

Cross-border Access to Clinical Trials in the European Union

Exploratory study on the views of key stakeholders regarding the need, challenges and potential for facilitation of cross-border access to clinical trials in the European Union

FINAL REPORT



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ABSTRACT

Objectives: To analyse the current situation of cross-border access to clinical trials in the EU, 1) from the regulatory and legal perspective (in particular, Directive 2011/24/EU), and 2) with an overview of real-life experience to identify the needs, challenges and potential for facilitation.

Methods: 1) A literature review; 2) semi-structured interviews with selected experts from European countries; and 3) an online survey were conducted. The questions addressed to Interviewees and survey participants were designed as complementary, in order to provide a basis for comparison of results. A combination of purposive and snowball sampling approach was used to identify potential Interviewees, who were invited to participate via email, or in person. The survey was disseminated broadly through the networks of the study partners and on social media. A wide range of clinical research stakeholders was included: patient representatives, investigators/physicians, policy and regulatory experts, academic and commercial sponsor representatives, and ethics committee members. The interviews were analysed according to the framework method for qualitative research and following the Qualitative Analysis Guide of Leuven (QUAGOL).

Results: Of eighty six contacted experts, 44% agreed to be interviewed; the majority were investigators/physicians (29%) and patient representatives (29%). Three hundred ninety six evaluable responses were collected in the survey, of which the majority came as well from investigators/physicians (46%) and patient representatives (33%). All European sub-regions were represented in the study. The highest response rate was from Western European countries (45% of Interviewees, 38% of survey respondents), while the lowest was from Eastern Europe (5% of Interviewees, 9% of survey respondents). The study suggested that cross-border participation in clinical trials occurs in practice, however very rarely. The possibility to access cross-border clinical trials was perceived as needed by 92% of survey respondents. The lack of access to treatment in the home country of the patient was described as the main motivation to participate in a clinical trial abroad (32% of physicians and 19% of patient representatives). The logistical and financial burden to the patient was perceived as the biggest challenge. Different stakeholders expressed diverging opinions regarding the allocation of financial and organisational responsibility for enabling the cross-border access to clinical trials. A number of proposals for improving the current system were provided. While survey respondents supported a change in EU legislation, Interviewees had more nuanced and critical opinions with respect to normative amendments. However, there was a general consensus among both interviewees and survey respondents on the need for reliable and accessible information regarding practical aspects of cross-border access to clinical trials.

Conclusions: There is a general consensus on the need for reliable and accessible information regarding practical aspects of cross-border. Therefore, the development of a multi-stakeholder, multi-national guideline with information about existing options and best practices for cross-border access to clinical trials in the EU could be an efficient first step towards providing patients in Europe with fair and patient-centric access to treatment innovation. Broader interdisciplinary research is recommended before discussing a change in the EU legislative framework.

Background and Partners: Access to clinical trials for patients living in another EU country remains an unregulated issue as also the implementation of Directive 2011/24/EU on the application of patients' rights in cross-border healthcare has not regulated the conditions for clinical trials. No comprehensive analysis regarding the occurrence, relevance and obstacles to such cross-border access has been conducted previously. In a collaborative effort, a team comprised of researchers from the European Forum for Good Clinical Practice (EFGCP), the European Organisation for Research and Treatment of Cancer (EORTC), KU Leuven and Patvocates, with the support of the European Federation of Pharmaceutical Industries and Associations (EFPIA), engaged in an exploratory study on this topic.

Objectives: The research project was conducted between April and November 2019 and had five main objectives, which reflected its exploratory nature:

1. To understand the regulatory and legal framework applicable to cross-border healthcare and clinical trials in the EU: does it help or hinder cross-border access of patients to clinical trials.
2. To develop an understanding of the frequency of enrolling patients from other EU countries in clinical trials, primarily in oncology trials.
3. To develop an understanding of the frequency of patients' interest in joining a clinical trial in another country.
4. To collect real life experience from physicians and patients with enrolling patients from other countries in a clinical trial.
5. To identify gaps and hurdles that have to be overcome to enable a routine opportunity for cross-border access to clinical trials.

Based on the insights gathered throughout the course of the study, the research team sought to understand whether the topic is of sufficient practical relevance to seek regulatory clarity on the rules for cross-border access to clinical trials on an EU level, or whether it would be better to provide best practices for enabling direct stakeholder solutions.

Methods: 1) A literature review; 2) semi-structured interviews with selected experts from European countries; and 3) an online survey were conducted. The questions addressed to Interviewees and survey participants were designed as complementary, in order to provide basis for comparison of results. A combination of purposive and snowball sampling approach was used to identify potential Interviewees, who were invited to participate via email, or in person. The survey was disseminated broadly through the networks of the study partners and on social media. A wide range of clinical research stakeholders was included: patient representatives, investigators, policy and regulatory experts, and academic and commercial sponsor representatives. The interviews were analysed according to the framework method for qualitative research and following the Qualitative Analysis Guide of Leuven (QUAGOL).

Results and interpretation by topic:

- *Participation, stakeholders and country representation in the project:* Of 86 contacted experts, 44% (n=38) agreed to be interviewed, and of them the majority were physicians (29%) and patient representatives (29%). Three hundred ninety-six responses were collected in the survey, of which the majority were investigators/physicians (46%) and patient representatives (33%). All European sub-regions were represented in the study. The highest response rate was from Western European countries (45% of Interviewees, 37% of survey respondents), while the lowest was from Eastern Europe (5% of Interviewees, 9% of survey respondents).

- *Study participants' experience with cross-border access to clinical trials:* 55% of Interviewees had direct experience, whereas 45% possessed indirect. In addition, the majority of Interviewees (87%,) had primarily professional experience, while only 13% had experience gathered exclusively during the course of their private lives (as patients or carers). In the survey, this question about experience allowed multiple responses. Overall survey participants possessed some form of experience. However, only 4% of respondents reported experience as a patient who participated in a clinical trial abroad. The very low absolute number of interview and survey respondents who reported personal patient experience could be an indication of the very low rate at which cross-border participation in clinical trials currently occurs.

- *Study participants' observations regarding frequency, increase or decrease in requests for inclusion in clinical trials:* Both interview and survey results showed that there is no predominant opinion on the matter of increase/decrease in interest or inclusion in cross-border clinical trials, nor any publicly available official statistics about frequency of cross-border participation. However, the results confirmed that cross-border participation occurs, although rarely.

- *Motivations to participate or not/recommend participation or not in a clinical trial conducted abroad:* In the interviews, the opinions of patients and patient advisors (physicians or patient organisation representatives) were aligned and hence in the report they were presented together. In the the interviews, as opposed to the survey, it was particularly interesting that Interviewees also provided reasons not to participate/recommend participation. Motivations to participate or recommend participation in a clinical trial abroad when no investigational site is open in the home country were: 1) access to innovative treatment; 2) the fact that patients tend to follow the opinion of their treating physician; 3) the willingness to contribute to science. Motivations to participate or recommend participation in a clinical trial abroad when an investigational site of the same clinical trial is open in the home country included: 1) geographical proximity, and 2) higher trust in the foreign country's healthcare system. In all cases the motivations were expressly linked to precision medicine and rare diseases.

Motivations not to participate or recommend participation constituted: 1) reluctance to travel; 2) the fact that the general view on clinical trials might be more critical in certain EU countries.

In the survey, patient representatives ranked highest "Access to a new treatment that is not marketed in my country of residence" (82%), followed by "No clinical trial site: Access to a new treatment that is not available in a similar clinical trial in my country of residence" (80%). Physicians also placed "Access to treatment" first (88%), while second came "Rarity: Incidence of patients with the protocol-required very specific in- and exclusion criteria is low" (46%).

- *Motivations for investigators and sponsors to recruit foreign patients:* In the interviews, the opinions of investigators and clinical trials sponsors were collected, whereas in the survey only sponsors were asked to respond to the specific question. In addition, the interviews allowed a glimpse into the motivations not to recruit foreign patients, which was not possible through the survey. In summary, according to interview participants, the motivations to recruit foreign patients included: 1) faster recruitment, 2) low recruitment rates, 3) (un)feasibility of opening trial centres across the EU, 3) to provide access to treatment. The motivations not to recruit foreign patients were: 1) the aim to enable patients to participate in the nearest hospital; 2) compliance with the strict and frequent visits to the site is burdensome for foreign patients.

In the survey, there was not much divergence in the number of sponsors' responses gathered for each option, however a slight preference was given to providing "Access to treatment" (57%), followed by "Rarity" (62%) and "Enhancement of patient recruitment" (65%).

- *European countries attractive for patients to seek participation in a clinical trial and reasons why:* In the interviews, the most attractive countries were not presented in concrete terms, however countries located in Western Europe were cited more frequently (Belgium, Germany, The Netherlands, France, the UK, and Spain). The reasons why included: neighbouring countries; countries where the language barrier is alleviated; countries where clinical trials sponsors are most likely to open sites, as no site is open in the country of residence of the patient; trust in the excellence of the foreign healthcare system; trust in the excellence of science of the host country; for reasons of cultural similarities and established frameworks for collaboration; the advice and knowledge of the treating physicians; publicity.

The results from the survey provided a strong confirmation for the insights gathered through the interviews, namely the opinion that countries located in Western Europe are most attractive (64%).

