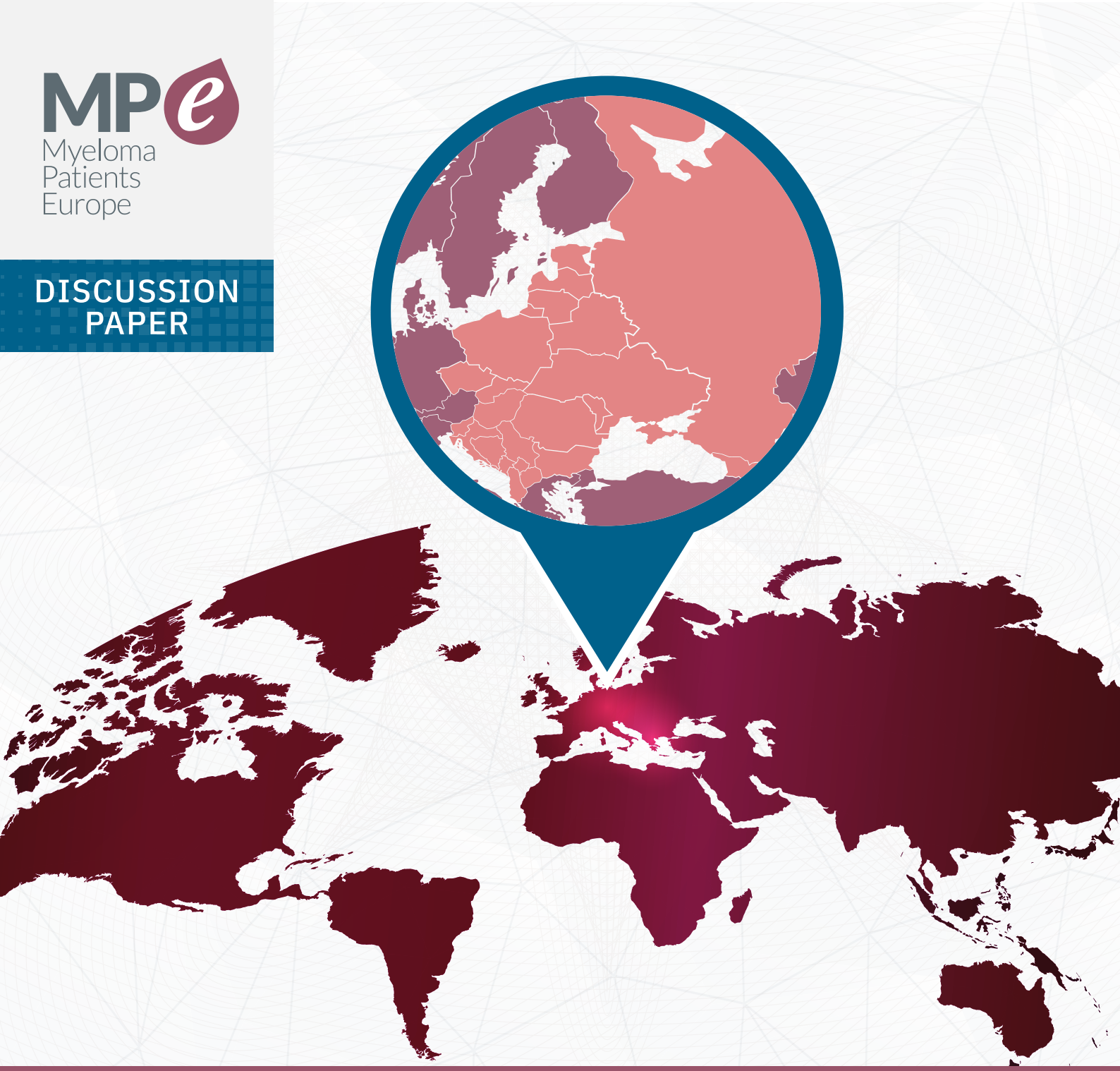
DISCUSSION PAPER



Addressing access barriers to myeloma clinical trials in Central and Eastern Europe

MPe ATLAS

MYELOMA ACCESS ATLAS

EDITION
Myeloma Patients Europe (MPE),
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EXECUTIVE SUMMARY

Clinical trials have many benefits. These include:

- facilitating investment in countries
- developing knowledge, expertise and capacity in disease communities
- understanding how medicines work in local populations to assist access and provide lifesaving alternatives

Myeloma Patient Europe (MPE) has been aware of the lack of clinical trials opening in many Central and Eastern European (CEE) countries, as well as inequalities in accessing participation of ongoing trials. To gather data, and further understand the access situation, MPE conducted research on barriers and facilitators to clinical trials, with a specific focus on CEE countries. The research was completed under the guidance of MPE members from across the region through its CEE workgroup.

The study was completed in three parts:

- An analysis of the availability and access to myeloma clinical trials across all CEE countries
- A literature review exploring barriers and facilitators to clinical trial access in Europe
- Interviews with haematologists, researchers, regulators and patients in three CEE countries (Poland, Croatia and Macedonia)

The research findings are summarised below, alongside recommendations for national and international stakeholders (including patient advocates, industry, researchers and policy makers) to address barriers to clinical trials. Recommendations were agreed with the MPE CEE workgroup.

It is important to note that there is no one-size-fits-all approach to addressing these challenges and further country-specific research is needed to understand the barriers and facilitators for conducting clinical trials in more detail. However, this discussion paper is designed to start a conversation about what can be done to address the European inequalities in access to clinical trials.

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Myeloma trial analytics

Between 1 January 2001 and 28 September 2020, only 6% of the 3,229 worldwide myeloma trials included patients from CEE. Of the 17 CEE countries that ran at least one myeloma clinical trial, 11 were EU members.

Trial analytics confirmed the variability in availability and access to myeloma clinical trials in CEE countries during the period of analysis.

As shown in Table 1, trial analytics indicated that the Czech Republic (128 trials), Poland (95 trials) and the Russian Federation (79 trials) were involved in the largest number of trials. In relative terms to myeloma prevalence, the Czech Republic, Hungary (66 trials) and Bulgaria (24 trials) were the CEE countries most efficient in conducting research given the number of trials relative to patient population and myeloma incidence. It was found that seven countries had no access to myeloma clinical trials and 12 countries had fewer than five clinical trials over 20 years.

Using the clinical trial analytics, MPE chose three countries for further analysis via qualitative interviews. Poland (95 trials), Croatia (eight trials) and Macedonia (three trials) were selected as in countries with high, medium and low clinical trial availability.

Literature review and stakeholder interviews

The literature review and stakeholder interviews highlighted three types of barriers and facilitators:

- Structural
- Clinical
- Patient and physician

STRUCTURAL BARRIERS

Patient population size

Our research found that the larger a country's population, the more there are patients and the more likely a trial will take place. Whilst an important factor, the Czech Republic, Bulgaria and Hungary show, however, that population size is not the only determinant of clinical trial set-ups.

TABLE 1: MYELOMA TRIALS RUN IN CEE COUNTRIES BETWEEN 1 JANUARY 2001 AND 28 SEPTEMBER 2020 (201 TRIALS)

	Country	Myeloma trials enrolling country specific patients	Frequency of country inclusion in myeloma trials enrolling CEE patients	Identified myeloma research centres	2022 population	2020 myeloma incidence	2020 myeloma 5-year prevalence	EU members	EU entry date
1	Czech Republic	128	63.7%	9	10,705,384	574	1,607	Yes	2004
2	Poland	95	47.3%	21	38,093,101	2,276	6,148	Yes	2004
3	Russian Federation	79	39.3%	20	142,021,981	5,132	13,816	No	N/A
4	Hungary	66	32.8%	9	9,699,577	436	1,169	Yes	2004
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10	Slovakia	12	6%	2	5,431,252	401	1,068	Yes	2004
11	Croatia	8	4%	3	4,188,853	281	712	Yes	2013
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15	North Macedonia	3	1.5%	0	2,130,936	35	88	No	N/A
16	Belarus	2	1%	1	9,413,505	334	878	No	N/A
17	Slovenia	2	1%	0	2,101,208	173	476	Yes	2004
18	Montenegro	0	0%	0	604,966	22	58	No	N/A
19	Albania	0	0%	0	3,095,344	36	92	No	N/A
20	Armenia	0	0%	0	3,000,756	31	79	No	N/A
21	Azerbaijan	0	0%	0	10,353,296	178	436	No	N/A
22	Bosnia & Herzegovina	0	0%	0	3,816,459	96	232	No	N/A
23	Moldova	0	0%	0	3,287,326	88	205	No	N/A
24	Kosovo	0	0%	0	1,952,701	N/A	-	No	N/A

More details on the analytics methodology and results in Appendices 6.1 and 6.2.

MPE, with the support of Consilium Scientific, has searched 18 clinical trial registries for all myeloma clinical trials, which recruited CEE patients between Sept 2001 and Sept 2020. Out of the 3,229 myeloma trials, 201 included at least one recruitment centre in CEE.

2020 myeloma incidence and prevalence: https://gco.iarc.fr/today/online-analysis-table, 2020

Country population: https://www.cia.gov/the-world-factbook/countries/

N/A: not available

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RECOMMENDATIONS

1. Academic researchers, policymakers, haematologists, and other relevant stakeholders are encouraged to work towards the establishment of joint cross-border research networks and initiatives in the CEE region, especially in the Balkans, to:
    - offer a sizeable myeloma patient population to clinical trial sponsors. This will incentivise an increase in commercially sponsored studies. The involvement of a third party to facilitate and support this effort is encouraged.
    - raise awareness and capacity of the role CEE countries can play in international research.
2. MPE to work with its members to:
    - identify, share and engage with existing pan-European research networks and collaborative initiatives, such as the European Clinical Research Infrastructures Network (ECRIN), to provide support and facilitate clinical trial preparation and implementation.
    - investigate barriers and facilitators to cross-border research networks and initiatives.

Health care funding, financial incentives for research and national cancer/rare disease plan or strategy

Many myeloma clinical trials do not run in CEE countries. Eighty percent of those that do run are conducted by the pharmaceutical industry, which often has more available resources than most academic centres to meet trial financial and logistic requirements.

The literature review and stakeholder discussions identified that predictable funding and political commitment are important for the facilitation of academic trials and the publication of trial results and to attract industry sponsors.

The existence of national cancer or rare disease plans is one indicator of political commitment. It is particularly beneficial despite putting any specific legislation in place.

RECOMMENDATIONS

3. Industry, academic researchers, health policymakers and other relevant stakeholders are encouraged to collaborate towards greater investments in research and development (R&D) in CEE countries, including the creation and maintenance of the necessary infrastructure to run clinical trials, as well as the coverage of standard of care treatments and specialised procedures.
4. European health policymakers, most notably in the CEE region, are encouraged to put comprehensive cancer plans in place with a core commitment to conducting clinical trials, thereby aligning with Europe's Beating Cancer Plan. Such plans need to be rolling and evaluated.

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Research infrastructure and qualified staff

Oncology and haematology require multiple and specialised procedures and capacities to collect and manage patient tissue/bone/blood samples and data (such as physical exams, biopsies, laboratory tests and biobanking). Variations in access and ability to use these techniques and gather data may make it difficult for some countries to run trials.

Adequate staffing is critical to trial set-ups: the (un)availability of trained nurses and the lack of appropriate training and support for some physicians participating in clinical trials was underlined. This situation has worsened with the increasing number of physicians and nurses leaving CEE countries to work in Western Europe. As well as physicians and nurses, governmental staff prepared to regulate innovative medicines and technologies, and attorneys with expertise in clinical trials are also needed to improve clinical trial operations.

Stakeholders confirmed that smaller hospital sites do not have the authorisation, myeloma expertise, equipment or staffing levels to conduct clinical trials, particularly for immunotherapies.

Another hurdle to research is the lack of hospital management's willingness to invest in clinical trials. One of the consequences has been the lack of time dedicated to clinical trial activities, with haematologists and nurses involved in clinical trials doing so in their own time.

RECOMMENDATIONS

5. European medical societies, research institutions and structures like the European Hematology Association (EHA), the European Society for Medical Oncology (ESMO) and the European Reference Networks (ERN) could potentially align on minimum staffing requirements, job descriptions, expertise and hospital infrastructure needed for cancer clinical trials to run effectively. This would help CEE countries prioritising R&D investment
6. More CEE countries could benefit from becoming members or observers of the ECRIN (the Czech Republic is the only ECRIN's CEE country member, while Slovakia and Poland are the two CEE country observers).
7. European and global medical societies should offer training and peer-to-peer support programmes on clinical trial methodology, with a particular emphasis on CEE, to ensure that healthcare professionals are upskilled and champion the initiation of clinical trials.
8. European and national policymakers should collaborate and find solutions to the health care professional 'brain drain", which negatively impacts CEE health care systems, R&D and ultimately patients.

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9. Research needs to be undertaken in Europe to understand the impact of the COVID-19 pandemic on the ability of European healthcare systems, including in the CEE region, to invest and conduct research and clinical trials.

Administrative and regulatory requirements and EU membership

Complex regulations relating to the governance of clinical trials, including patient informed consent and ethics committee submission, lengthen the time taken to activate national and international trials and delay study results. In some countries this is the opposite, and the lack of regulations governing and enabling research acts as a major barrier to clinical trials.

Polish stakeholders stated that the administrative burden has been a major barrier to running clinical trials, especially academic trials. They pointed to the Czech Republic's success in conducting research, which originates from streamlined and fast clinical trial agreement negotiation and registration processes.

Given the levels of resources needed to overcome those hurdles, it is more likely for clinical trials to be run by pharmaceutical companies than academic sponsors, as lower return on investment is expected due to uncertain reimbursement outcomes.

EU membership is a facilitator to setting up clinical trials and for bringing a drug to market in the region. This is thanks to its centralised regulatory process, fast track approval, pre-licensing access, scientific advice on trial design and implementation, and a 10-year market exclusivity for orphan drugs. Additionally, the EU Clinical Trial Regulation 536/2014, which came into application on 31 January 2022, and includes a Clinical Trials Information System (CTIS), aiming at harmonising processes and ensuring the EU remains an attractive site for clinical trials.

Stakeholders confirmed that Poland and Croatia's earlier EU accession within the CEE region has been a favourable factor, while one of the hypotheses put forward to partly explain North Macedonia's low clinical trial rank (15/24) is the lack of EU membership.

RECOMMENDATIONS

10. EU cancer patient advocacy groups and other stakeholders should monitor the implementation of the EU Clinical Trial Regulation 536/2014 to ensure approval clinical trial timelines are met.
11. Non-EU members from CEE could align as much as possible with the EU Clinical Trials Regulation 536/2014 to streamline clinical trial initiation and conduct.
12. CEE health policymakers, cancer patient organisations and medical societies could

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review best practices in countries that have a relatively larger share of clinical trials (e.g., the Czech Republic, Bulgaria, and Hungary) to understand how procedures in place have favoured streamlined regulatory processes and raised the international profile of their medical and scientific communities.

13. Researchers and other stakeholders in CEE should promote the creation of contract templates, hereby shortening the contract negotiation time prior to the opening of clinical trials.

International R&D collaborations

International collaboration via organisations such as the European Hematology Association (EHA), the American Society of Hematology (ASH) and the European Myeloma Network (EMN), is key to educating, training and nurturing the next generation of clinical researchers. This type of collaboration provides opportunities to work with experienced clinical trial organisations and improve healthcare through investment in local infrastructure and training of investigators and healthcare personnel.

The Czech Republic's strong collaboration with Western Europe, the recognised high R&D profile of its haematologists and its volume of publications were cited as key factors for the high number of myeloma clinical trials it ran according to Polish, Croatian and North Macedonian stakeholders. They concur that the international R&D profile needed to attract commercial sponsors depends on academic clinical trial publications. Seeking best practices from other disease areas in increasing international collaboration was recommended by North Macedonian stakeholders.

RECOMMENDATIONS

14. International and European medical societies and journals should grant dedicated funding and/or reduced fees to academic scientific authors in lower- and middle-income CEE countries to cover publication fees and attend congresses.

See also recommendations 1 and 12

Geographical distribution of centres

The local availability of clinical trials appropriate for a patient's cancer type and stage plays a large role in reducing or increasing rates of participation in a trial. Clinical trials often take place in hospitals with large centres of expertise (usually in key cities), as smaller institutions may not have the qualified staff, equipment, data management programmes or resources.

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Patient burden and additional costs are high for Polish and North Macedonian myeloma patients who live remotely from their treatment centres. This negatively impacts patient participation, according to interviewed stakeholders.

RECOMMENDATIONS

15. Industry sponsors and CEE academic researchers could encourage patient participation to clinical trials by allowing routine tests and exams to be done at patients' local hospitals, vs. remote investigating centres.
16. The Industry should provide travel and accommodation allowances to CEE patients and their carers (if needed) to incentivise them to participate in clinical trials. This will reduce biases of selection, whereby only wealthier patients or those living closer to trial sites, can afford to take part in clinical trials.
17. The global research community should agree with the industry on a short list of clinical trial data management programmes for smaller hospitals to choose from. This would lead to economies of scale and allow smaller hospitals across CEE to meet clinical trial data management requirements.

CLINICAL BARRIERS

Trial design

Even where clinical trials are potentially available, patients within a country may not be able to participate due to narrow eligibility criteria. Reasons for narrow eligibility criteria in clinical trials relate to the rarity of a disease and/or the presence of a genetic or molecular marker, the investigator's desire to maintain patient safety and establish a study cohort with similar patient profiles, and different standards of care in prior treatment lines. This leads to the underrepresentation of specific subgroups of patients (e.g., patients with progressive disease or chronic illnesses, older adults, racial and ethnic minority populations, and patients in low-middle income countries with a different standard of care).

Heterogeneity in clinical practice

A lack of myeloma guidelines and variety in standard of care mean that patients' eligibility varies substantially within and across countries. Polish patient care, for example, including myeloma care, suffers from a lack of standardisation, which reduces the chance of patients being eligible for trial inclusion. Health care practice disparities between

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and within treatment centres is potentially an unfortunate consequence of a lack of consensus between Polish haematologists.

One major hurdle for Croatian and North Macedonian patients has been the lack of access to generic backbone therapies bortezomib and lenalidomide, which are central to all new myeloma combination therapies submitted for inclusion on the reimbursement list. Additionally, the time-limited conditional budgets for the administration of treatments not on the North Macedonian reimbursement list further contributes to disparities in inclusion in clinical trials between patients. Of the patients who are not covered under the conditional budget, only the wealthiest who get treated abroad have access to these therapies. Even treatments on the North Macedonian reimbursement list (thalidomide, cyclophosphamide and melphalan) have been largely unavailable to patients. This lack of availability represents an additional obstacle to the attractiveness of the country as a trial site for industrial sponsors.

RECOMMENDATIONS

18. Trial sponsors should consider the use of broader inclusion criteria, which more closely reflect real-life patient populations, including patients based in CEE countries.
19. Industry sponsors should support equal access to trials for all myeloma patients regardless of the region they live in. Industry protocol designs should consider the heterogeneity of standards of care across different regions, such as CEE. Partnerships with academia and country-specific trial arms could also be considered to assist with national access questions.
20. Policymakers should consider the benefit of establishing or joining existing voluntary cross-border collaborations on pricing and reimbursement operating in the CEE region, that aim to improve access to innovative medicines and therapies. These include the Baltic Procurement Initiative (2012): Estonia, Latvia and Lithuania; the Valletta Declaration (2017): Cyprus, Greece, Ireland, Italy, Malta, Portugal, Romania, Spain, Slovenia, Croatia; the Fair and Affordable Pricing (FAAP) initiative (2017): the Czech Republic, Hungary, Poland and Slovakia.
21. Key opinion leaders and haematologists should work together and agree on national treatment guidelines to ensure patients are treated uniformly based on the best available evidence and reimbursement decisions, thus all having equal chance to access available clinical trials.

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22. Industry, health policy makers, cancer patient organisations and other stakeholders need to jointly explore models of fair pricing in line with national gross domestic product to ensure that European cancer standards of care, including generics, are affordable in CEE countries. Access to standard of care is a critical element of setting up and running oncology clinical trials.

PHYSICIAN AND PATIENT BARRIERS

Physician barriers

Physicians play a vital role in helping patients determine treatment choice. Patients often look to their physicians to inform them of clinical trials, which may be a just as important part of the treatment. Physicians may not ask eligible patients about trial participation due to multiple reasons. These include a lack of information on trials, preferences and beliefs (concern for patients' capacity or willingness to complete the trial and/or potential preferences or concern of interference with the physician-patient relationship), as well as institutional or clinic time and reimbursement constraints. The role of trial registries is important in educating physicians and patients about the availability of trials. Improvement in the quality and accuracy of data provided on ongoing trials, as well as complementary initiatives, are needed to speed up the identification process of candidates.

RECOMMENDATIONS

23. Medical societies and cancer patient organisations should promote the use of the EU Clinical Trials Register, which provides clear and accessible information to haematologists and myeloma patients participating in clinical trials in their countries.
24. National and international professional organisations, like EHA and ESMO, should set up training programmes for oncology healthcare professionals in CEE on communicating clinical trials information to patients.
25. Industry and academic researchers should engage patients and/or patient representatives:
    - to ensure that informed consent forms are clear and concise documents about the benefits and risks of each trial. These should be translated into the languages used within the countries a trial is being opened in.
    - inform the design of their clinical trials following the EUPATI Engagement Roadmap and to ensure they reflect patient preferences.

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Patient barriers

The influence of patient-related factors and patient choice represents only a small portion of barriers to trial participation overall. Willingness or unwillingness to participate in a trial depends on two types of patient-based factors:

- information and knowledge about the availability of trials, their objectives and execution, and the way in which physicians communicate with them about trials
- individual factors such as socioeconomic situation, cost concerns, and health literacy

A further barrier to patient participation in clinical trials is individual patient preferences: hope of therapeutic benefits; fear of side effects, uncertain outcomes, and scientific experiments; fear of losing control over their own treatment; worries about the impact on relatives and caregivers; reticience of leaving the care of their primary physician to pursue new treatment options while on a clinical trial; feeling of mistrust in clinical trials; and fear of placebo-controlled trials.

According to interviewees, Polish patients' hesitancy to enrol is commonplace due to a lack of or limited information, as well as mistrust in medical research. This again demonstrates the importance of empowering patients with adequate information on trials to assist decision-making.

When a trial is available, financial and logistical issues (or patient perceptions on these issues) may also play a role in trial participation. Alongside worries on reimbursement of standard medical costs, patients also incur significant additional costs and logistical challenges (i.e., gas or train/flight ticket, food, accommodation and childcare), while facing wage loss as they often require travel to distant institutions to receive treatment and tests. The limited coverage of bortezomib and lenalidomide in North Macedonia via the conditional budget constitutes an obstacle for the establishment of trials in the country and for patients participating in trials, who cannot afford to pay for them out of their own pockets.

RECOMMENDATIONS

26. European and national cancer patient organisations should provide information to patients in lay language about trials running in their country.
27. National cancer patient organisations should conduct further research on country-specific socio-economic and cultural barriers to setting up clinical trials in the CEE region.

2. CONTEXT AND OBJECTIVES

ABOUT MYELOMA PATIENTS EUROPE

Myeloma Patients Europe (MPE) is an umbrella organisation of myeloma and AL amyloidosis patient groups across geographical Europe. MPE currently has 48 members based in 31 countries. The mission of the organisation is to provide education, information and support to member groups, and to advocate at European, national and local levels for the best possible research and equal access to treatment and care. To achieve its aims, MPE works directly with its members, healthcare professionals, reimbursement authorities, regulators, politicians, pharmaceutical companies and the media to ensure all stakeholders collaborate to improve patient outcomes and reduce inequalities across Europe.

Access to medicines in some CEE countries is particularly challenging. MPE has been increasingly undertaking work with individual members in the CEE region via one its core programmes, the Myeloma Access Atlas. The Myeloma Access Atlas is an online platform designed to provide myeloma and AL amyloidosis patient advocates with the information and tools needed to work effectively on access issues. The Atlas provides country-specific and comparative information on European health systems, including data on system performance and access to myeloma treatments. The aim behind the data and tools provided is to identify, understand and overcome variation in access to treatment and care in Europe. MPE has set up a CEE Workgroup to understand and interpret the data generated through the Atlas and to better coordinate action at a European level on regional access issues in CEE. Initiatives and projects conducted through the Workgroup result from a two-way dialogue between members in CEE and MPE.

This discussion paper on *Addressing access barriers to myeloma clinical trials in Central and Eastern Europe* is the first project generated through the Workgroup, as a result of feedback and consultation with participating members.

ABOUT MYELOMA

Myeloma, also known as multiple myeloma, is a rare and incurable cancer of the bone marrow affecting around 50,000 patients in Europe each year. The most common symptoms of myeloma include bone pain, recurring infection, kidney damage and fatigue. Myeloma is a relapsing and remitting cancer: patients will start treatment and may enter a period of remission before the reappearance of symptoms. During remission phases, patients will either continue treatment or undergo observation. Relapses can occur several times during myeloma, when it is again necessary to start or change treatment. The treatment landscape of myeloma is very complex and can include a stem cell transplant and combinations of three to four drugs at a time, such as chemotherapy, immunotherapy and steroids.

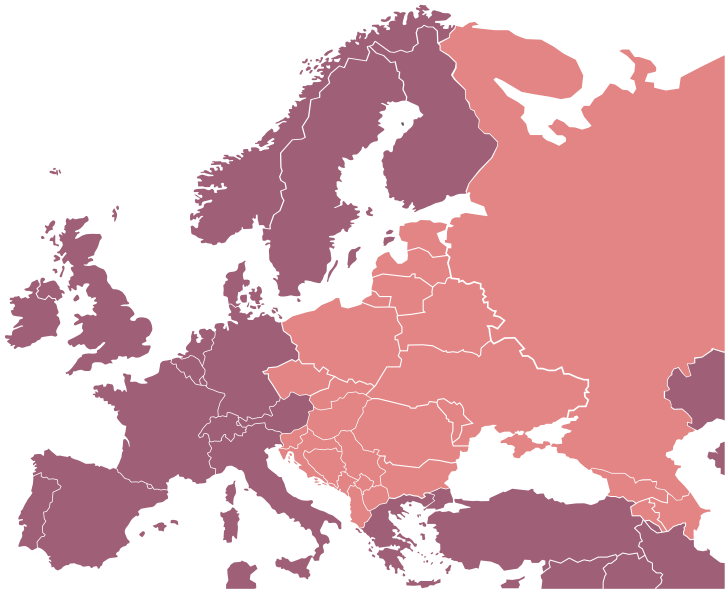
Myeloma is the second most common blood cancer after leukaemia. It primarily affects people who are over the age of 65. However, 40% of myeloma patients were between 15 and 64 years-old in 2020 (see Table 1). A Swedish data set shows half of patients who reported being employed at time of diagnosis had to stop working or retire (Goodwin JA, 2013).