- *European countries of origin for patients seeking participation in a clinical trial conducted abroad and reasons why:* In the interviews, EU Member States located in Central and Eastern Europe were more frequently mentioned. A clear list emerged regarding the reasons why patients from certain countries would seek cross-border access to clinical trials: neighbouring countries; when the healthcare system in the country of residence of the patient is perceived as less developed in comparison to other EU Member states' systems; countries where less clinical trials are conducted; countries where a new promising treatment is currently not available.

According to survey participants, patients residing in Southern (30%) and Eastern Europe (29%) are more likely to seek access to a clinical trial abroad. However, it was interesting to observe that Germany and UK were in the top 10 countries of origin.

- *Challenges to participate in or organise cross-border clinical trials:* The interviews provided an in-depth look not only into the challenges that patients face when seeking to participate in a clinical trial abroad, but also into the challenges that investigators and sponsor have to address when setting forth to recruit foreign patients. In summary, these included (non exhaustive): cost coverage; language barrier; procedural challenges (e.g. reimbursement constrains, the investigational site not willing to recruit foreign patients, navigating the foreign healthcare system, lack of an appropriate system for patient referral, legal and regulatory procedure); vulnerability of the patients; travel distance; cultural barriers; Brexit and other political constrains.

In the survey, this topic was explored in a two-fold way. First, the opinions of survey respondents who have not tried to participate (or who have not tried to help a patient participate) in a clinical trial abroad were gathered, thus providing a theoretical insight into the challenges for cross-border access to clinical trials. Second, the views of study respondents with practical experience were collected. Both groups ranked the highest "The logistical and financial burden to the patient".

- *Study participants' opinions on the statement "Cross-border access to clinical trials is needed or not needed":* In the interviews, the majority of participants supported the need. This was strongly confirmed by 92% of survey respondents. In contrast to the survey, the interviews provided additional thoughts on this statement. According to Interviewees, in an ideal situation patients would not have to travel in order to access experimental treatment. Also, caution was raised that, if facilitated, cross-border access might be wrongly diverted. A counter-argument to the statement "Cross-border access to clinical trials is needed" was provided, namely that the main aim of sponsors should be to bring clinical trials closer to the patient and thus alleviate the need for cross-border access. According to some, the most suitable course of action would be to do both, aiming to facilitate cross-border participation and to open investigational sites in more EU Member States.

- *Study participants' opinions on potential limitations to cross-border access to clinical trials:* In the interviews, a very slight preference for no limitations was reported. Patients were not in favour of any limitations, whereas physicians primarily would support the regulation of some constraints. Interviewees' opinions included that cross-border access to clinical trials should be limited to early phase clinical trials, rare diseases, precision medicine clinical trials, clinical trials that do not have an open site in the patient's home country, neighbouring countries, cases where no treatment is available in the patient's home country.

In the survey, there was a strong support for no limitations (55%), nevertheless the combined number of responses for different limitations was higher (n=262, the question allowed multiple responses). The ranking of pre-defined options in the survey closely resembled the limitations that were spontaneously shared by Interviewees. Namely, according to survey results, respondents primarily supported that cross-border access should be limited to: rare diseases (25%), therapy schemes not available to the patients in the country of residence (25%), life-threatening diseases (16%).

- *Study participants' opinions about allocation of responsibility regarding logistics:* In both interviews and survey there was a strong support for the opinion that the patient should not have to carry the burden of organising logistics.

Interviewees proposed five frameworks. However, no concrete terms for organisation were suggested. The solution frameworks included: 1) variations on joint support, 2) support provided solely by the patient's home country; 3) support provided by the sponsor; 4) support provided by a special navigator; 5) support organised centrally at EU level.

In the survey, respondents showed a very high preference for the commercial sponsor (60%) to be responsible for logistics, followed by the National Contact Points (NCPs) (43%). However, during the course of the interviews it became clear that the NCPs may not be suitable actors for provision of logistical support, due to their lack of expertise in clinical trials, their general reluctance to take up this role, and the lack of resources attributed to them. Allocation of responsibility to the non-commercial sponsor and the investigator/clinical trial site received almost the same number of responses (38%).

- *Study participants' opinions about allocation of responsibility for costs coverage:* The solution frameworks that emerged from the interviews took into account both study related costs and standard of care medical costs. In the survey, all costs were looked at together.- Interviewees proposed main solution frameworks: 1) the sponsor should cover all additional expenses; 2) costs should be allocated differently based on whether the sponsor is commercial/academic one; 3) sponsor (regardless commercial/academic) should always be supported by home and/or host country healthcare systems. The survey results showed a clear preference for allocation of responsibility to the commercial sponsor (81%). Non-commercial sponsors were ranked immediately after (46%), closely followed by the relevant healthcare provider of the patient's country of residence (40%). Support for the role of the host country (which was a solution brought up by only one of the Interviewees) was reported to a significant extend in the survey. Namely, by the responses gathered for "Healthcare system of the country where the study is run" (22%) and for "The investigator or clinical trial site" (19%), in total n=115. There was an agreement as regards the responsibility of sponsors, and in particular commercial sponsors, but a significant divergence in views when it came to the allocation of responsibilities for other involved stakeholders.

- *Specific topics from the interviews: regulatory and organisational environment for cross-border access to clinical trials:* These included 1) the study participants' opinions on the current (EU and national) legislation; 2) the identification of current actions that would facilitate cross-border access to clinical trials; and 3) opinions how sponsors select countries in which to open clinical trials.

- *Study participants' view on future actions: Nineteen solutions were proposed in the interviews. In the report they are presented in two groups. First, study participants' suggestions that directly address cross-border access to clinical trials (1)-(16). These included, e.g. multi-stakeholder guidelines with pragmatic solutions; amending Directive 2011/24/EU in order to include clinical trials in its scope; optimisation of the ways relevant information is disseminated; establishing a stronger role for the European Reference Networks in cross-border clinical trials participation. Second, suggestions that addressed other related issues (e.g., the need to have more clinical trials open closer to where patients live) and which indirectly could alleviate the need for cross-border access (17-19).*

In the survey, the highest ranked recommendation was “Reliable and easily accessible information for patients, physicians and patient organisations about the legal and administrative framework for patients crossing borders for clinical trials” (68%, followed by “A change in relevant EU legislation is needed in order to harmonize the conditions for cross-border access to clinical trials within the EU” (67%). However, Interviewees had more nuanced and critical opinions with respect to normative amendments.

Conclusions: There is a general consensus on the need for reliable and accessible information regarding practical aspects of cross-border. Therefore, the development of a multi-stakeholder, multi-national guideline with information about existing options and best practices for cross-border access to clinical trials in the EU could be an efficient first step towards providing patients in Europe with fair and patient-centric access to treatment innovation. Broader interdisciplinary research is required before discussing a change in the EU legislative framework.

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The presentation and discussion of the results in this report represent the view of the research consortium and the Advisory Committee.

The research consortium does not take any responsibility for the accuracy of the statements of stakeholders involved in the study (Interviewees or survey respondents).

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LIST OF ACRONYMS:

ATMP	Advanced Therapy Medicinal Product(s)
CBCT(s)	Cross Border Clinical Trial(s)
CEE	Central and Eastern Europe
CJEU	Court of Justice of the European Union
CRO(s)	Contract Research Organisation(s)
EC	European Commission
ECA	European Court of Auditors
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFGCP	European Forum for Good Clinical Practice
EORTC	European Organisation for Research and Treatment of Cancer
EPF	European Patients Forum
EURORDIS	European Organisation for Rare Diseases
ERN(s)	European Reference Network(s)
GDPR	General Data Protection Regulation
NCP(s)	National Contact Point(s)
TEU	Treaty on European Union
TFEU	Treaty on the Functioning of the European Union

1. INTRODUCTION

Clinical trials investigating new therapy concepts are generally of high interest to patients with severe and life-threatening conditions, cancer in particular.¹ However, the possibility to join a clinical trial differs per country, as clinical research remains concentrated in high-income countries.² Moreover, numerous regulatory and legal barriers make the conduct of pan-European clinical trials challenging.³

Directive 2011/24/EU on the application of patients' rights in cross-border healthcare (hereafter the "Directive") sets out the conditions under which a patient may travel to another EU country to receive medical care and reimbursement, however, participation in clinical trials abroad is not included in its scope.

In 2019, the European Federation of Pharmaceutical Industries and Associations' (EFPIA) Oncology Platform identified the need to better understand the interest of patients, physicians and sponsors in enabling cross-border enrolment of patients in clinical trials, and to investigate how frequently such cross-border inclusion currently occurs and which factors are helping or hindering it. To this end, EFPIA's Oncology Platform provided an unrestricted grant to a research consortium consisting of researchers from the European Forum for Good Clinical Practice (EFGCP), the European Organisation for Research and Treatment of Cancer (EORTC), the Catholic University of Leuven (KU Leuven), and the Patvocates Network, with the aim to generate information on this topic.

SCOPE OF THE STUDY

The research project was conducted between April and November 2019 and had 5 main objectives which reflected its exploratory nature:

To understand the regulatory and legal framework applicable to cross-border healthcare and clinical trials in the EU: does it help or hinder cross-border access of patients to clinical trials.

To develop an understanding of the frequency of enrolling patients from other EU countries in clinical trials, primarily in oncology trials.

To develop an understanding of the frequency of patients' interest in joining a clinical trial in another country.

To collect real life experience from physicians and patients with enrolling patients from other countries in a clinical trial.

To identify gaps and hurdles that have to be overcome to enable a routine opportunity for cross-border access to clinical trials.

¹ See, e.g., Slevin M, Mossman J, Bowling A, Leonard R, Steward W, Harper P, McIlmurray M, Thatcher N. "Volunteers or victims: patients' views of randomised cancer clinical trials", *British Journal of Cancer*, 1995, 71, p. 1270-1274; Nurgat ZA, Craig W, Campbell NC, Bisset JD, Cassidy J, Nicolson MC. "Patient motivations surrounding participation in phase I and phase II clinical trials of cancer chemotherapy", *British Journal of Cancer*, 2005, 92(6), p.1001-1005,

Walsh E, Sheridan A. "Factors affecting patient participation in clinical trials in Ireland: A narrative review", *Contemporary Clinical Trials Communications*, 2016, 3, p.23-31, Moorcraft SY, Marriott C, Peckitt C, Cunningham D, Chau I, Starling N, Watkins D, Rao S. "Patients' willingness to participate in clinical trials and their views on aspects of cancer research: results of a prospective patient survey", *Trials*, 2016, 17 (17)

² Drain PK, Parker RA, Robine M, Holmes KK, "Global migration of clinical research during the era of trial registration" *PLoS ONE* 13(2)

³ Negrouk A, Lacombe D, Meunier F. "Diverging EU health regulations: The urgent need for co-ordination and convergence", *Journal of Cancer Policy*, September 2018, Vol.17, pp.24-29

Djurisic S, Rath A, Gaber S, Garattini S, Bertele V, Ngwabyt S, Hivert V, Neugebauer E, Laville M, Hiesmayr M, Demotes-Mainard J, Kubiak C, Jakobsen J, Gluud B. "Barriers to the conduct of randomised clinical trials within all disease areas", *Trials*, 2017, 18

Based on the insights gathered throughout the course of the study, the research team sought to understand whether the topic is of sufficient practical relevance to seek regulatory clarity on the rules for cross-border access to clinical trials on an EU level, or whether it would be better to provide recommendation on best practices for enabling stakeholder solutions.

STUDY DESIGN AND APPROACH

The study employed a mixed methods research design, consisting of a desk research (literature search and review of relevant EU legislation), a qualitative research part (semi-structured interviews), and a quantitative research part (a survey). Research activities were clustered in three phases:

- **Phase 1: Organisation of the study:** the aim was to develop a common understanding about the scope of the study and the tasks that need to be performed.
- **Phase 2: Data collection and analysis:** the aim was to collect relevant information from different sources and stakeholders. With the desk research the research team set out to investigate the rationale and scope of the Cross-border Healthcare Directive, specifically approaching it with cross-border participation in clinical trials as focus. Furthermore, the objective of the literature search was to uncover to what extent cross-border access to clinical trials in the EU is part of the current scholarly debate. The qualitative and quantitative research arms of the study were developed together, and the questions addressed to Interviewees and survey participants were designed to be complementary, in order to provide basis for comparison of results.
- **Phase 3: Analysis and Final Report:** the aim was to describe, consolidate and critically assess the results, and to discuss them in this report.

KEY POINTS ABOUT THE CROSS-BORDER HEALTHCARE DIRECTIVE

History of inception of the Directive

The right to patient mobility for access to healthcare beyond national borders has never been disputed as long as the patients bear the costs themselves. However, the real issue, as pointed out by De La Rosa, is that patients, in exercising their right to mobility, should continue to be socially insured beneficiaries of care within a collective and socialized framework.⁴ This requires bypassing the principle of territoriality.⁵ Regulation (EC) 883/2004 on the coordination of social security systems established a fiction of law to allow this access of care.⁶ It provides that patients are covered as if they were persons insured by the State providing the care (hereafter “host country”).⁷ Prior authorisation to receive treatment outside the patient’s country of affiliation (hereafter “home country”) must be granted by the competent national authorities. It is important to note that in order to receive reimbursement, the persons concerned must submit an S2 form

⁴ De La Rosa S. “The Directive on cross-border healthcare or the art of codifying complex case law”, *Common Market Law Review* 2012, 49, p. 15–46

⁵ The principle of territoriality requires that the insured must be a resident of the country where they receive care benefits, see also Cornelissen R. “The principle of territoriality and the Community regulations on social security”, *Common Market Law Review* 1996, 33, p. 439–471

⁶ Also important in this respect is Regulation (EC) No 987/2009 of the European Parliament and of the Council of 16 September 2009 laying down the procedure for implementing Regulation (EC) No 883/2004

⁷ Art.19, Art. 20 of Regulation 883/2004

‘Entitlement to scheduled treatment’ completed up by the competent institution and which states that the required authorisation has been granted.⁸

Regulation 883/2004 was adopted based on the freedom of movement of persons. With the *Kohll* and *Decker* cases⁹, the CJEU developed new ways of support to reimburse medical care and further established a line of jurisprudence in this field. It must be noted that the participation in a clinical trial across border was not part of the aforementioned CJEU cases. The Directive on Cross-border Healthcare was designed to codify and clarify the solutions that emerged from this case law and to complement the existing social security regulations. Unlike Regulation 883/2004, the Directive was based on the freedom of service provision. Furthermore, in literature it has been discussed that the Directive was a compromise which was very difficult to achieve between the EU institutions.¹⁰

Mechanism of reimbursement of costs

Pursuant to Art. 7(1) of the Directive, the Member State of affiliation shall ensure the costs incurred by an insured person who receives cross-border healthcare are reimbursed, if the healthcare in question is among the benefits to which the insured person is entitled in the Member State of affiliation. Art. 7(4) further specifies that the costs of cross-border healthcare shall be reimbursed or paid directly by the Member State of affiliation up to the level of costs that would have been assumed by the Member State of affiliation, had this healthcare been provided in its territory. Moreover, the Directive is without prejudice to the rules established with Regulation (EC) No 883/2004 and specifically requires that where the patient is entitled to cross-border healthcare also under Regulation 883/2004, and the application of that Regulation is more advantageous to the patient, the patient’s attention should be drawn to this by the Member State of affiliation.¹¹

Main differences between the Cross-border Healthcare Directive and Regulation 883/2004

- Under the Directive, patients are reimbursed for treatment abroad as if the treatment was provided in their home countries, whereas under the Regulation, patients are entitled to healthcare abroad as if they were insured under the social security system of the Member State of treatment.¹²
- The Directive is aimed at the free movement of patients, while the Regulation is based on the free movement of workers.¹³
- The rationale of the Directive is a reimbursement to the patient who has paid the service before, while the rationale of the Regulation is a reimbursement of the cost between institutions, which is a system more beneficial for the patient. However, as the Regulation is based on the free movement of workers, it only exceptionally allows the reimbursement of expenses in situations of travel with a specific purpose of receiving medical treatment. Pursuant to Art. 20 of the Regulation, a citizen can

⁸ For a detailed overview of the social security Regulations, see “The coordination of healthcare in Europe: Rights of insured persons and their family members under Regulations (EC) No 883/2004 and (EC) No 987/2009”, issued by European Commission, Directorate-General for Employment, Social Affairs and Inclusion, Unit B.4, February 2011

⁹ Case C-120/95, *Decker v. Caisse de maladie des employés privés*, ECLI:EU:C:1998:167 and Case C-158/96, *Kohll v. Union des caisses de maladie*, ECLI:EU:C:1998:171

¹⁰ As put by De La Rosa, evidence in this respect is the dual legal basis used for the Directive, the oft-repeated references to the need to preserve the competence of the Member States, both in the recitals (e.g. recitals 7, 10, 18, 33) and in the body of the Directive, the excess of justification (64 recitals) and finally, the length of time needed for its adoption. The EU Commission launched a broad consultation process to open the debate and to consider Union action on patient mobility in 2006, the final text of the Directive was adopted in 2011, and Member States had time to transpose the Directive into their national law until 25 October 2013)

¹¹ Art. 7(1) and recital 31 of the Directive

¹² See also Commission Report on the operation of Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, Brussels, 21.9.2018, COM(2018) 651 final, available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2018:651:FIN>

¹³ Nicolas P. “Rare diseases policies, European reference centers, and cooperation initiatives” in Den Exter A. (ed.) “Cross-border health care and European Union law”, Erasmus University Press (2017)

travel to another country with the purpose of receiving a treatment only when the treatment cannot be given in his country within a time-limit which is medically justifiable.