In a study of the World Health Organisation (WHO), based on 2012 figures, the incidence of this blood cancer is projected to increase by 17% by 2025, making myeloma a top priority for the research field.

RATIONALE AND OBJECTIVES

Clinical trials are fundamental to finding a cure for myeloma and improving quality of life. For many cancer patients who have exhausted all standard of care (SOC) treatment options and even some who have not, clinical trials provide hope for successful treatment outcomes (Babiker HM, 2019). However, over the last few years, multiple patient advocates have informed MPE of the lack of opening of clinical trials in many CEE countries, as well as inequalities in access between CEE patients participating in ongoing trials.

It is estimated that, even in the US where most clinical trials are conducted, less than 1% of the population participates in them despite the claim from more than 70% of the population that they would if recommended by their physician (Barrios CH, 2018) (Sacristán, 2016). Available data in the literature on cancer patient participation in clinical trials comes from the US. Most adult US cancer patients do not participate in clinical trials. Estimates of US adult cancer patients' participation in clinical trials range from 2% to 8%, even though most Americans view clinical trial participation favourably (Unger JM, 2019) (Babiker HM, 2019) (Ellis S, 2019) (Steensma D.P., 2018) (Sacristán, 2016) (Rivers D, 2019). The rate of participation is likely similar, if not lower in other regions of the world, including CEE countries. This gap between the patients' willingness and actual participation rates suggests there are numerous barriers to participation that need to be explored.



MPE plays a significant role in advocating for fair and equal access to myeloma clinical trials in Europe. This paper aims to start an important discussion on the barriers preventing patients from participating in clinical trials, with a focus on CEE countries, and the minimum standards patient organisations and individual advocates need to campaign for to ensure myeloma clinical trials are conducted in their country and that patients have access to.

OUR APPROACH

MPE undertook two consecutive studies between September 2020 and August 2021 to better understand the barriers and facilitators to clinical trials in CEE countries and more broadly outside of the region. MPE took a broader definition of CEE than that of the World Bank. In addition to Bulgaria, Croatia, the Czech Republic, Hungary, Poland, Romania, the Slovak Republic, Slovenia, Estonia, Latvia and Lithuania, it also included Western Balkan countries (Albania, Bosnia and Herzegovina, North Macedonia, Montenegro, Serbia and Kosovo), the European Union (EU)'s Eastern European Neighbourhood Policy Partners (Armenia, Azerbaijan Belarus, Georgia, the Republic of Moldova and Ukraine) and the Russian Federation.

The first study consisted of CEE myeloma trial analytics over the past 10 years, while the second included a literature review on minimum standards of infrastructure required to conduct clinical trials in all countries [See Appendices 6.1, 6.2, 6.3 and 6.4]. In a third step, interviews with Polish, Croatian and North Macedonian stakeholders were conducted to further examine collected data [see Appendix 6.5 for more details on country selection and interviewee list].

Utilising the results and analysis of these two studies, MPE has developed a call to action for patient organisations, advocates and other stakeholders with recommendations on what can be done to improve patient participation in trials and reduce inequalities in access.

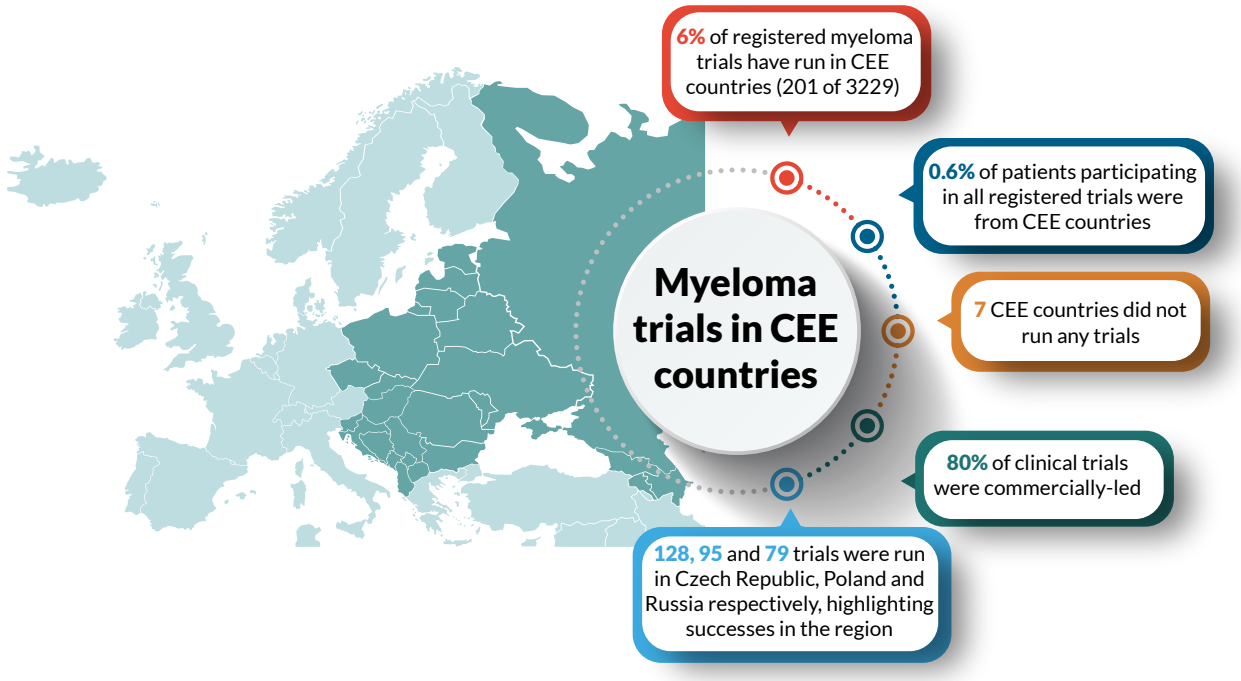
MPE plays a significant role in advocating for fair and equal access to clinical trials in Europe

3. GLOBAL OVERVIEW OF MYELOMA CLINICAL TRIALS IN CEE

This section shows a summary of the results of the CEE myeloma clinical trial analytics, which constitutes the first of three parts of the present study. The second and third parts of the study — a literature review exploring barriers and facilitators to clinical trial access in Europe and interviews with physicians, researchers, regulators, and patients in Poland, Croatia, and Macedonia — are summarised in section 4.

Between 1 January 2001 and 28 September 2020, 3,229 myeloma trials enrolling 2,770,000 patients were recorded across 18 global trial registries [see list of registries in Appendix 6.1]. Only 201 clinical trials enrolled CEE patients across 100 research centres/hospitals. In other words, only 6% of the totality of myeloma trials registered worldwide included patients from CEE (see Table 4 in Appendix 6.1). EU membership seems to be a facilitator to setting up clinical trials: of the 17 CEE countries that ran at least one myeloma clinical trial, 11 are EU members [see Table 1 and Appendix 6.2 for more details on myeloma research centres].

Trial analytics show the CEE leaders in myeloma research in terms of numbers of registered trials relative to recorded myeloma incidence are the Czech Republic, Hungary and Bulgaria, (see Table 1). Complementary studies are needed to "map" and understand what infrastructure is in place supporting myeloma research in these countries relative to other CEE countries.



Global overview of myeloma trials in CEE between January 2001 and September 2020

Table 1: Myeloma trials run in CEE countries between 1 January 2001 and 28 September 2020 (201 trials)

	Country	Myeloma trials enrolling country specific patients	Frequency of country inclusion in myeloma trials enrolling CEE patients	Identified myeloma research centres	2022 population	2020 myeloma incidence	2020 myeloma 5-year prevalence	EU members	EU entry date
1	Czech Republic	128	63.7%	9	10,705,384	574	1,607	Yes	2004
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16	Belarus	2	1%	1	9,413,505	334	878	No	N/A
17	Slovenia	2	1%	0	2,101,208	173	476	Yes	2004
18	Montenegro	0	0%	0	604,966	22	58	No	N/A
19	Albania	0	0%	0	3,095,344	36	92	No	N/A
20	Armenia	0	0%	0	3,000,756	31	79	No	N/A
21	Azerbaijan	0	0%	0	10,353,296	178	436	No	N/A
22	Bosnia & Herzegovina	0	0%	0	3,816,459	96	232	No	N/A
23	Moldova	0	0%	0	3,287,326	88	205	No	N/A
24	Kosovo	0	0%	0	1,952,701	N/A	-	No	N/A

More details on the analytics methodology and results in Appendices 6.1 and 6.2.

MPE, with the support of Consilium Scientific, has searched 18 clinical trial registries for all myeloma clinical trials, which recruited CEE patients between Sept 2001 and Sept 2020. Out of the 3,229 myeloma trials, 201 included at least one recruitment centre in CEE.

2020 myeloma incidence and prevalence: https://gco.iarc.fr/today/online-analysis-table, 2020

Country population: https://www.cia.gov/the-world-factbook/countries/

N/A: not available

Of note, the data in table 1 only shows clinical trials run in research centres identified through myeloma trials, which were run in CEE and registered in ClinicalTrials.gov or any of the 17 primary registries in the WHO registry network. If there aren't any centres reported in Table 1, it does not mean that research centres do not exist in these countries.

Of the 201 registered clinical trials over this period, 114 were due to report their results by September 2019 and should have had results available by September 2020. Of those 114 trials, 86.9% (n=99) reported results either in a journal and/or a registry, but 10% of the data was still missing by September 2020. Results reporting in registries is more frequent than in journals with 58.8% (n=67) vs. 28% (n=32) respectively. Of note, 26% (n=30) of trials that uploaded results in registries were never published. The proportion of trials that reported both in registries and journals is 32% (n=37).

About 40% of the 114 trials featured enrolment data (i.e., numbers of patients recruited to participate) (n=46) and included a total of 4,822 patients [see Table 2 below and Appendix 6.2 for more details].

Table 2: CEE patient enrolment data published between 1 January 2001 and 28 September 2020 (46/201 trials)

	US National Library of Medicine database and European Union Clinical Trial register (17 CEE only trials)	US National Library of Medicine database (12 NCT Trials)	European Union Clinical Trial register (17 EU trials)	Total 46 trials
Total patient enrolment (patients)	2,426	4,825	5,137	12,388
CEE patient only enrolment (patients)	2,426	1,369	1,027	4,822
% CEE patients across trials	100%	28.4%	20.5%	

In the 29 trials, that ran in both the US and the EU (see Table 2) and included patients from CEE countries, CEE patients represented on average about 24.05% of the trial population. However, if we consider all myeloma trials run worldwide (n=3,229), only 0.6% of recruited patients are from CEE countries [See Appendix 6.2 for calculation details].

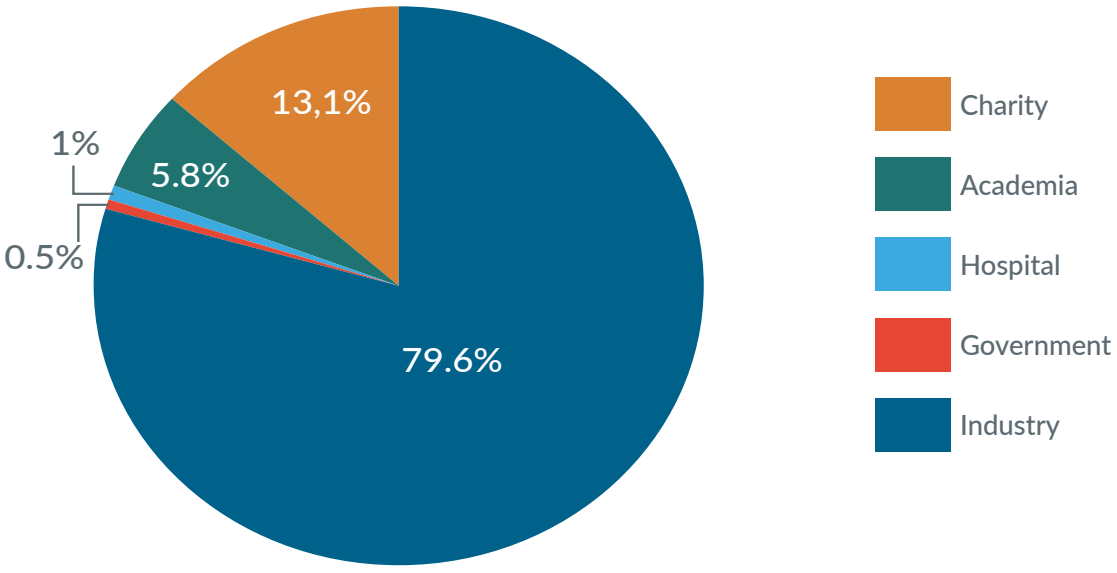
In trials recruiting patients from CEE countries, the average duration was 59 months (4.9 years) with varying duration according to the trial type as shown in Table 3. The average duration was calculated by taking the start date and the end date of clinical trials reported in registries.

Table 3: Myeloma trial duration by phase (148/201 trials)

Type of trials	Duration in months (years)
Phase 1	45 (3.8)
Phase 2	53 (4.4)
Phase 3	68 (5.7)
Phase 4	29 (2.4)
Early Access	42 (3.5)
Observation	13 (1)

Our findings also show that close to 80% of myeloma clinical trials including CEE research centres and patients were run primarily by the pharmaceutical industry [See Figure 1]. While a disproportionate amount of industry-run clinical trials is common, we hypothesise that this heavy reliance is primarily due to the level of investment and resource available to industry sponsors, relative to charity, academic, government and hospital stakeholders in the region.

Figure 1: Who is running myeloma trials?



4. BARRIERS AND FACILITATORS TO SETTING UP CLINICAL TRIALS

Following the completion of the myeloma clinical trial analytics, MPE initiated a literature review on the minimum requirements, as well as the incentives and disincentives, to conduct myeloma clinical trials in the European Union and non-EU CEE countries. Of the 2,696 articles extracted from the PubMed, Scopus, and Lens databases, 24 were eventually selected. The full search strategy is outlined in Appendix 6.3.

MPE used Siembida et. al.'s narrative approach to organise the literature review results (Siembida, et al., 2020). This framework details the clinical trial enrolment process and subsequent patient participation as a series of steps, phrased as questions. For successful enrolment and participation, all these questions require a positive answer:

Does a clinical trial exist?

This refers to whether a study for that disease and patient population has been developed and activated.

Is the clinical trial accessible?

This refers to whether that study is available at the site where the patient has sought cancer treatment.

Is the patient eligible?

This refers to whether the patient fulfils the eligibility criteria.

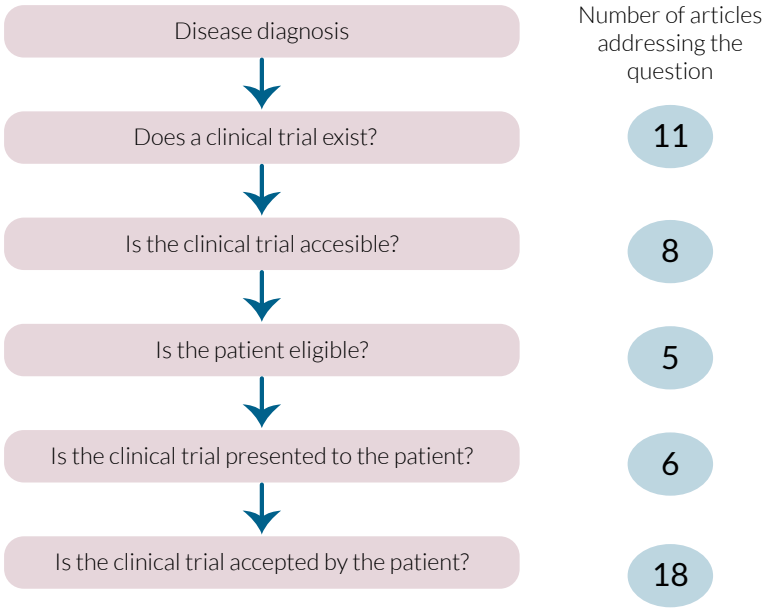
Has the clinical trial been presented?

This refers to whether the treating physician has offered participation in a clinical trial as a treatment option to an eligible patient.

Has the clinical trial been accepted?

This refers to whether the patient has provided written informed consent to be enrolled onto that study.

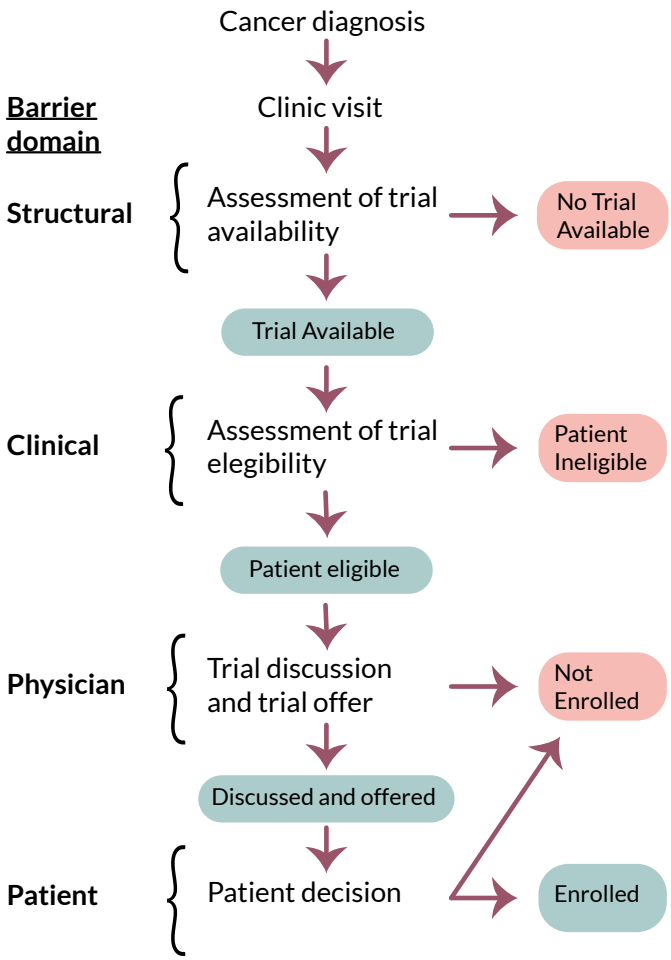
Figure 2: Organisation of the literature review results according to Siembida et al.'s narrative approach (total of 24 articles)



(Siembida, et al., 2020)

MPE cross-checked Siembida et al.'s narrative approach with that of Unger et al. below (Unger JM, 2019), whereby step one and two correspond to structural barriers (relating to trial availability), while step three addresses clinical challenges (relating to patient eligibility). Steps four and five deal with physician and patient barriers (see Figure 3).

Figure 3: Unger's conceptual framework to barriers to clinical trials



The results of the literature review were structured and analyses in line with these two frameworks.

(Unger JM, 2019)

The results of the literature review were structured and analyses in line with these two frameworks.

MPE then used the clinical trial analytics to select three countries for further analysis via qualitative interviews. Poland (95 trials), Croatia (eight trials) and Macedonia (three trials) were selected as in countries with high, medium, and low clinical trial availability. The stakeholder perspectives from Poland, Croatia, and Macedonia complemented the information gathered via the literature review.

4.1. STRUCTURAL BARRIERS AND FACILITATORS (RELATING TO TRIAL AVAILABILITY)

4.1.1. LITERATURE REVIEW AND STAKEHOLDER PERSPECTIVE

4.1.1.1. DOES A CLINICAL TRIAL EXIST?

Patient population size

Trial analytics

Patient population size is determined by the rarity of the condition and the size of a country's population. Both are correlated to the number of trials run in a country. Trial analytics confirm that the larger a country's population is — and the more common the disease — the bigger the pool of eligible patients to participate in a trial and the more likely a trial will take place.

- With a population of 38 million people and a five-year prevalence of 6,148 myeloma patients in 2020, Poland ranks second with 95 myeloma trials set up between 2001 and 2020
- With a population of four million people and a five-year prevalence of 712 myeloma patients, Croatia ranks eleventh out of 24 CEE countries with eigth myeloma trials set up between 2001 and 2020
- With a population of two million people and a five-year prevalence of 88 myeloma patients, North Macedonia ranks fifteenth out of 24 CEE countries with three myeloma trials set up between 2001 and 2020 (see table 1)

In relative terms, the Czech Republic, Bulgaria and Hungary are the more efficient CEE countries for including patients in trials or setting up trials (see table 1), given the number of trials conducted relative to the myeloma patient population. Population size is therefore not the only determinant of clinical trial set-ups.

Polish, Croatian and Macedonian stakeholder perspectives

Stakeholders all agreed that population size is the first decision-making factor for pharmaceutical industry sponsors to set up a clinical trial. Sponsors are likely to favour a de-risking strategy of their investment and will choose countries with the largest patient populations, except in diseases that primarily affect specific racial and ethnic minority groups.

> *"According to my experience with sponsors, the size of the patient population is one of the main factors of attractiveness."*
>
> POLISH UNIVERSITY CLINIC HAEMATOLOGIST

> *"When we looked at the table, the small percent of myeloma clinical trials in Croatia did not surprise us. Croatia is not a champion of clinical trials because of the size of the market (…) The goal of industrial sponsors is to minimise the cost of clinical trials, not only myeloma clinical trials. To do that, they must be most effective in choosing as few sites as possible. They will target countries with big populations"*
>
> CROATIAN CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

> *"We have myeloma patients — 60 newly diagnosed patients per year. The problem is the willingness of commercial sponsors to set up clinical trials in Croatia."*
>
> CROATIAN HAEMATOLOGIST

> *"We are not attractive for clinical trials. Only two million citizens. It's not enough (…). Pharmaceutical companies work for profit. They will go to countries where there are many patients and a potential market. We don't have those two conditions."*
>
> NORTH MACEDONIAN PATIENT ORGANISATION REPRESENTATIVE.

Further exploring the impact of population on clinical trials, despite its larger number of patients, stakeholders outlined that Poland's full potential is currently untapped due to structural and clinical barriers.

> *"Poland has proven that it is able to recruit patients, but this is not enough (…) We are second after the Czech Republic, which has a smaller population (less than 10 million) and a smaller population of myeloma patients. We can't say that the market is saturated in Poland."*
>
> POLISH CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

> *"Taking into account the Polish population, the number of clinical trials could be higher."*
>
> POLISH HEALTH AUTHORITY REPRESENTATIVE

North Macedonian stakeholders outlined that despite recent efforts to increase clinical trials in the country, the numbers participating remained low. There have also been difficulties in diagnosing and reporting new cancer patients due to the COVID-19 crisis, given the burden on the healthcare system and patients not presenting. This situation may further impact the market size and attractiveness of North Macedonia for sponsors.

> *"The inclusion of North Macedonia in clinical trials is very recent, especially in haematology. Since 2005, we have set up 100 clinical trials in North Macedonia, all pathologies combined."*
>
> NORTH MACEDONIAN CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

> *"This low ranking is not surprising. The attractiveness of the country is not sufficient despite the efforts of the recent years."*
>
> NORTH MACEDONIAN PATIENT ORGANISATION REPRESENTATIVE

> *"Because of the COVID-19 crisis, we observed a decrease of the number of newly diagnosed patients with lymphoma. The same observation has been made for myeloma patients."*
>
> NORTH MACEDONIAN PATIENT ORGANISATION REPRESENTATIVE.

Health care funding, financial incentives for research and national cancer/rare disease plan or strategy

Literature review

Clinical trials, and especially confirmatory randomised controlled trials (RCTs), are both costly and time-consuming. Lack of funding remains one of the largest barriers towards their completion (Djurisic S, 2017) (Chan A.Y.L., 2020) (Rath A, 2017). Given the expense and length of setting up trials, it can be hypothesised that sponsors are likely to direct their resources towards countries able to provide a supportive environment for research and where access is more likely in the long run. However, this is anecdotal and requires further exploration.

Trial analytics highlighted that many clinical trials do not run in CEE countries and 80% of those that do run are conducted by the pharmaceutical industry. Literature also highlighted a considerable percentage of trials have depended on support from pharmaceutical companies as trial finance and logistic requirements often exceed available resources in most academic centres (Barrios CH, 2018). For example, the cost of supplying a standard of care drug in a country where it is not routinely covered makes the trial impossible in the absence of substantial funding, especially for academic trials (Tang M, 2019).

Academic trials are generally underfunded and short lived, despite their importance in optimising cancer care (e.g., new combinations of standards care, multimodal treatment regimens or cost-effectiveness evaluations). Without high-quality academic trials, general public-health issues, country-specific questions of limited interest for pharmaceutical companies may not be addressed (Djurisic S, 2017). There are also likely to be structural and

Many clinical trials do not run in CEE countries and 80% of those that do run are conducted by the pharmaceutical industry.

institutional barriers to establishing academic clinical trials within countries, that were not covered in depth by the literature but that need to be explored.

The coverage status of standard of care may contribute to longer timelines and increased costs for study activation (Tang M, 2019) (Djurisic S, 2017). Given the speed of innovation currently seen in cancer trials (e.g., in diagnostics and CAR-T), and the inequality in access to specialised procedures and existing medicines, it can be hypothesised that the gulf between countries that can run precision trials, and those that cannot, is increasing. In addition, the further countries get from the 'standard of care' set by leading countries (such as the US and Germany), the less likely countries are to attract trials and investment.