Other key features of the Directive that are of potential interest in the topic on cross-border access to clinical trials

- **National Contact Points (NCPs) for cross-border healthcare:** pursuant to Art. 6 of the Directive, each Member State shall designate one or more NCPs. The objective of NCPs is to provide patients with information concerning healthcare providers, patients' rights, complaints procedures and mechanisms for seeking remedies, according to the legislation of that host country, as well as the legal and administrative options available to settle disputes, including in the event of harm arising from cross-border healthcare. At the start of the research project, the research team specifically set out to investigate whether NCPs could play a potential role as facilitators for cross-border access to clinical trials.
- **Special focus on rare diseases:** Art. 13 of the Directive establishes that the EU Commission shall support Member States in cooperating in the development of diagnosis and treatment capacity of rare diseases, more specifically by making healthcare professionals aware of the existing tools to assist them in the correct diagnosis of rare diseases (the Orphanet Database, the European Reference Networks) and by making patients, healthcare professionals and those bodies responsible for the funding of healthcare aware of the possibilities offered by Regulation (EC) No 883/2004 for referral of patients with rare diseases to other Member States even for diagnosis and treatments which are not available in the Member State of affiliation.
- **European Reference Networks (ERNs):** the Directive established the launch of the system of the ERNs which marked a major change for the delivery of quality and accessible cross-border healthcare to EU citizens. Pursuant to Art. 12, the European Commission shall support the Member States in the establishment of the ERNs. The ERNs should have at least 3 of 8 proposed objectives¹⁴ (Art. 12(2)) and should be established between healthcare providers and centres of expertise in the Member States, in particular in the area of rare diseases. The objectives of the ERNs designate them as privileged hubs for research. At the current moment there are 24 ERNs which work on a range of issues, including bone disorders, childhood cancer and immunodeficiency across 26 countries. They were launched in March 2017¹⁵ and as of November 2018 are officially operational.¹⁶ However, their long-term sustainability is challenged by limited funding, awareness among patients and healthcare professionals, support from hospital managers, and the limited human resources available to work

¹⁴ Art. 12(2) of the Directive:

- (a) to help realise the potential of European cooperation regarding highly specialised healthcare for patients and for healthcare systems by exploiting innovations in medical science and health technologies;
- (b) to contribute to the pooling of knowledge regarding sickness prevention;
- (c) to facilitate improvements in diagnosis and the delivery of high-quality, accessible and cost-effective healthcare for all patients with a medical condition requiring a particular concentration of expertise in medical domains where expertise is rare;
- (d) to maximise the cost-effective use of resources by concentrating them where appropriate;
- (e) to reinforce research, epidemiological surveillance like registries and provide training for health professionals;
- (f) to facilitate mobility of expertise, virtually or physically, and to develop, share and spread information, knowledge and best practice and to foster developments of the diagnosis and treatment of rare diseases, within and outside the networks;
- (g) to encourage the development of quality and safety benchmarks and to help develop and spread best practice within and outside the network;
- (h) to help Member States with an insufficient number of patients with a particular medical condition or lacking technology or expertise to provide highly specialised services of high quality.

¹⁵ Final report from the 3rd Conference on European Research Networks. 9-10 March, Vilnius, available at:

https://ec.europa.eu/health/sites/health/files/ern/docs/ev_20170309_frep_en.pdf

¹⁶ Final report from the 4th Conference on European Research Networks. 21-22 November, Brussels, available at:

https://ec.europa.eu/health/sites/health/files/ern/docs/ev_20181121_frep_en.pdf

on ERN-related initiatives.¹⁷ It has been acknowledged that the ERNs possess the capacity to concentrate expertise and thus present potential opportunities for collaboration in clinical trials.¹⁸ In a Statement adopted in June 2019, the ERN Board of Member States agreed with the engagement of ERNs with the pharmaceutical industry, in particular on clinical trials and research projects.¹⁹ As there is no legal provision for the collaboration between ERNs and industry, the Board of Member States offered guidance on the matter.²⁰ No specific mention as regards cross-border participation to clinical trials was made in that guidance. As in the case of NCPs presented above, the research team set out to investigate whether ERNs could be facilitators for cross-border access to clinical trials. However, it must be stressed here that the EU Commission specifically acknowledged in its last implementation report that, in the case of ERNs, “*it is the medical knowledge that travels and not the patient*”.²¹ This view is shared also by EURORDIS.²² Such an institutional viewpoint might be perceived as a possible obstacle to establishing ERN’s potential role for the facilitation of cross-border clinical trial participation. Moreover, as regards ERNs, the Commission can take measures but not harmonize any laws or regulations of the Member State.

Current operation of the Directive

The Directive was subject of several assessment reports by the EU Commission and the most recent one was published in September 2018. It was shown that cross-border patient mobility within the EU had a slight increase trend over the years 2015-2017, however it remained low in absolute numbers. According to the EU Commission’s report, the reasons for the increase trend were two-fold. First, it might have been due to the improvements in providing information to EU citizens and the better awareness on patient rights. Second, it might have been due to the collaboration between the EU Commission and the Member States on this matter, and the interaction between the Directive and the Social Security Regulation. In addition, the report concluded that the Directive has improved legal certainty for cross-border patients.²³

In its 2019 special report on EU actions for cross-border healthcare, the European Court of Auditors (ECA) provided information that the number of citizens claiming reimbursement for medical care received abroad under the Directive is low (approximately 200 000 claims a year – fewer than 0.05 % of EU citizens).²⁴ It is interesting to note that, in comparison, the claims made under Regulation 883/2004 are approximately 2 million a year.

CROSS-BORDER ACCESS TO CLINICAL TRIALS IN THE EU: A GAP IN LAW AND LITERATURE

In order to answer the question whether cross-border access to clinical trials in the EU is currently part of the EU legal framework and of relevant scholarly debate, a literature search was performed on the Official

¹⁷ Final report from the 4th Conference on European Research Networks. 21-22 November, Brussels

¹⁸ Maggie de Block, Minister of Health (Belgium), as quoted in the Final report from the 4th Conference on European Research Networks

¹⁹ Statement of the ERN Board of Member States on European Reference Networks (ERNs) & industry, adopted on 25 June 2019, available at: https://ec.europa.eu/health/sites/health/files/ern/docs/statement_industry_conflictinterest_en.pdf

²⁰ Statement of the ERN Board of Member States on European Reference Networks (ERNs) & industry, adopted on 25 June 2019

²¹ Commission Report on the operation of Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, Brussels, 21.9.2018, COM(2018) 651 final, available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2018:651:FIN>

²² See <https://www.eurordis.org/content/about-european-reference-networks>

²³ Commission Report on the operation of Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, Brussels, 21.9.2018, COM(2018) 651 final, available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2018:651:FIN>

²⁴ European Court of Auditors. “Special report on EU actions for cross-border healthcare: significant ambitions but improved management required”, June 2019, available at: https://www.eca.europa.eu/Lists/ECADocuments/SR19_07/SR_HEALTH_CARE_EN.pdf

Journal of the EU, PubMed, and HeinOnline. Spontaneous findings through Google Scholar and Limo (the KU Leuven libraries' search engine which allows access to journals, electronic databases and e-books to which the university owns a license) were also reviewed.

It was established that the issue is not regulated in the EU's body of law. In particular, no specific EU legislative act addresses cross-border participation in clinical trials. As already discussed above, the matter is also neither included in the scope of the Cross-border Healthcare Directive, nor of the Social Security Regulation. Based on the freedom of movement²⁵ and the freedom of services²⁶, it could be established that the participation in a clinical trial outside of the patient's home country cannot be forbidden in the EU, hence it is possible for patients who can afford to cover the associated costs. However, the real issue, as it used to be the case with cross-border healthcare before the adoption of the Social Security Regulation and the Cross-border Healthcare Directive, lies in the question whether such costs can be reimbursed. Moreover, there is no clear guidance as on how the complex navigation between healthcare systems in the context of a clinical trial can be performed by patients.

With respect to the academic debate, the topic of cross-border access to clinical trials has not been comprehensively discussed so far in the EU.

It must be noted that in a 2013 Position Statement on the EU Commission proposal for a Regulation on Clinical Trials, the European Patients Forum (EPF) brought attention to the issue of cross-border participation in clinical trials.²⁷ In particular, they advocated that a provision allowing cross-border access to clinical trials should be included in the Clinical Trials Regulation (CTR). This request was not included in the final text of the CTR. In addition, EPF specified that the potential to apply the Cross-border Healthcare Directive in the context of clinical trials should also be explored.

Conclusion:

Due to the identified gap in literature and in the academic debate, this research project is of special importance by being the first exploratory study to systematically collect data and provide a comprehensive look into the need, occurrence and challenges of cross-border access to clinical trials.

REPORT FORMAT

The reporting of results from the desk research, including the evaluation of the Cross-border Healthcare Directive as a starting point of the study, was presented in this introduction.

The reporting of results from the interviews and the survey follows in *Section 2. Methodology*. The methodological choices regarding the interview's design, conduct and analysis are presented, followed by the respective methodological explanation for the survey. In *Section 3. Results and Interpretation*, the results from both the qualitative and the quantitative parts of the project are structured by topic (15 topics in total) and reported together, in order to allow easy comparison between interviews and survey data. A summary of key results and conclusion is also presented per topic.

²⁵ Article 3(2) of the Treaty on European Union (TEU); Article 21 of the Treaty on the Functioning of the European Union (TFEU); Titles IV and V TFEU; Article 45 of the Charter of Fundamental Rights of the European Union

²⁶ Article 56 of the TFEU

²⁷ European Commission proposal for a Regulation on Clinical Trials (COM(2012) 369 final) EPF Position Statement, February 2013, available at: <https://www.eu-patient.eu/globalassets/policy/clinicaltrials/epfs-position-statement-ctr---feb-2013-new-format.pdf>

Finally, in *Section 4. Discussion, conclusions, and recommendations for future actions* the results are discussed, limitations of the study are reflected on, and recommendations for future actions are provided. The recommendations are provided by the research team and the Advisory Committee, based on the critical evaluation of the proposals provided by study participants.

1. METHODOLOGY

PART I: INTERVIEWS

Thirty-eight semi-structured interviews with representatives from seven stakeholder groups who were involved in the cross-border conduct of clinical trials and/or had experience with the implementation of the Cross-border Healthcare Directive were performed between May and September 2019. The Interviewees represented patient organisations, pharmaceutical industry, investigators/physicians, ethics committees, policy experts, academic clinical trial sponsors, and National Contact Points (see Table 1).