In relation to political commitment to funding clinical trials, national policy decisions also play a role and the literature review found that the existence of national cancer plans may indicate a potential 'readiness' of the country to respond in the field of orphan drugs and rare diseases – although they do not put specific legislation in place (Gammie T., 2015) (Chan A.Y.L., 2020). For example, the Czech Republic, Bulgaria, Estonia, Latvia, Macedonia, Poland, Romania and Serbia had established national plans for rare diseases in 2015, while Slovakia and Hungary had not (Gammie T., 2015), which may have a bearing on the level of research. A detailed analysis of country-specific policies on research was outside of the scope of this project but is something that should be explored in future research.

Polish, Croatian and Macedonian stakeholder views

While Poland has benefited from better access to both academic and industry sponsored clinical trials than other CEE countries, discussions with Polish healthcare authority representatives highlighted that investigation centres' financial contributions are unpredictable, representing an important barrier for industry sponsors. The planning and set-up of oncology and haematology clinical trials has therefore been challenging due to volatile and unpredictable funding commitments.

Croatian and North Macedonian stakeholders outlined that there are low numbers of clinical trials being run in the respective countries and that when physicians are involved in clinical trials, they generally receive funds from industry sponsors rather other sources. Academic trials are rare in these countries, confirming perspectives outlined in the literature review that they suffer from lack of resources and under-funding.

> ***"There are many more academic trials in Western Europe than in CEE. I do not say that there aren't any trials, but the number is low. I think it is related to a lack of funding."***
>
> CROATIAN CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

> ***"Academics are not in this sprint. All the clinical trials are supported by pharmaceutical companies."***
>
> NORTH MACEDONIAN CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

Croatian and North Macedonian stakeholders also agreed that the lack of academic clinical trials is attributable to the lack of public funding for research and development, hindering their ability to

establish and conduct clinical trials. Additionally, the high cost of publication may also be a disincentive for CEE academic researchers to publish – an issue specifically highlighted in North Macedonia. For some specialised haematology journals, the cost of publication is equal to the average Macedonian salary. Without publications, the chances of being financed are slim, hereby impacting research capacity (less dedicated staff and new equipment).

> *"It's a vicious circle. There is a small number of scientific publications, a lack of visibility of research potential and North Macedonian haematologists are not chosen to be part of randomised clinical trials"*
>
> NORTH MACEDONIAN HAEMATOLOGIST

The lack of long-term political commitment and funding in North Macedonia was mentioned as a key challenge.

> *"The appointment of the Director of the Centre of Investigation depends on the governing political party. Every four years, there is a risk of change of party and change of direction that could impact the willingness to participate in clinical trials. Political influence and decision-making are centralised. To make matters worse, there is also a lack of predictability on the funding of generic bortezomib and lenalidomide. Both backbones are available on a "conditional" budget, pending on fulfilling the treatment requests in a previous period and for which a specific quantity was obtained. Haematologists depend on health authorities' willingness to maintain and renew the payment of these drugs out of the conditional budget."*
>
> NORTH MACEDONIAN PATIENT REPRESENTATIVE

The stakeholder interviews supported the importance of high levels of political commitment and consistent investment in research and development within countries to facilitate the establishment and availability of clinical trials for patients. Consistent funding for medicines and access to a good standard of care is also important in supporting clinical trials, particularly in comparative RCTs. A predictable and supportive research environment, including financial incentives, for both companies and academic researchers is key. Further research is required to understand the exact types of research and development investment that need to take place to advance industry sponsored and academic clinical trials.

The existence and potential positive impact of rare disease or cancer plans was not raised by interviewees.

Research infrastructure and qualified staff

According to the European Research Infrastructure Consortium, research infrastructure is understood as major scientific equipment or sets of instruments; knowledge-based resources such as collections, archives, or structures for scientific information; enabling information and communications technology-

based infrastructures such as Grid, computing, software and communication, or any other entity of a unique nature essential to achieve excellence in research. Such infrastructures may be 'single-sited' or 'distributed' (an organised network of resources).

Literature review

A core element of this project was to understand what research infrastructure and workforce planning countries require to be able to run clinical trials effectively and safely. While there was not extensive detail in the literature on this topic, despite its importance, the core perspectives are summarised and discussed. Further studies should expand on the specificities of this topic and mapping out and reaching consensus on the minimum standards required in healthcare systems to conduct clinical trials.

Literature highlighted that precision oncology and haematology trials, such as those using immunotherapies, require multiple and specialised procedures (physical exams, tumour biopsies, laboratory tests such as next-generation sequencing, special investigational product preparation such as in CAR-T, timely pharmacokinetic sampling and routine imaging evaluation) and capacities to collect and manage patient tissue/bone/blood samples, and capture, store, share and manage patient data. Labelling, transport and storage requirements were highlighted too (Arai RJ, 2019) (Babiker HM, 2019). Variations in access to these listed specialised procedures and in patient material and data management may also impact on the ability of countries to run precision trials in cancer. Many precision medicines coming with specific safety issues, such as cytokine release syndrome and infusion reactions, require extra monitoring. Countries therefore need investment in hospitals, laboratories, diagnostics, scanning machinery and the specialised training and workforce to ensure access to these procedures.

Looking at the topic of workforce planning, the literature emphasised that adequate staffing is critical for the set-up of cancer clinical trials and to fulfil protocol-driven requirements (such as testing, monitoring and follow-up requirements) (Arai RJ, 2019) (Babiker HM, 2019) and to prevent disruption due to workflow issues. In many cancer trials, the availability of nurses is a crucial element as they play a role in the enrolment, treatment administration, informed consent, care and monitoring of patients. The recruitment of nurses is often difficult in healthcare systems, often due to pay parity issues (Babiker HM, 2019). The excessive workload on nurses and lack of investment in healthcare systems and training programmes are often cited as barriers to the availability of nurses. Research specialist nurses, or nurses with experience in research, are often required by healthcare systems/hospitals to run clinical trials – however this expertise may not be widely available.

Clinical trials in cancer mainly rely on the role of physicians to act as principal investigators either for the operation of a trial in a country or for a specific hospital/local site. The ability of physicians to do this relies on high-quality training in clinical trials. The literature emphasised that physicians may lack the appropriate support for participating in clinical trials (Unger JM, 2019). Inadequate knowledge and understanding of clinical trial methodology, especially randomized controlled trials, has been flagged as a barrier (Rath A, 2017). Past surveys from the ECRIN have also highlighted the need for support in training staff on the conduction of clinical trials and to educate physicians about rare diseases (Djurisic S, 2017). Nothing arose from the literature on whether there are different skills, training and knowledge required for physicians participating in academic vs. industry clinical trials.

As well as physicians and nurses, additional non-hospital-based stakeholders are also needed to

facilitate optimal cancer clinical trial operations, namely governmental staff prepared to regulate biotechnology and handle innovative products and attorneys with expertise in clinical trials (Arai RJ, 2019). The benefits of a 'patient navigator' (i.e., a care coordinator) to facilitate the elimination of barriers and movement through the process have also been documented (Babiker HM, 2019) (Ahaghotu C, 2016) (Cartmell KB, 2020).

Polish, Croatian and Macedonian stakeholder perspectives

The stakeholder interviews confirmed the significance and impact of disparities in infrastructure, equipment, and staff experience and training on the conduction of clinical trials. Poland compared favourably in the interviews and in the trial analytics with 21 identified myeloma research centres, although it was not without its challenges.

Interviews discussed that trial expertise is more likely to be found in countries with larger populations and developed healthcare systems. Access to trials may also vary within countries, between larger hospital centres with myeloma expertise and smaller, local hospitals. Smaller hospital sites neither have the authorisation nor the myeloma specialists, necessary equipment and facilities, and the qualified staff to even perform stem cell transplantation, let alone invest in clinical trials. This points to the role of myeloma specialists, expertise centres and key opinion leaders as being important in attracting and conducting research.

> *"Poland is attractive because of the size of their population and the level of development of the healthcare system"*
>
> POLISH HAEMATOLOGIST

> *"It will be easier to find a haematologist able to initiate a clinical trial in a big hospital such as Zagreb than in smaller hospitals (e.g., in Zadar hospital with only two haematologists: their time is dedicated to conventional patient care)."*
>
> CROATIAN HAEMATOLOGIST

> *"Macedonian haematologists are not specialists of one disease. They care for all the haematological malignancies."*
>
> NORTH MACEDONIAN HAEMATOLOGIST

> *"Lack of equipment for very advanced methods might be an issue, although in some areas we are quite well equipped."*
>
> NORTH MACEDONIAN HAEMATOLOGIST

Hospital management in both Poland and Croatia has overall shown a lack of willingness to invest in clinical trials. One of the consequences has been the lack of time dedicated to clinical trial activities, with

haematologists and nurses involved in clinical trials doing it on their own time.

> *"In Poland, there aren't many haematologists specifically dedicated for the coordination of the clinical trial and it is an issue."*
>
> POLISH CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

The lack of qualified staff to run clinical trials in Croatia is also attributed to a potential boomerang effect of the 2013 EU accession. Large numbers of Croatian medical, technical and support staff (e.g., data management or clinical coordination) have migrated to Western Europe in search of better work conditions. This has been an unexpected effect of EU membership and, anecdotally, is one that has been seen in other CEE countries.

Discussions from within the cancer advocacy and policy communities on Europe's Beating Cancer Plan have confirmed that the number of physicians and nurses leaving Eastern countries to work in Western and Central Europe continues to increase, despite significant Member State investment in their training. This situation causes significant issues for cancer patient treatment and care in the countries that they leave in the absence of specialist physicians, multi-disciplinary decision-making, a lack of continuity of care and hospitals facing staffing shortages. This situation is most profound in rural or community-based hospitals and areas.

Retention and incentivisation for healthcare professionals involved in clinical trials to work in CEE countries is important for the conduct of clinical trials. EU and national policies designed to increase the attractiveness and conditions of professions to deter 'brain drain' are therefore urgently needed.

Administrative and regulatory requirements and EU membership

Literature review

Administrative and regulatory requirements

Administrative and bureaucratic burden involves patient information and informed consent processes, ethics committee submission, insurance acquisition, activation of clinical centres, data protection rules, investigator reimbursement (Rath A, 2017) and payer systems (Babiker HM, 2019).

It is often cited that excessive administration and bureaucratic "red-tape" governing the establishment and regulation of clinical trials negatively impacts on the number of trials in a country or geographical area. It is documented that complex and heterogeneous regulations can increase the burden of documentation and compliance on investigators (Barrios CH, 2018) (Tang M, 2019), which can lengthen the time taken to activate national and international trials and delay study results (Barrios CH, 2018) (Arai RJ, 2019) (Rath A, 2017). Not only does it lengthen the time to set up clinical trials, it also reduces the willingness and ability of physicians to get involved in clinical research and may contribute to early trial terminations (Haddad RI, 2015).

An essential requirement of any clinical trial is to guarantee that patients are fully aware of protocol procedures and understand properly the risks and benefits involved as well as treatment alternatives, if

applicable. This information is provided in the informed consent form (ICF) and must be objective, adapted to local culture and presented in lay terms (Arai RJ, 2019). Informed consent procedures are handled by ethics committees. Patients' fear of subjecting themselves to large volumes of paperwork associated with the informed consent (Babiker HM, 2019) (Byrne M, 2017) is a deterrent. The complexities of consent forms and procedures prevent most notably racial and ethnic minority populations from participating (Salman A, 2015), as well as patients with low socio-economic backgrounds (Sacristán, 2016) (Nipp RD L. H., 2019).

As well as informed consent procedures, ethics committees review clinical trial proposals and protocols to see if research is ethical, conforming to recognised national and international ethical standards and respects the safety, rights and well-being of patients that participate. Local ethics committee procedures have been identified as an important barrier to participation in academic research by oncologists, particularly in low-middle income countries (Tang M, 2019). Complex systems of ethical approval can lead to additional bureaucracy and delays in approval of clinical trials. In Europe, there is no centralised system of ethical review, meaning that researchers potentially must go through multiple levels (e.g., national and institutional) of ethical review to open clinical trials – particularly where they are multi-centre and multi-country. The EU Clinical Trial Regulation 536/2014 has tried to streamline the length of time it can take for regulatory approval, which could have a favourable impact in EU member states.

It can be speculated that a high level of human and financial resource is required to open clinical trials (which can potentially explain the higher level of industry trials in CEE countries vs. academic trials) and countries with easier-to-navigate systems of ethical approval are favourable for the conduct of trials. As a result, industrial sponsors have often shied away from setting up trials in low and middle-income countries, such as some in the CEE region, as they expect a lower return on investment, higher costs and are uncertain of reimbursement at the end of process.

EU directives, regulations, and membership

Regulatory timelines are considered one of the most important elements in the conduct of clinical trials. When pharmaceutical companies carry out their category planning, timelines for assessment and approval are considered a key indicator of a country's attractiveness (Barrios CH, 2018).

The original EU Clinical Trials Directive 2001/20/EC hampered clinical trial development, especially academic trials, as it required that all clinical trials in the EU be conducted in compliance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, including the requirement for single sponsorship of multicentre trials and increased auditing by regulators (Tang M, 2019) (Haddad RI, 2015). Additionally, the fact it was a Directive meant individual countries devised their own laws to reach the targeted goals (as opposed to EU Regulations, which are directly applicable). This caused regulatory approval for clinical trials across the EU to become exceptionally complex (Djurisic S, 2017)

While it is documented that the EU Directive 2001/20/EC has generated delays in clinical trial activation in countries with limited clinical trial experience (Tang M, 2019) (Djurisic S, 2017), trial analytics suggest that the regulatory approval of drugs at EU level is a benefit for smaller countries with limited health care resources. It removes the regulatory hurdle for sponsors, which would have not deliberately chosen to apply for marketing authorisation in those countries had they not been part of the EU.