RECRUITMENT OF PARTICIPANTS

Purposive sampling was applied for the selection of potential participants (see Table 2 for an overview of the inclusion criteria). This strategy was complemented by a snowball sampling approach. Potential Interviewees were contacted and invited to participate via e-mail, or in person.

44% (n=38) out of n=86 contacted experts agreed to be interviewed. Of them, 33 participants had their workplace in 13 different EU Member States (Germany, Belgium, Bulgaria, UK, Romania, Italy, Sweden, Denmark, France, Spain, Lithuania, Slovakia, Estonia), 1 participant in Switzerland, 3 participants in Norway, and 1 participant in the United States. The aim was to balance the Interviewees' background evenly across the targeted stakeholder groups. However, the achievement of this goal depended on the different groups' response rate. Investigators/physicians and patients/patient representatives were the two stakeholder groups which demonstrated the highest interest in participating in the study. It is important to note that only one representative from the 28 EU National Contact Points agreed to be interviewed. The other contacted persons refused, stating as reason their lack of expertise on the topic of clinical trials.

The majority of physicians involved in the study had expertise in oncology and related areas of indications such as haematology and pulmonology. Also, the area of expertise of the other interviewed stakeholder groups was primarily in oncology. The views of paediatric experts were also included, however, the focus of the study remained mainly on participation of adult subjects in clinical trials.

Table 1. Number of experts interviewed per stakeholder group

Stakeholder Group	Number and % of Experts Interviewed
Patients/patient representatives	11 (29%)
Pharmaceutical industry	5 (13%)
Investigators/physicians	11 (29%)
Ethics committees	3 (8%)
Policy experts	6 (16%)

Academic clinical trials sponsors	1 (3%)
National Contact Points	1 (3%)
TOTAL	38

Table 2. Inclusion criteria for the recruitment of representatives of each stakeholder group

Stakeholder Group	Inclusion Criteria for Recruitment of Representatives
Patients/patient representatives	<ul style="list-style-type: none"> • Is a patient or has experience working as a patient representative • Speaks fluently English • Works or has worked in a Member State of the European Union
Pharmaceutical industry	<ul style="list-style-type: none"> • Holds a senior management position at a pharmaceutical company • Is actively involved in decision-making • Speaks fluently English • Works or has worked in a Member State of the European Union
Investigators/physicians	<ul style="list-style-type: none"> • Has been actively involved in clinical trials as a principal investigator or has experience with referring patients abroad/receiving foreign patients • Holds a senior position at a university hospital • Speaks fluently English • Works or has worked in a Member State of the European Union
Ethics committees	<ul style="list-style-type: none"> • Is member of an ethics committee based in a Member State of the European Union • Speaks fluently English • Works or has worked in a Member State of the European Union
Policy experts	<ul style="list-style-type: none"> • Has experience with clinical research and patient recruitment • Speaks fluently English • Works or has worked in a Member State of the European Union
Academic clinical trials sponsors	<ul style="list-style-type: none"> • Holds a senior position at an organisation involved in the conduct of academic clinical trials • Speaks fluently English • Works or has worked in a Member State of the European Union
National contact points	<ul style="list-style-type: none"> • Holds a position at a designated National contact point as established under Directive 2011/24/EU on patients' rights in cross-border healthcare • Speaks fluently English • Works or has worked in a Member State of the European Union

INTERVIEW PREPARATION

An informed consent form (Annex I) was signed by each expert who agreed to participate in the study. The form provided an overview of the objectives of the study, the research team, and the funding of the project. Furthermore, it outlined the organisational aspects of the interview. Questions of confidentiality, privacy, and the participants' rights were also addressed. Assurance was provided to Interviewees that their privacy was guarded, and their identity would not be made public.

TIMING AND LOGISTICS OF INTERVIEWS

The interviews were conducted between May and September 2019. For logistical reasons, most discussions took place over Skype®, however a number of interviews were performed in person or via telephone. A total of three persons from the research team performed the interviews. An interviewer team was required in order to complete the research project in a timely manner. All interviewers had to follow the same interview guide (Annex II). The sessions were digitally recorded, and all interviews were subsequently transcribed by a third party, namely language-skilled students from KU Leuven, contracted by EFGCP. The students signed non-disclosure agreements in relation to the research data they had access to in the course of their work.

CONTENT OF INTERVIEWS

The interview questions were categorised in two main parts. The topics defined by the research team to investigate are presented in summary below. For the full Interview Questionnaire, please see Annex II. All Interviewees were asked the same questions in the same order to allow for inter-group comparisons and to minimize the risk of bias. However, during the discussion and depending on the answers given by the participants, some additional question emerged and were posed with the aim of capturing the participants' opinions and experience in the most optimal way.

➤ **Part 1: Current situation in cross-border access to clinical trials** (Question 1 to 13)

- *Study participants' experience with cross-border access to clinical trials.*
- *Study participants' observations regarding increase or decrease in patients' requests for inclusion in clinical trials organised outside their home country.*
- *Investigators' opinion regarding whether an increase in cross-border clinical trial participation would reduce patient recruitment timelines due to the number of patients who participate in clinical trials abroad.*
- *Motivations for patients to pursue participation in a clinical trial conducted abroad.*
- *Motivations for patient advisors (representatives of patient organisations and treating physicians) to recommend participation in a clinical trial conducted abroad.*
- *Motivations for clinical trial sponsors to facilitate recruitment of foreign patients.*
- *Study participants' opinion about which EU Member States are attractive for patients to seek participation in a clinical trial and reasons why.*
- *Study participants' viewpoint about EU Member States of origin of patients seeking participation in a clinical trial abroad and reasons why.*
- *Study participants' opinion about the challenges for patients participating in a clinical trial abroad.*

➤ **Part 2: Organisational framework of access to cross-border clinical trials** (Questions 14 to 24)

- *Study participants' knowledge about Directive 2011/24/EU on patients' rights in cross-border healthcare.*
- *Study participants' opinion about the statement: "Cross-border participation in clinical trials in Europe is needed/not needed" and their reasons why.*
- *Study participants' opinion whether cross-border participation in clinical trials should be limited, and their reasons why.*
- *Study participants' opinion about the allocation of responsibility for handling the logistics of clinical trial participation of patients coming from abroad.*
- *Study participants' opinion about the allocation of responsibility for covering the costs of study participation of patients coming from abroad.*
- *Study participants' view about which actions could facilitate cross-border participation in clinical trials.*
- *Study participants' perceptions about the current national legislation in their country of residence in terms of enabling cross-border access to clinical trials.*
- *Study participants' perceptions about the current EU legislation in terms of enabling cross-border access to clinical trials.*

PROCEDURE FOR ANALYSIS

The interviews were analysed according to the framework method for qualitative research (Gale et al., 2013; Spencer et al., 2014) and following the Qualitative Analysis Guide of Leuven, QUAGOL (Dierckx de Casterlé et al., 2012). This approach involves going through several different steps.

Step 1: Transcription of interviews

Transcription of interviews was outsourced to a third party, as described above, in order to ensure the completion of the study in a timely manner. All coded transcripts were stored securely and will be kept until such time as they might be used for future studies.

Step 2: Familiarisation with the interviews

Familiarisation with the interviews was mainly achieved through reading the transcripts and listening to the audio recordings. This stage was of crucial importance for the researcher who was responsible for analysing the data, as a number of interviews were conducted by two other research team members.

Step 3: Coding

In this stage, the transcripts were analysed sentence by sentence and descriptive labels were added to excerpts discussing a particular topic through the use of the NVivo® software, which is specifically designed for qualitative data analysis. This process is referred to as coding.

To a large extent, the coding list was pre-defined by the topics included in the question forming the interview guide. However, open coding was additionally applied in order to fully grasp the intricacies of opinions and to structure the emerging concepts and ideas in the most suitable way.

Step 4: Developing a working analytical framework

In this stage, a working analytical framework was developed by coding a limited number of transcripts (namely, 5 transcripts which the research team collectively agreed to provide the richest data) and grouping related codes together into categories in NVivo®. The coding of the 5 transcripts was conducted individually by two members of the research team. It was subsequently compared; ambiguities and overlaps were cleared out and discussions were held with one of the principal investigators in order to ensure an unbiased approach.

Step 5: Applying the analytical framework

Once a working analytical framework had been established, it was applied to all transcripts by attaching the appropriate codes to specific sections of text through the use of NVivo®.

Step 6: Interpreting the data

Finally, the data was examined to identify connections and patterns within and between the stakeholder groups.

PART II: SURVEY

SURVEY DESIGN, CONTENT AND DISSEMINATION

The research team prepared a survey questionnaire consisting of 25 questions (see Annex III), of which 16 were compulsory for answer. The questionnaire was designed to be in line with and complementary to the interview guide, in order to provide a basis for comparison between the quantitative and qualitative arm of the research project. The questionnaire was set up in English and it was uploaded on the SurveyMonkey® online software. The survey was active between May 29 and July 31, 2019. The survey opened with an introductory message that provided information about the research project and its objectives, the legal basis for processing the personal data of participants and the period for storage of data collected through the survey. In order to participate in the survey, respondents had to provide consent for the processing of their personal data by ticking “Yes”. The survey was disseminated very broadly, via direct messaging to individuals from the networks of all collaborating organisations, and via social media (e.g., LinkedIn, Twitter). The dissemination via direct messaging was targeted only at persons who had provided consent for receiving communications of such nature.