To harmonise processes and ensure the EU remains an attractive site for clinical trials, the European Commission proposed the EU Clinical trial Regulation 536/2014, which came into application on 31 January 2022. This regulation is a binding legislative act and must be applied in its entirety across the EU. It includes a Clinical Trials Information System (CTIS), which contains a single European clinical trial registration portal. This portal is a 'one-time' consent for use of patients' data, tissues and biological samples. The EU Clinical Trial Regulation also caters for a new category of 'low-intervention clinical trials' with simplified, risk proportional monitoring (Tang M, 2019). It is key that the patient advocacy community monitors the implementation of this regulation during the implementation phase to ensure it benefits patients and their participation in clinical trials, particularly in countries where this has been more difficult to date.

Literature suggests that EU membership is a facilitator to setting up clinical trials and for bringing a drug to market in the region. The reasons for this are complex but two core areas were highlighted:

- EU membership provides additional research and development incentives to drug sponsors in the form of fast track approval and pre-licensing access, as well as scientific advice or consultation concerning the design and implementation of orphan drug trials (Chan A.Y.L., 2020) (Gammie T., 2015)
- Orphan medicines which receive marketing authorisation in the EU benefit from patent protection in the form of market exclusivity. Market exclusivity is a key incentive, which is intended to encourage the development of medicines for rare diseases. It protects them from competition from similar medicines with similar indications, which cannot be marketed during the exclusivity period. Market exclusivity duration ranges from five years (Australia), seven years (United States), 8-8.5 years for paediatric orphan drugs (Canada) to 10 years (European Union, Japan, Taiwan) (Chan A.Y.L., 2020) (Gammie T., 2015)

While not expressly covered in the literature review, it can also be raised that EU health policies such as the European Reference Networks incentivise research in Europe as they demonstrate the role of established networks of expertise across countries and within disease areas. In addition, standards are in place that streamline the good manufacturing practice (GMP) of medicines and minimum standards to be upheld, meaning clinical trials and medicines always meet a high standard supporting the safety of patients and the accuracy of results obtained. Finally, while there were issues with the original EU Clinical Trial Directive, the new regulation is working to streamline and centralise the regulation of clinical trials, which may further reduce the regulatory burden for both commercial and academic stakeholders in the future. Moving forward, the role of specific EU policies should be explored for specific success in incentivising research to take place – however, this was outside of the scope of this research. There are also likely to be national variations in incentives for pharmaceutical companies to conduct clinical trials in countries (such as tax incentives), which should be explored in further studies.

Polish, Croatian and Macedonian stakeholder perspectives

In discussions around administration, bureaucracy and ethics, Polish stakeholders concluded that the complexity of their health care system, its clinical trial procedures and the lack of contract templates have led to very long registration delays. The resulting administrative burden has been a major barrier,

particularly for non-commercial clinical trials. They pointed out the Czech Republic's success in conducting research, which originates from a streamlined and fast clinical trial agreement negotiation and registration process.

> *"The Polish health system is complicated. I think that one of the main reasons could be the organisation of the system."*
>
> POLISH HEALTH AUTHORITY REPRESENTATIVE

> *"The process of registration is not easy for sponsors especially for those that are non-commercial. There are several administrative documents required (agreements, letter of authorisation, etc. in original version and translated)."*
>
> POLISH HEALTH AUTHORITY REPRESENTATIVE

> *"Negotiating clinical trial agreements is quicker and more efficient in the Czech Republic than in Poland. Because of this, we suffer from delays in the initiation of clinical trials. We cannot start a trial in Poland when the other countries have already finished."*
>
> POLISH CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

As a result, key reforms were introduced early 2019 in Poland with changes in the Act on the Pharmaceutical Law to simplify procedures for obtaining permission for clinical trials. Most specifically, applications for permissions to start clinical trials will not require a prior review by bioethics commissions or submission of certain related documentation.

Administrative and regulatory requirements have not been raised by Croatian and Macedonian stakeholders. This could be related to the lack of experience of researchers in setting up and participating in clinical trials. Due to the small sample size of interviewees, additional field work is needed to further explore these types of barriers to clinical trials.

According to Polish and Croatian interviewees, earlier EU accession was also underlined as a favourable factor (2004 for Poland and the Czech Republic vs. 2013 for Croatia), while one of the hypotheses put forward to partly explain North Macedonia's low clinical trial rank (15/24) is the lack of EU membership.

> *"We have now patients treated with CAR-T cells (11 patients), which proves that things are moving forward. I think that this is due to our recent accession to the EU."*
>
> CROATIAN HAEMATOLOGIST

> *"When we analyse the table, we can distinguish EU member countries, except the Russian Federation and the other countries. The EU members seem to succeed at conducting many myeloma clinical trials."*
>
> NORTH MACEDONIAN HAEMATOLOGIST

Interviewees were asked why they thought the EU was a successful place to do research. Polish stakeholders outlined that as an EU member, Poland benefits from the introduction of new regulations to improve the clinical trial registration process. In April 2021, the draft of a law to increase the attractiveness of conducting clinical trials in Poland (Act on Clinical Trials of Medicinal Products Used in Humans, AoCTMPUH) was published for consultation. This new regulation implements the EU Clinical trial Regulation 536/2014 in clinical trials on medicinal products for human use and repeals Directive 2001/20/EC.

International R&D collaborations

Literature review

International collaboration is key to educate, train and nurture the next generation of clinical researchers, as it provides opportunities to work with experienced clinical trial organisations and improve healthcare through investment in local infrastructure, and training of investigators and healthcare personnel (Tang M, 2019)(Barrios CH, 2018). In Europe, such collaboration and education are facilitated by organisations such as the European Haematology Association (EHA), the American Society of Haematology (ASH) and the European Myeloma Network (EMN). The advocacy community also runs initiatives to support this. However, there is little information detailing the breadth, impact and success of these types of initiatives – particularly in CEE countries.

Polish, Croatian and Macedonian stakeholder perspectives

Polish and Croatian interviewees attributed the high number of clinical trials run in the Czech Republic to the high R&D profile of haematologists, the volume of publications and their strong collaboration with Western Europe. They concur that academic clinical trials are needed to publish and have impact at an international level.

> *"At the university, there are incentives to participate/lead clinical trials. We need scientific papers with high impact to aspire to a better position, to get grants, international visibility. If we do not publish, we take the risk of losing our job."*
>
> POLISH UNIVERSITY CLINIC HAEMATOLOGIST

The promotion of non-commercial oncology, cardiology and rare disease clinical trials has been high on the Polish health policy agenda with the launch in March 2019 of the Medical Research Agency (Agencja Badań Medycznych, ABM). Interviewees expected the number of clinical trials conducted in Poland to increase in the near future.

In Croatia, the lack of academic clinical trials, attributable to the lack of public R&D funding, was said to have participated to decreasing the country's R&D reputation. Like their Serbian, Slovenian and Bosnian counterparts, Croatian haematologists are trapped in a Catch-22: low numbers of myeloma clinical trials do not allow them to acquire sufficient experience to either convince sponsors to set up research sites in their country or include them in an international research collaboration.

> *"Sites must show that they have already done clinical trials and succeded."*
>
> CROATIAN CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

> *"It is very difficult to be included in an international collaboration usually initiated by a large country with an important population of patients. For example, countries like Poland and the Czech Republic do not see the interest to start a collaboration with Croatian haematologists. Why would they do this? They have enough patients."*
>
> CROATIAN HAEMATOLOGIST

> *"Key opinion leaders should create a value proposition (specific to each sponsor) to prove their clinical expertise and testify about the willingness of patients to participate in clinical trials."*
>
> CROATIAN CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

Despite this, there have been recent academic collaborations involving Croatia, Slovenia and North Macedonia to improve clinical trials and the volume of scientific publications on myeloma. Broader 'alliances' and 'networks' of physicians and hospitals across the CEE region to incentivise an increase in commercially sponsored studies and build upon the work that has been done to date would be welcome.

Reliance on industry sponsors has led North Macedonian haematologists and health authorities to increase their efforts of promoting their country's clinical research attractiveness. This has not been without its difficulties.

> *"Stakeholders do their best to promote the country, but it is not enough. Choosing North Macedonia is very difficult because the country suffers from a lack visibility in the scientific field."*
>
> NORTH MACEDONIAN CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

The trial analytics and literature review both confirm the lack of visibility of North Macedonian research. Moreover, no North Macedonian myeloma expert is a member of an international or European haematological malignancies network or society.

> *"I don't say there aren't any collaborations, but it is rare."*
>
> NORTH MACEDONIAN CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

Discussions also pointed to the fact there may be best practice examples from other disease areas. There are opportunities for North Macedonian haematologists to learn from immunologists' experiences in increasing international collaboration.

> *"For example, in immunology four to five years ago, despite there wasn't any initial experience in clinical investigation, physicians were included in international collaboration. Today, there are four to five clinical trials opened for Macedonian patients."*
>
> NORTH MACEDONIAN CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

4.1.1.2. IS THE TRIAL ACCESSIBLE?

Geographical distribution of centres

Literature review

In countries where clinical trials run, there may still be barriers to patients accessing them. The local availability of clinical trials appropriate for a patient's cancer type and stage plays a large role in reducing or increasing rates of participation in a trial. More than half (55.6%) of all cancer patients do not participate in trials because no trial is available for the patient's cancer type and stage at the treatment centre. Having to travel to participate in a trial can also be an overwhelming burden to patients (Unger JM, 2019) (Napoles A, 2017). This may be a particular issue in countries where a large percentage of the population lives in rural settings.

Clinical trials often take place in hospitals with large centres of expertise, often based in key cities. Factors influencing trial location decisions include lack of staff and equipment, lack of data management skills and high-cost data management software tools. The data management programme used is often determined by the pharmaceutical company sponsoring a trial. Investigators can quickly find themselves having to enter data for various trials in numerous unstandardised software tools. Smaller institutions may not have the resources to dedicate additional time and effort in entering data on various software platforms. One solution to this may be an open-source approach to data management for clinical trials (Babiker HM, 2019).

Polish, Croatian and Macedonian stakeholder perspectives

The geography of patients was a theme raised by both the Polish and Macedonian stakeholders.

Despite having the largest number of 21 identified myeloma specialised centres (see Table 1), patient burden and additional costs are high for Polish patients who live remotely. The lack of proximity between centres and patients, which has been particularly acute since the COVID-19 crisis, has resulted in additional travel costs and affected the ability of patients to participate in clinical trials, or even to continue their treatment.

Similarly, the Skopje University Hospital, the only hospital which provides haematological care, is not easily accessible for all North Macedonian patients as the population is spread throughout the country. It takes many patients on average one to two hours by bus to reach Skopje. This negatively impacts patient participation as 50% of patients included in trials drop out due to the travel burden according to interviewees.

4.1.2. RECOMMENDATIONS (STRUCTURAL BARRIERS)

4.1.2.1. DOES A CLINICAL TRIAL EXIST?

Based on the information generated from the literature review, feedback from participants in country-specific interviews and from MPE member organisations in CEE countries, MPE makes the following multi-stakeholder recommendations on addressing structural barriers to conducting clinical trials:

Patient population size

1. Academic researchers, policymakers, haematologists, and other relevant stakeholders are encouraged to work towards the establishment of joint cross-border research networks and initiatives in the CEE region, especially in the Balkans, to:
    - offer a sizeable myeloma patient population to clinical trial sponsors. This will incentivise an increase in commercially sponsored studies. The involvement of a third party to facilitate and support this effort is encouraged.
    - raise awareness and capacity of the role CEE countries can play in international research.
2. MPE to work with its members to:
    - identify, share and engage with existing pan-European research networks and collaborative initiatives, such as the European Clinical Research Infrastructures Network (ECRIN), to provide support and facilitate clinical trial preparation and implementation.
    - investigate barriers and facilitators to cross-border research networks and initiatives.

Health care funding, financial incentives for research and national cancer/rare disease plan or strategy

3. Industry, academic researchers, health policymakers and other relevant stakeholders are encouraged to collaborate towards greater investments in research and development (R&D) in CEE countries, including the creation and maintenance of the necessary infrastructure to run clinical trials, as well as the coverage of standard of care treatments and specialised procedures.
4. European health policymakers, most notably in the CEE region, are encouraged to put comprehensive cancer plans in place with a core commitment to conducting clinical trials, thereby aligning with Europe's Beating Cancer Plan. Such plans need to be rolling and evaluated.