The survey consisted of two parts. The investigated topics are presented in summary below (see Annex III for a full presentation of the survey questionnaire). Most questions included pre-formatted answers, and where answers could largely vary from these, the “Other” option was available to the respondents. Pre-defined answers were proposed by the patients, patient representatives and healthcare professionals that collaborated in the preparation of the survey methodology and tool, and they were also based on the information collected through the literature review. Due to the highly exploratory nature of the project, 12 out of the 25 questions were of the multiple answer multiple choice type, and 3 focused entirely on gathering information about available official statistics or additional information on cross-border access to clinical trials. In addition, 5 were single answer multiple choice, 3 were matrix questions, and 2 were open-ended.

- **Part 1: General questions** (Questions 1 to 5)
 - *Country and stakeholders' representation in the survey.*
 - *Study participants' experience with cross-border access to clinical trials.*
- **Part 2: The current situation** (Questions 6 to 25)
 - *Study participants' observations regarding increase or decrease in patients' requests for inclusion in clinical trials organised outside their home country.*
 - *Investigators' opinion about the highest number of foreign patients who have participated in their clinical trials.*
 - *Study participants' opinions about frequency of patients' participation in clinical trials conducted abroad.*
 - *Motivations for patients to pursue participation in a clinical trial conducted abroad.*
 - *Motivations for treating physicians to recommend participation in a clinical trial conducted abroad.*
 - *Motivations for clinical trial sponsors to recruit foreign patients.*
 - *Study participants' opinion about which EU Member States are attractive for patients to seek participation in a clinical trial and reasons why.*
 - *Study participants' opinion about EU Member States of origin of patients seeking participation in a clinical trial abroad and reasons why.*
 - *Study participants' opinion about the challenges for patients participating in a clinical trial abroad.*
 - *Study participants' opinion about the statement: "Cross-border participation in clinical trials in Europe is needed/not needed" and their reasons why.*
 - *Study participants' opinion about the allocation of responsibility for handling the logistics of clinical trial participation of patients coming from abroad.*
 - *Study participants' opinion about the allocation of responsibility for covering the costs of study participation of patients coming from abroad.*
 - *Study participants' view about which actions could facilitate cross-border participation in clinical trials.*

SURVEY ANALYSIS

The analysis of collected data was done with support from KU Leuven's Biostatistics and Statistical Bioinformatics Centre (L-BioStat). All descriptive tables included in Annex IV were produced using SAS software, version 9.4 of the SAS System for Windows.

Data cleaning only included checking for errors as of Question 4 on opinions and experiences, not on general information on the respondents asked in Questions 1 to 3.

Data analysis consisted of presenting the frequencies for each question and considering associations between answers. Due to the direct correlation with the Interview Questionnaire, most of the quantitative data gathered through the survey could be compared with the in-depth insights from the qualitative part of the study. This is reflected in the approach chosen to present the results in this report, namely by grouping corresponding survey and interviews results under the relevant topics.

From the total of 396 eligible questionnaires, 68% (n=276) of respondents provided answers to all 16 compulsory questions.

The detailed data analysis report produced by KU Leuven's Biostatistics and Statistical Bioinformatics Centre (L-BioStat) can be found in Annex IV of this document. The survey results are reported here by way of textual and visual summaries of the main findings and detailed reporting of the conclusions drawn by the research team. When deemed suitable, references are made to the L-BioStat's report attached in the aforementioned Annex.

2. RESULTS AND INTERPRETATION

Preliminary, high-level results of the study were presented during the ECCO 2019 European Cancer Summit on 13th September 2019 in Brussels, Belgium. Selected results were shared at the Nordic NECT Semi-annual Meeting on 30th October 2019 in Aarhus, Denmark. The complete final results are described in this report. In addition, at least one paper presenting the research project and its results will be submitted for publication in a scientific journal.

In the following section, the results of the study are presented across the main topics that were investigated in both the qualitative and quantitative parts of the project. The interviews insights are described first, followed by the corresponding survey results. Quotes from the interviews are reported verbatim. In some instances, light editing was deemed necessary in order to improve readability, e.g., parasite words were deleted. Identifying information such as names and locations was removed from the quotes. This is signified by the use of brackets.

Several topics from the interviews that could not be compared with corresponding parts of the survey are reported in the Topic 14: “Specific topics from the interviews”. Also the study participants’ views on the regulatory and organisational environment for cross-border access are presented there.

TOPIC 1: COUNTRY REPRESENTATION IN THE PROJECT

An important aim of this research project was balanced representations of stakeholders from all over Europe.

INTERVIEWS

Following a purposive sampling strategy, all Interviewees contacted for the study were based in Europe or possessed a comprehensive view over the situation in the field of cross-border access to clinical trials in Europe (as was the case with the sole representative who was based in the United States).

Most Interviewees were based in Belgium (26%, n=10), followed by Germany (11%, n=4), UK (8%, n=3), Norway (8%, n=3), Denmark (8%, n=3), and Italy (8%, n=3) (see Figure 1). In addition, the majority of countries represented in the study were EU Member States (13 countries: Germany, Belgium, Bulgaria, UK, Romania, Italy, Sweden, Denmark, France, Spain, Lithuania, Slovakia, Estonia), which reflects the pre-defined scope of the project, namely investigating the need, challenges and future facilitation of cross-border access to clinical trials specifically in the EU.

For further comparison with the corresponding survey results, the distribution of participants’ countries is also presented according to the world regions (see Figure 2). The United Nations geoscheme of Europe, created by the United Nations Statistics Divisions, was used for the ascribing of countries to regions.²⁸

²⁸ <https://www.worldatlas.com/articles/the-four-european-regions-as-defined-by-the-united-nations-geoscheme-for-europe.html>. Distribution of countries / regions was retrieved on 23 July 2019.

Figure 1. Participants' countries of workplace

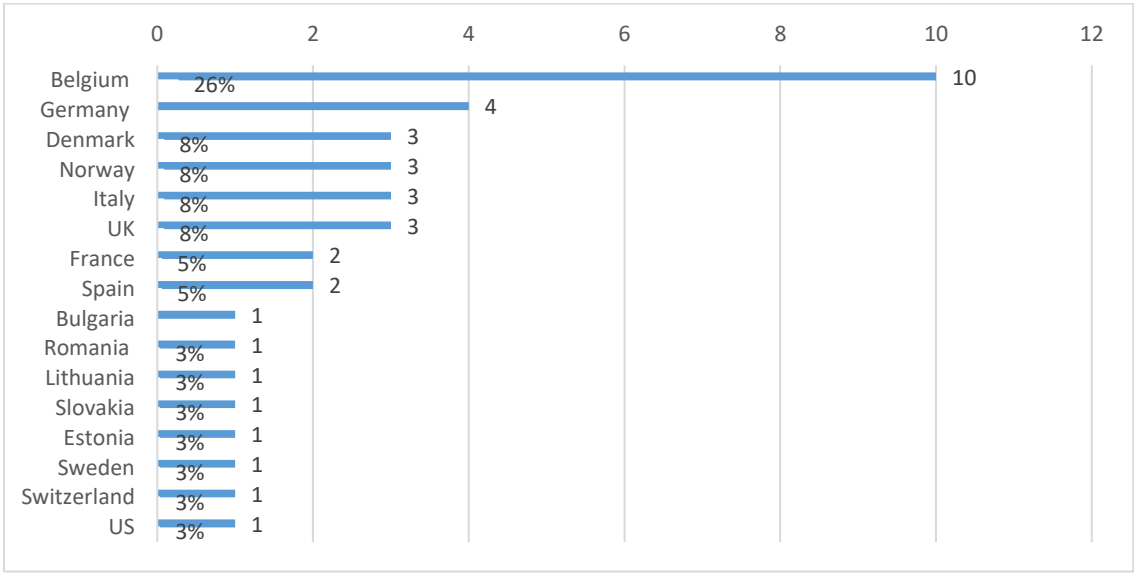
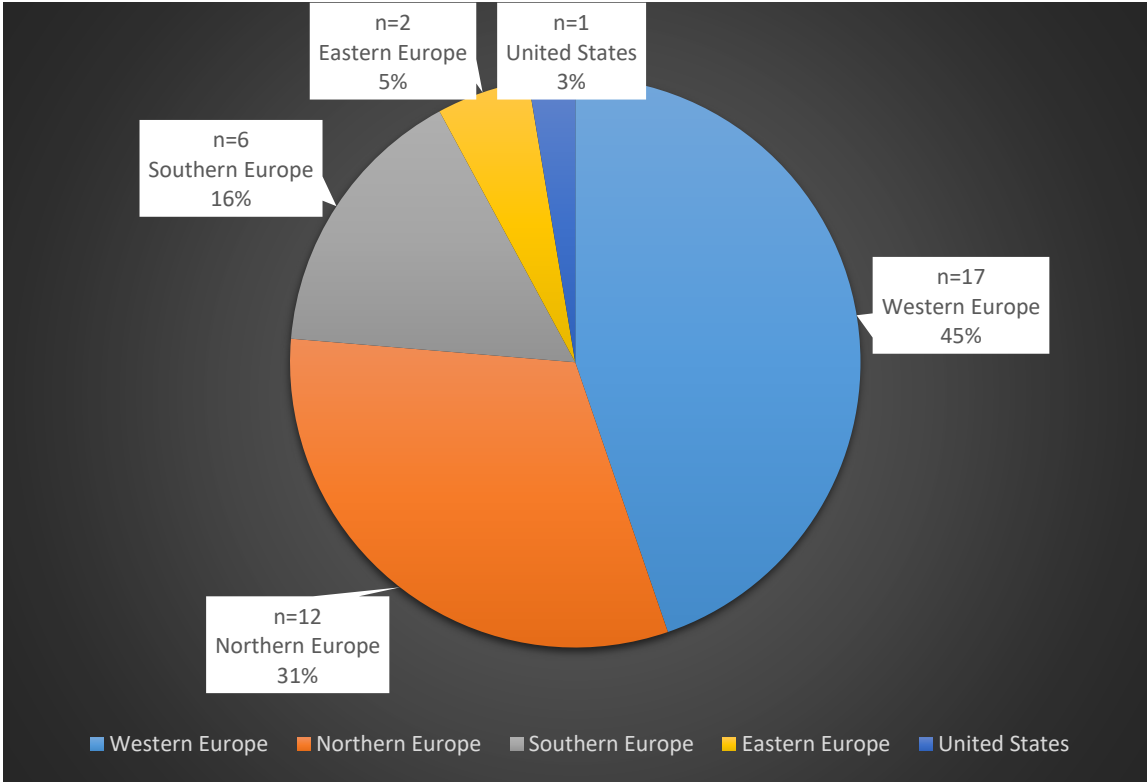