Research infrastructure and qualified staff

5. European medical societies, research institutions and structures like the European Hematology Association (EHA), the European Society for Medical Oncology (ESMO) and the European Reference

Networks (ERN) could potentially align on minimum staffing requirements, job descriptions, expertise and hospital infrastructure needed for cancer clinical trials to run effectively. This would help CEE countries prioritising R&D investment

6. More CEE countries could benefit from becoming members or observers of the ECRIN (the Czech Republic is the only ECRIN's CEE country member, while Slovakia and Poland are the two CEE country observers).
7. European and global medical societies should offer training and peer-to-peer support programmes on clinical trial methodology, with a particular emphasis on CEE, to ensure that healthcare professionals are upskilled and champion the initiation of clinical trials.
8. European and national policymakers should collaborate and find solutions to the health care professional 'brain drain", which negatively impacts CEE health care systems, R&D and ultimately patients.
9. Research needs to be undertaken in Europe to understand the impact of the COVID-19 pandemic on the ability of European healthcare systems, including in the CEE region, to invest and conduct research and clinical trials.

Administrative and regulatory requirements and EU membership

10. EU cancer patient advocacy groups and other stakeholders should monitor the implementation of the EU Clinical Trial Regulation 536/2014 to ensure approval clinical trial timelines are met.
11. Non-EU members from CEE could align as much as possible with the EU Clinical Trials Regulation 536/2014 to streamline clinical trial initiation and conduct.
12. CEE health policymakers, cancer patient organisations and medical societies could review best practices in countries that have a relatively larger share of clinical trials (e.g., the Czech Republic, Bulgaria, and Hungary) to understand how procedures in place have favoured streamlined regulatory processes and raised the international profile of their medical and scientific communities.
13. Researchers and other stakeholders in CEE should promote the creation of contract templates, hereby shortening the contract negotiation time prior to the opening of clinical trials

International R&D collaborations

14. International and European Medical societies and journals should grant dedicated funding and/or reduced fees to academic scientific authors in lower- and middle-income CEE countries to cover publication fees and attend congresses. Industry sponsors and CEE academic researchers could encourage patient participation to clinical trials by allowing routine tests and exams to be done at patients' local hospitals, vs. remote investigating centres.

See also recommendations 1 and 12.

4.1.2.2. IS THE CLINICAL TRIAL ACCESSIBLE?

Geographical distribution of centres

15. Industry sponsors and CEE academic researchers could encourage patient participation to clinical trials by allowing routine tests and exams to be done at patients' local hospitals, vs. remote investigating centres.
16. The Industry should provide travel and accommodation allowances to CEE patients and their carers (if needed) to incentivise them to participate in clinical trials. This will reduce biases of selection, whereby only wealthier patients or those living closer to trial sites, can afford to take part in clinical trials.
17. The global research community should agree with the industry on a short list of clinical trial data management programmes for smaller hospitals to choose from. This would lead to economies of scale and allow smaller hospitals across CEE to meet clinical trial data management requirements.

4.2. CLINICAL BARRIERS AND FACILITATORS (TRIAL ELIGIBILITY)

4.2.1. LITERATURE REVIEW AND STAKEHOLDER PERSPECTIVE

Trial design

Literature review

Even where clinical trials are potentially available, patients within a country may not be able to participate due to the narrow eligibility criteria. Anecdotally, patient advocates are aware of issues with trials not opening in countries where patients have not received the prior lines of therapy specified in the trial eligibility criteria. The main reason for this is lack of reimbursement for the standard of care myeloma treatments.

The literature highlights that eligibility criteria is often too narrow, excluding many patients (Haddad RI, 2015) (Salman A, 2015) (Steensma D.P., 2018) (Ahaghotu C, 2016) (Byrne M, 2017) (Nipp RD L. H., 2019). The narrowness of trials' eligibility criteria is often influenced by the rarity of a disease and/or the presence of a genetic or molecular marker, constituting a hurdle to patient recruitment (Arai RJ, 2019). This has been documented in indications such as myelodysplastic syndromes (MDS), head and neck cancer (Haddad RI, 2015) and breast cancers (Unger JM, 2019) but there is an awareness of the issue across many other cancers.

In the US, despite the high prevalence of clinical trials, when a trial was available only 21.5% of cancer patients were eligible. Clinical trials exclude patients for many reasons related to the desire to maintain patient safety, and to establish a study cohort with similar patient profilesto assess more accurately the response of patients to different treatments. Patients with progressing disease miss out on the limited array of therapeutic options they have in these situations, while multiple clinical trials compete for the same patient population (Babiker HM, 2019) (Unger JM, 2019) (Vuong I, 2020). Older adults, racial and ethnic minority populations and patients with chronic illnesses are particularly under-represented in clinical trials, thereby limiting the general application of results in a real-world

setting (Steensma D.P., 2018) (Nipp RD H. K., 2019). The same can potentially be said about over-representation in trials (particularly global randomised controlled clinical trials) of high-income countries vs. low- and middle-income countries such as those in CEE.

A fine balance is required in the design of clinical trials to ensure patient enrolment is achievable (Haddad RI, 2015). There is a need for trial designs adapted to the small population size and clinical heterogeneity (Rath A, 2017). Pragmatic trials, which measure the benefit the treatment produces in routine clinical practice, could represent an alternative to RCTs. They are intended to inform decisions in common practice. Eligibility criteria are more inclusive, comparisons are made against standards of care instead of placebo and follow-up tends to evaluate longer-term effects than RCTs (Rath A, 2017).

Polish, Croatian and Macedonian stakeholder perspectives

Stakeholder interviews did not raise the issue of strict inclusion and exclusion criteria on patient participation. Comments centred around local standards of care.

Heterogeneity in clinical practice

A lack of guidelines and divergence in standard of care mean that patients' eligibility vary substantially within and across countries (Babiker HM, 2019). This can mean that it is difficult to run country-specific and multi-country clinical trials with comparable populations of patients, as patients' prior lines of therapy are different and the 'standard of care' in which to compare the new treatment with is also different. In the example of head and neck cancer, primary surgery is more used in Germany, Austria and Switzerland in untreated and locally advanced cases than in the US, France and Belgium where non-surgical approaches are preferred (Haddad RI, 2015).

Polish, Croatian and Macedonian stakeholder perspectives

The lack of standardised care in Poland was raised as a major issue. Heterogenous clinical practice between Polish haematologists have hampered the adoption of health care guidelines. The unfortunate consequence of this lack of consensus has been the exclusion of many patients from multi-centre trials. Patient care, including myeloma care, is impacted on by a lack of standardisation, which reduces the chance of patients being eligible for trial inclusion.

> ***"Each professor works with their own evidence-based medicine, and it is an issue for patients. If patients A and B potentially correspond to the criteria of eligibility of a CT protocol, the fact that they receive different prior therapies could exclude them from a CT."***
>
> POLISH CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVE

In addition, stakeholders outlined that senior physicians impose their clinical practice on younger physicians, thereby preventing the emergence of new models of treatment and opportunities for setting up clinical trials. Polish medicine often has a culture based on the relationship of authority, where their opinions may not always count.

Heterogeneity in clinical practices were not raised by Croatian and North Macedonian interviewees. Due to the small sample size of interviewees, additional field work is needed to further explore these types of barriers to clinical trials.

Heterogeneity in access to treatment and care was also an important hurdle to clinical trial inclusion. Polish interviewees pointed out that oncology care is better organised than haematology care, with oncology patients having a specific treatment card granting faster access to treatments, including clinical trial medicines. The reasons for this disparity were not identified in this study but the ramifications are that the standard of care is not certain for Poland for triallists.

> *"Oncology patients in Poland receive a DiLO card (Oncology diagnosis and treatment card) to ensure faster access to tests and treatment. However, patients with haematologic malignancies don't go down this route and don't receive a DiLO card. Why? I don't know."*
>
> POLISH PATIENT ORGANISATION REPRESENTATIVE

One major hurdle in some Balkan countries, such as North Macedonia, has been the lack of access to generic backbone therapies bortezomib and lenalidomide, which are central to all new myeloma combination therapies.

Until generic myeloma treatments are registered on the reimbursement list, many recent therapies cannot be approved for reimbursement. Additionally, the time-limited conditional budgets for the administration of treatments not on the North Macedonian reimbursement list further contributes to disparities in inclusion in a clinical trial between patients. Of the patients that are not covered under the conditional budget, only the wealthiest get treated abroad to access to these therapies.

Even treatments that are registered on the North Macedonian reimbursement list such as thalidomide, cyclophosphamide and melphalan (oral and IV for transplants), have been largely unavailable to patients. This lack of availability represents an additional obstacle to the attractiveness of the country for industrial sponsors.

> *"Pharmaceutical companies do not invest in countries that don't include new treatments in their reimbursement list."*
>
> NORTH MACEDONIAN PATIENT ORGANISATION REPRESENTATIVE

4.2.2. RECOMMENDATIONS (TRIAL ELIGIBILITY)

Based on the information generated from the literature review, feedback from participants in country-specific interviews and from MPE member organisations in CEE countries, MPE makes the following multi-stakeholder recommendations on trial eligibility:

18. Trial sponsors should consider the use of broader inclusion criteria, which more closely reflect real-life patient populations, including CEE patients. Co-morbidities, which have limited impact on cancer outcomes, should not be exclusion criteria in myeloma trials.
19. Industry sponsors should support equal access to trials for all myeloma patients regardless of the region they live in. Industry protocol designs should consider the heterogeneity of standards of care across different regions, such as CEE. Partnerships with academia and country-specific trial arms could also be considered to assist with national access questions.
20. Policymakers should consider the benefit of establishing or joining existing voluntary cross-border collaborations on pricing and reimbursement operating in the CEE region, that aim to improve access to innovative medicines and therapies. These include the Baltic Procurement Initiative (2012): Estonia, Latvia and Lithuania; the Valletta Declaration (2017): Cyprus, Greece, Ireland, Italy, Malta, Portugal, Romania, Spain, Slovenia, Croatia; the Fair and Affordable Pricing (FAAP) initiative (2017): the Czech Republic, Hungary, Poland and Slovakia.
21. Key opinion leaders and haematologists should work together and agree on national treatment guidelines to ensure patients are treated uniformly based on the best available evidence and reimbursement decisions, thus all having equal chance to access available clinical trials.
22. Industry, health policy makers, cancer patient organisations and other stakeholders need to jointly explore models of fair pricing in line with national gross domestic product to ensure that European cancer standards of care, including generics, are affordable in CEE countries. Access to standard of care is a critical element of setting up and running oncology clinical trials.

4.3. PHYSICIAN AND PATIENT BARRIERS AND FACILITATORS

4.3.1. LITERATURE REVIEW AND STAKEHOLDER PERSPECTIVES

4.3.1.1. IS THE CLINICAL TRIAL PRESENTED TO THE PATIENT?

As well as structural barriers preventing the initiation of clinical trials, there may also be situations where clinical trials are available within countries, but patients are not made aware of it.

Physicians play a vital role in helping patients determine treatment choice. Patients often look to their physicians to inform them of clinical trials, which may be a just as an important part of the treatment (Barrios CH, 2018) (Unger JM, 2019). Physicians may not ask eligible patients about trial participation for multiple reasons. These include a lack of information on trials, treatment preferences and beliefs, is it institutional or limited clinic time and/or reimbursement constraints (Unger JM, 2019). Most of the literature on this topic has a US focus, but it is interesting to consider the wider application of this hypothesis in other countries.

Physicians' access to information

Literature review

The lack of awareness about the availability of protocols or the existence of clinical trials, even in their disease community, is likely to be a major inhibitor for physicians and other healthcare providers to discuss clinical trial participation with their patients (Ellis S, 2019) (Gammie T., 2015) (Salman A, 2015) (Napoles A, 2017) (Nipp RD L. H., 2019). While the reasons for these are not addressed comprehensively in the literature, further studies should explore whether this relates to capacity (time) and resourcing issues, a lack of physician engagement in national and international disease communities and the relevant medical education systems, and/or the availability of continuous professional development. There may also be differences between the knowledge of physicians in academic-based centres and those in more locally based, community hospitals. Reviews suggest cancer patients who receive multidisciplinary care, which is more likely to be available in academic centres or well-resourced healthcare systems, are more likely to be offered clinical trials (Ellis S, 2019).

Information strategies aimed at research-naïve cancer physicians should be encouraged (Gammie T., 2015) (Ellis S, 2019). The role of trial registries, such as US-based ClinicalTrials.gov and EU-based clinicaltrialsregister.eu, is important in educating physicians and patients about the availability of trials (Barrios CH, 2018). As eligibility determination is challenging and often requires a time-consuming manual chart review; the global application of these platforms could speed up the process of identifying candidates for clinical trials.

Of note, the literature review indicates there are disparities in availability, quality and clarity of online registries for clinical trials (Barrios CH, 2018) (Gammie T., 2015), including:

- Information on trial locations is not always available or complete, making it difficult for patients and physicians to identify potential studies to join
- Trial analytics also showed that despite providing broad access to physicians, patients and organisations (Barrios CH, 2018), the WHO trial portal provides poor quality data. Outdated data, missing values, data entry errors and poor formatting are commonplace, with duplicates not appropriately managed

As information on ongoing trials is not always available or complete, examples of advanced patient screening platforms and advocacy tools for clinical trials have been developed such as the INTEGRATE project in breast cancer. This tool identified eligible patients by matching patient characteristics to the required criteria of each trial. This has helped speed up the identification process of candidates (Barrios CH, 2018) and has empowered patients in seeking information on clinical trials.