Figure 2. Distribution of participants' countries according to the sub-regions



SURVEY

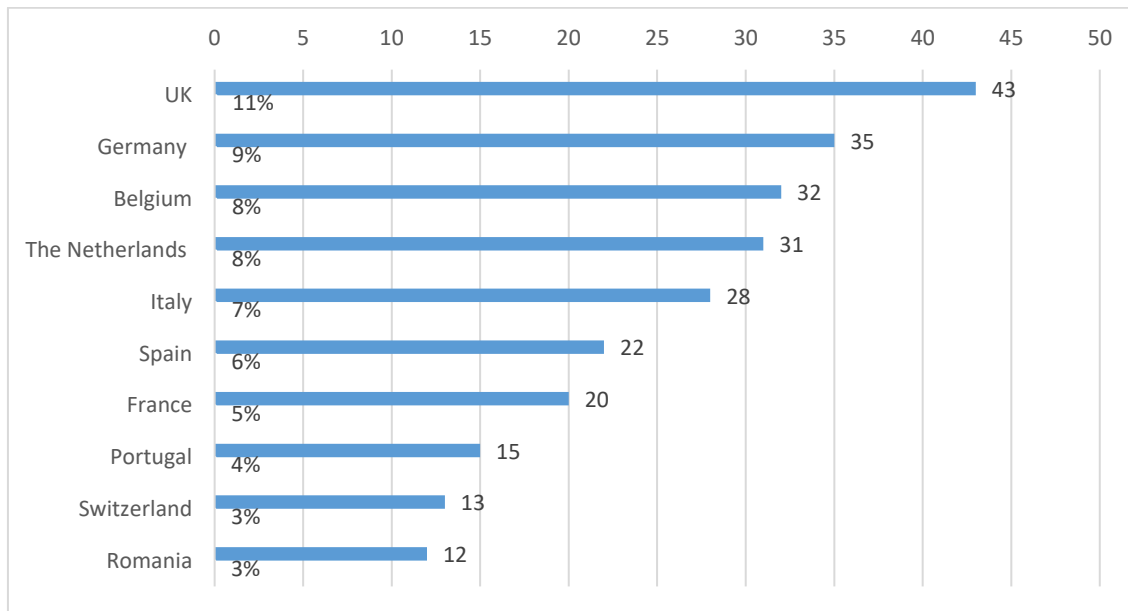
The first question of the survey referred to the country where the respondent was based:

QUESTION 1: IN WHICH COUNTRY ARE YOU BASED?

All 396 survey participants provided an answer. As the respondents' countries of origin were very diverse, the countries were grouped as sub-regions according to the United Nations geoscheme of Europe.

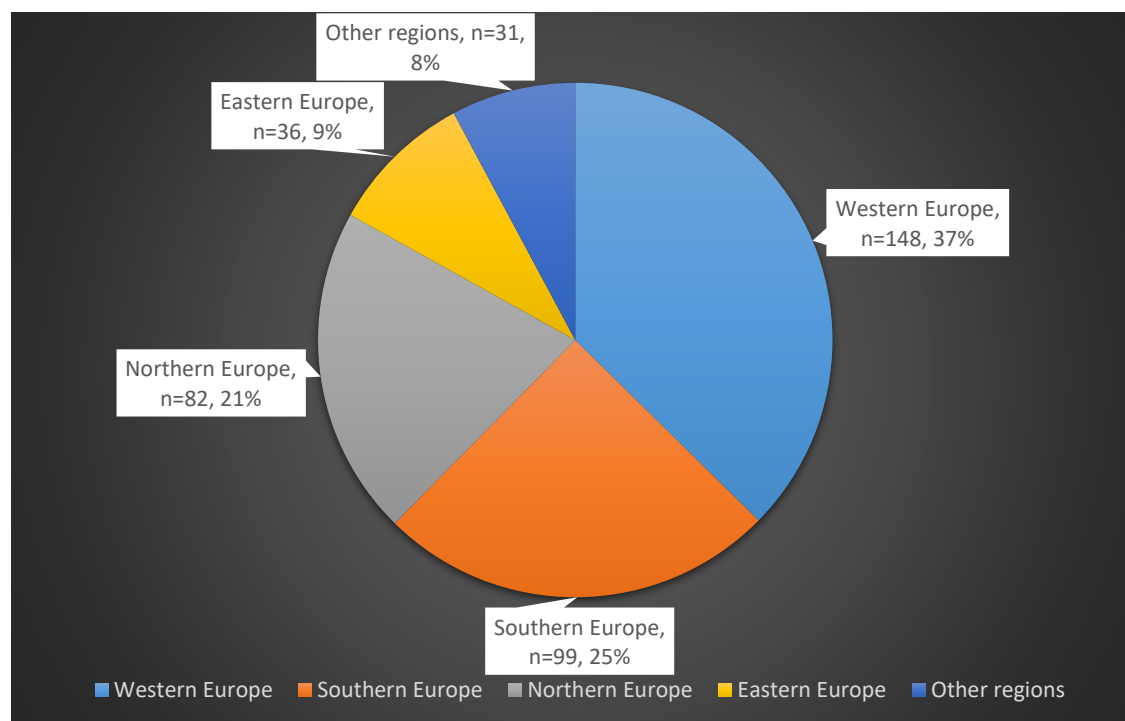
As the questionnaire placed special emphasis on Europe and it was mostly distributed in European countries, the answers reflected that situation, however few answers were received from other continents and countries as well. The ten countries with highest representation in the survey were the United Kingdom, Germany, Belgium, The Netherlands, Italy, Spain, France, Portugal, Switzerland, and Romania (Figure 3).

Figure 3. List of countries with the highest number of responses



For the presentation of data in the pie chart presenting percentages of country affiliation (Figure 4) the answers provided by respondents based outside of the EU were grouped under "Other".

Figure 4. Distribution of participants' countries according to the sub-regions



KEY RESULTS: TOPIC 1

The research project strived to enable a balanced representation of the EU countries. In practice, the results showed that the highest response rate was from Western European countries (45% (n=17) of Interviewees, 38% (n=148) of survey respondents), while the lowest was from Eastern Europe (5% (n=2) of Interviewees, 9% (n=36) of survey respondents). In a follow-up research it would be important to further investigate the reasons for the lower response rate from Eastern European countries. In respect to Southern and Northern Europe, the percentage of representation was different in the interviews and in the survey. In the survey, the two sub-regions were almost equally represented (Southern Europe 24% (n=99), Northern Europe 21%, n=82), while in the interviews more participants were from Northern Europe (32%, n=12) than from Southern Europe (16%, n=6). This could be explained mainly with the complementary use of the snowballing sampling approach and the fact that all Northern European experts recommended colleagues from the same sub-region. These showed high willingness to contribute to the study. The low response from Eastern European countries in comparison to the three other regions despite a very strong survey dissemination and interview invitation effort could be support to the comments from some Eastern European Interviewees about limited awareness and interest of local physicians and patients of the cross-border access to clinical trials option. The high response from Western European countries could also mean that cross-border access to clinical trials is primarily happening in Western European countries.