Polish, Croatian and Macedonian stakeholder views

The only country that outlined the lack of physician awareness of clinical trials was Poland. This could potentially relate to the higher numbers of trials available in Poland that physicians need to be aware of compared to Croatia and North Macedonia. Lack of awareness of ongoing myeloma clinical trials was a particular issue in Poland, as haematologists outside of the larger academic treatment centres are unlikely to be myeloma specialists or clinical trial specialists. They also may not be aware of the latest clinical trials in myeloma.

> *"I consulted five haematologists before I started my treatment. All of them had a PhD or a Professor title, however it was only the last one, who recommended a non-standard therapy and mentioned a clinical trial. I am a very stubborn person, and I did a lot of research on my own but not all patients are like that."*
>
> POLISH PATIENT ORGANISATION REPRESENTATIVE

Physicians' beliefs, attitudes and preferences

Literature review

As well as not being aware of clinical trials, physicians' beliefs and preferences can have a considerable impact on the participation of patients.

They may choose not to offer trial participation out of concern for patient's capacity or willingness to complete the trial and/or potential preferences (Salman A, 2015) (Barrios CH, 2018) (Napoles A, 2017). The literature suggests that distance from a physician's practice to the nearest clinical trial site is inversely associated with physician referral to and patient enrolment in a trial (Napoles A, 2017).

The literature also highlights that some physicians may also have difficulty coping with the uncertainty inherent to the participation of their patients in clinical trials. For example, as they assess the benefit-risk ratio, they may incorrectly estimate the probability and severity of challenges associated with clinical trial participation for their patient (Nipp RD 2019). Their beliefs of potential repercussion on the physician-patient relationship can also contribute to their decision-making, such as fear of losing their patients to trial investigators (Ellis S, 2019) or concern of interference with the physician-patient relationship (Unger JM, 2019).

Some physicians may not see the clinical significance or value of trials for their patients (Salman A, 2015) (Napoles A, 2017). This highlights how physicians' awareness of potential benefits are essential, especially in low-middle-income countries where clinical trials are not as frequently available (Barrios CH, 2018).

Polish, Croatian and Macedonian stakeholder views

The impact of physicians' beliefs and attitudes on patient participation was not raised as an issue during interviews.

Physician communication skills

Another issue raised in the literature is the role of communication between healthcare professionals and patients on clinical trials (Cartmell KB, 2020). It is outlined that physicians who have little exposure to clinical trials in their medical training often lack the knowledge and skills needed to initiate the conversation on trials as a treatment option. Given the limited availability of clinical trials in many CEE countries, this issue is particularly pertinent in the region. There is a need for training of healthcare professionals to enable the counsel of patients on clinical trials as treatment options, as well as concise trial information to refer patients accordingly (Ellis S, 2019) (Salman A, 2015). Physicians' communication skills are also necessary to assist with the informed consent process, which is often long and complex, and can negatively impact on patient recruitment to clinical trials, especially in ethnic minorities (Vuong

I, 2020) (Babiker HM, 2019) (Djurisic S, 2017). Patients might struggle to accurately understand the benefits and risks of participating in the clinical trial – reducing their willingness to participate (Nipp RD 2019). There is evidence showing that the process of informed consent is more complicated in countries with limited health literacy (Tang M, 2019), such as low-income countries and low-middle income countries (Arai RJ, 2019) – it would be interesting to explore the differences across CEE.

4.3.1.2. IS THE CLINICAL TRIAL ACCEPTED BY THE PATIENT?

US data shows that structural and clinical factors are the reasons why more than three out of four cancer patients (77.1%) did not participate in trials. This suggests that the influence of patient-related factors and patient choice represents only a small portion of barriers to trial participation overall (Unger JM, 2019). When eligible patients are offered trial participation, they agree to take part more than 50% of the time (Unger JM, 2019) (Ellis S, 2019). Variations in this across Europe, particularly in CEE countries, would be interesting to explore given the unique socio-economic factors at play within countries.

Patient willingness to participate in a trial

The literature also discusses the role of patient-based factors (such as willingness to participate) in availability of and ability to recruit to clinical trials. Patients' motivation for trial participation may also include their potential desire to extend their lives but also the willingness to help others and contribute to scientific research (Barrios CH, 2018) (Byrne M, 2017) (Rivers D, 2019) (Nielsen ZE, 2019). The amount of altruism and hope of a therapeutic benefit might differ for patients depending on cancer diagnosis and prognosis. Patient willingness to participate in trials may relate to their understanding of the trial, how their physician communicates with them about the trials and their individual situation (such as their socioeconomic situation, cost concerns and health literacy).

Patient access to information

Literature review

As well as a willingness to participate in clinical trials, a further barrier to patients is a lack of information about clinical trial availability and process.

Patients and their caregivers often encounter substantial difficulty in finding an appropriate trial, even when one or more exists in a country (Babiker HM, 2019). A limited understanding of rationale and the process of trial participation have also been associated with reduced patient enrolment (Haddad RI, 2015) (Ahaghotu C, 2016) (Napoles A, 2017) (Byrne M, 2017) (Vuong I, 2020) (Nipp RD L. H., 2019) (Rivers D, 2019).

Initiatives, such as Trials4Me, which uses Google Maps to locate sites participating in clinical trials from the Clinicaltrials.gov database, have facilitated patient searches for trials. In the same way there are searchable trial databases for physicians (ClinicalTrials.gov), platforms should be available with unified and standardised information directed to patients (Sacristán, 2016). Empowering patients with information on trials can help them identify where they already exist in a country and could also potentially increase the political demand for more trials to be available. Written patient information on

clinical trials (both generally and on specific trials), including on trial design and endpoints, is helpful to assist patients in their decision-making (Barrios CH, 2018). Awareness of recruiting clinical trials may also be achieved by using different recruitment media, including print materials, web promotion and social media, as well as more traditional methods like journal articles (Haddad RI, 2015). Recent evidence also shows that social medica has increased clinical trial enrolment and help identify breast cancer patients with rare tumour types (Barrios CH, 2018).

Polish, Croatian and Macedonian stakeholder perspectives

Reflecting on the topic of physician and patient awareness of clinical trials, interviewees in Poland outlined that patients in the healthcare system often encounter difficulties in accessing the information they need on availability of clinical trials or to support their decision-making on clinical trial participation. This was related to resource and the capacity of physicians to focus on issues like clinical trials.

> *"Unfortunately, physicians don't get any administrative support and they are the main point of contact for all patient issues and questions. This makes it very hard for a patient to get all the answers they need due to lack of physicians' time."*
>
> POLISH PATIENT ORGANISATION REPRESENTATIVE.

Interviewees in North Macedonia focused on patient awareness barriers to trial participation, highlighting that patients' low health literacy means they rely solely on their physicians for information on clinical trials. In a country where both industry and academic trials are limited, it is rare that patients discuss trials with their haematologist. This implicit trust in their physicians and often low health literacy also mean that patients are unlikely to ask about clinical trials themselves.

> *"Educational level is very low. Only 3-4% of the population have a high educational level. Patients generally trust their haematologist."*
>
> NORTH MACEDONIA HAEMATOLOGIST

> *"People trust their haematologist."*
>
> NORTH MACEDONIAN CONTRACT RESEARCH ORGANISATION (CRO) REPRESENTATIVES

Interviewees also touched on the issue of a lack of patient information on clinical trials (both generally and in relation to specific trials) to support them in decision-making. When trials were available, Croatian and Macedonian interviewees reported a lack of patient understanding as trial leaflets and informed consent forms (ICF) were not always available in the local language.

Control, hope, trust and mistrust

Literature review

A further barrier to patient participation in clinical trials is individual patient preferences. The literature highlights that the hope of therapeutic benefits (such as improved survival and quality of life) represents a motivating factor for participation in clinical trials (Nielsen ZE, 2019). It is outlined that patients who chose to participate often wish to survive as long as possible, while patients who decline participation often prioritise quality of life (Nielsen ZE, 2019). Fear of side effects and scientific experiments (Unger JM, 2019) (Salman A, 2015) (Cartmell KB, 2020) (Vuong I, 2020) (Nielsen ZE, 2019), uncertain outcomes (Byrne M, 2017) (Rivers D, 2019) (Nipp RD, 2019), fear of losing control of their own treatment (Unger JM, 2019), worries about the impact on relatives and caregivers, and a need to gain control over their disease (Nielsen ZE, 2019) are also top reasons patients decline participation.

Another barrier to patients participating is a reticience of leaving the care of their primary physician, with whom they have established a strong relationship of trust, to pursue new treatment options on a clinical trial (Babiker HM, 2019) (Salman A, 2015). The trust patients have in the physician who informs them about the study also plays an important role in their decision to participate or not (Nielsen ZE, 2019)

Positive findings are more likely to be published compared to neutral results or harmful effects. Selective reporting has been detrimental to patients' trust in clinical trial benefits (Djurisic S, 2017). This feeling of mistrust in clinical trials, especially of drug company sponsored ones (Babiker HM, 2019), and health care systems remains prevalent (Ahaghotu C, 2016) (Byrne M, 2017). It is even more acute in racial and ethnic minorities due to the impact of historic research abuses and concerns of beings used as 'guinea pigs' (Rivers D, 2019) (Vuong I, 2020) (Nielsen ZE, 2019).

The fear and use of placebo-controlled trials have also been challenges to clinical trial patient recruitment (Chino F, 2019) (Rivers D, 2019) (Arai RJ, 2019) (Rath A, 2017) (Napoles A, 2017) (Steensma D.P., 2018) (Sacristán, 2016).

Polish, Croatian and Macedonian stakeholder perspectives

Only the interviews conducted in Poland reflected upon the issue of individual patient preferences towards participating in clinical trials.

According to interviewees, Polish patients' hesitancy to enrol is commonplace due to a lack of or limited information – again demonstrating the importance of empowering patients with adequate information on trials to assist decision-making.

Patients generally feel mistrust in medical research due to an overall lack of information on the potential benefits of clinical trials for patients. It was also raised that a lack of involvement of patients in clinical trial design may be a disincentive for willingness to participate in a clinical trial, as patient-relevant factors haven't been considered.

> *"There is a general opinion that patients taking part in clinical trials are like guinea pigs."*
>
> POLISH PATIENT ORGANISATION REPRESENTATIVE

Specific differences in experience depending on socio-economic and ethnic factors were not outlined in discussions but should potentially be explored in further studies.

Patient financial and logistical challenges

Literature review

When a trial is available, financial and logistical issues (or patient perceptions on these issues) may also play a role in trial participation. Alongside worries about reimbursement of standard medical costs, patients also incur significant additional costs and logistical challenges (i.e., gas or train/flight ticket, food, accommodation and childcare), while facing wage loss, as they often must travel to distant institutions to receive treatment and tests. These have been documented as a disincentive to pursue clinical trials as a treatment option (Babiker HM, 2019) (Unger JM, 2019) (Steensma D.P., 2018) (Ahaghotu C, 2016) (Byrne M, 2017) (Cartmell KB, 2020) (Nipp RD L. H., 2019) (Nipp RD H. K., 2019) (Chino F, 2019).

Polish, Croatian and Macedonian stakeholder perspectives

Polish and Croatian interviewees did not reference the issues of financial and logistical challenges with trial participation. However, North Macedonian stakeholders outlined that the limited coverage of bortezomib and lenalidomide via the conditional budget constitutes both an obstacle for the establishment of trials in the country and for patients participating in trials, who cannot afford to pay them out of their own pockets.

4.3.2. RECOMMENDATIONS (PATIENT AND PHYSICIAN BARRIERS)

Based on the information generated from the literature review, feedback from participants in country-specific interviews and from MPE member organisations in CEE countries, MPE makes the following multi-stakeholder recommendations on addressing patient and physician barriers to clinical trials:

4.3.2.1. IS THE CLINICAL TRIAL PRESENTED TO THE PATIENT?

23. Medical societies and cancer patient organisations should promote the use of the EU Clinical Trials Register, which provides clear and accessible information to haematologists and myeloma patients participating in clinical trials in their countries.
24. National and international professional organisations, like EHA and ESMO, should set up training programmes for oncology healthcare professionals in CEE on communicating clinical trials information to patients.
25. Industry and academic researchers should engage patients and/or patient representatives
    - to ensure that informed consent forms are clear and concise documents about the benefits and risks of each trial. These should be translated into the languages used within the countries a trial is being opened in.
    - inform the design of their clinical trials following the EUPATI Engagement Roadmap and to ensure they reflect patient preferences.

4.3.2.2. IS THE CLINICAL TRIAL ACCEPTED BY THE PATIENT?

26. European and national cancer patient organisations should provide information to patients in lay language about trials running in their country.
27. National cancer patient organisations should conduct further research on country-specific socio-economic and cultural barriers to setting up clinical trials in the CEE region.

5. CONCLUDING REMARKS

MPE and its member organisations aim to improve access to clinical trials to all European patients. MPE acknowledges the limitations of this discussion paper. While solid trial analytics and a thorough literature review were conducted, only 11 stakeholders from three countries were interviewed. The present discussion paper and recommendations point to actionable and concrete policy initiatives, which all stakeholders involved can take part in, as well as a starting point for future discussions and research.

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The present discussion paper and recommendations point to actionable and concrete policy initiatives, as well as a starting point for future discussions and research

6. APPENDICES

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