Conclusion:

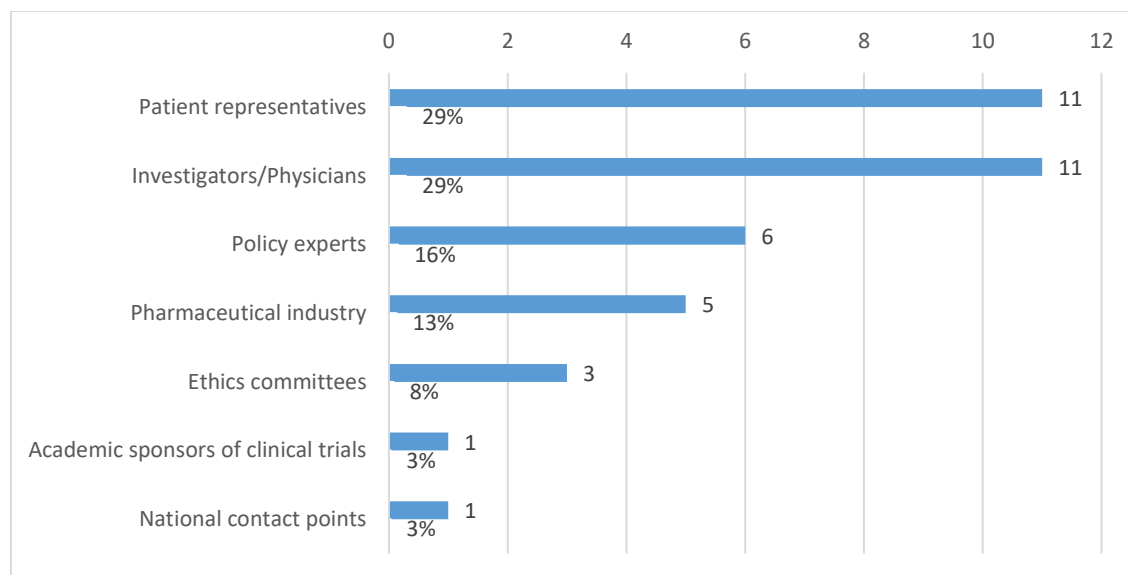
The majority of information received in this research project represents the situation in Western European countries in comparison to CEE countries.

TOPIC 2: STAKEHOLDERS REPRESENTATION IN THE PROJECT

INTERVIEWS

The second request for information in both the interviews and the survey related to the stakeholder background of the respondent.

Figure 5. Stakeholders' representation in the interviews



SURVEY

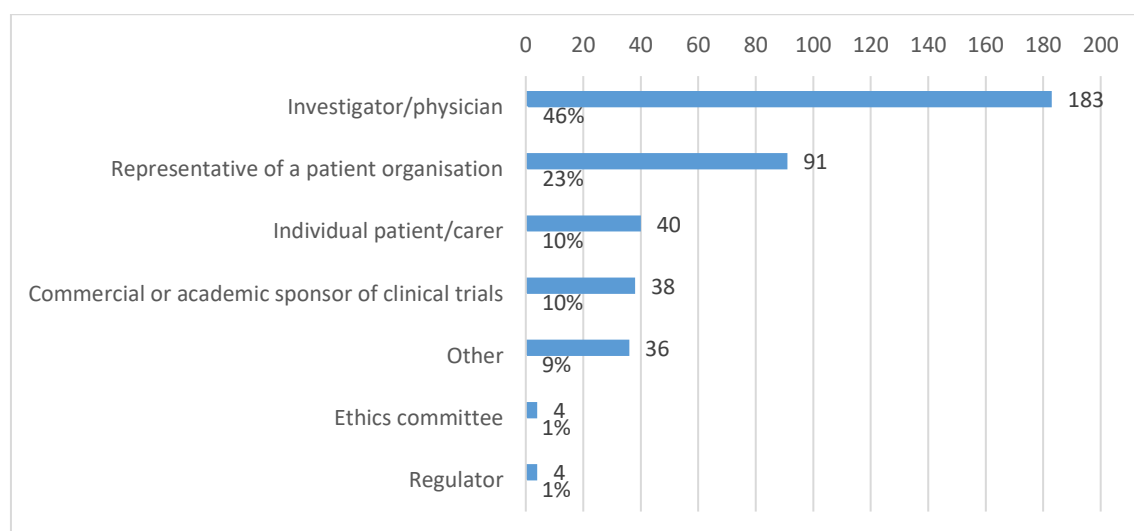
Responses were collected in

QUESTION 2: TO WHICH STAKEHOLDER GROUP DO YOU BELONG?

All 396 survey respondents provided an answer. The questionnaire was mostly intended to the stakeholders involved in clinical trials, although “Other” respondents, potentially not or only indirectly involved in clinical trials were encouraged to respond as well. Most of the responses were provided by stakeholder group of investigators/physicians. But an important contribution to the results of this survey was also received from the patients’ community. Out of the total number of respondents that correctly indicated their stakeholder status, 46% (n=183) were investigators/physicians, 33% (n=131) were patients, patient advocates and representatives of patient organisations, 10% (n=38) were sponsors (commercial or academic) and 9% (n=36) came from “Other” backgrounds.

Figure 6 provides an overview of the numbers of respondents for all stakeholder groups.

Figure 6. Number of respondents per stakeholder group



Associations were performed between the answers provided to Question 1 (Countries where the respondents were based) and Question 2 (Stakeholder groups). Figures 7-10 provide an overview of the distribution of stakeholders across the EU countries grouped according to the world regions. The highest number of Investigators/physicians representative came from Western and Southern Europe (36%, n=66 and 32%, n=58 respectively). The highest number of representatives of patient organisations and individual patients/carers came from Northern (26%, n=24 representatives of patient organisations and 45%, n=18 individual patients/carers) and Western Europe (34%, n=31 representatives of patient organisations and 22%, n=9 individual patients/carers). The stakeholder group of regulators was not represented at all from Southern and Western Europe, whereas 3 regulators (75%) from Northern Europe and 1 regulator (25%) from Eastern Europe completed the survey. Highest representation of sponsors came from Western Europe (58%, n=22). The highest number of respondents that chose to reply with “Other” was also from Western Europe (50%, n=18).

Figure 7. Distribution of stakeholder representation: Eastern Europe

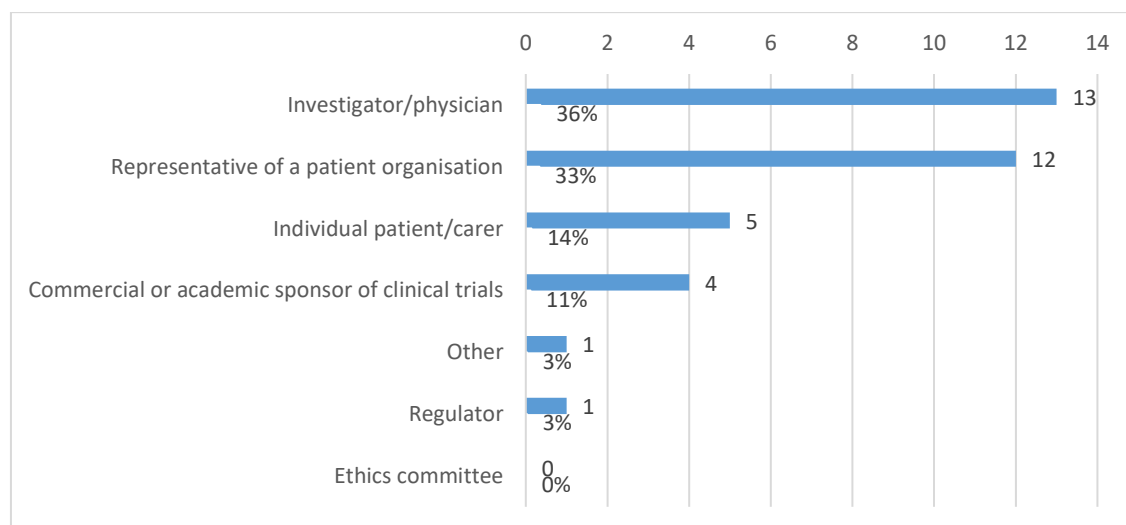


Figure 8. Distribution of stakeholder representation: Northern Europe

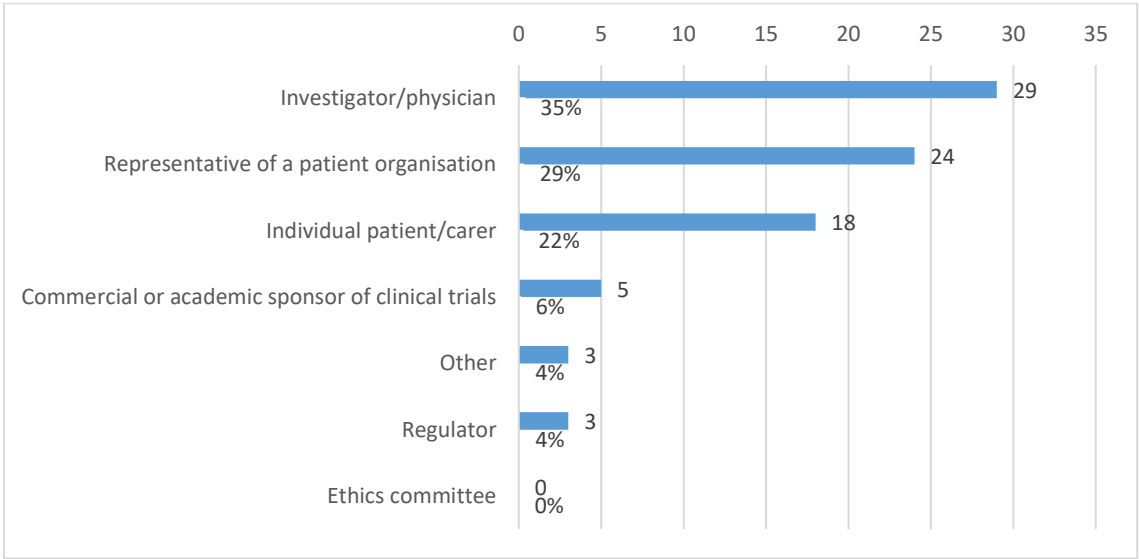


Figure 9. Distribution of stakeholder representation: Southern Europe

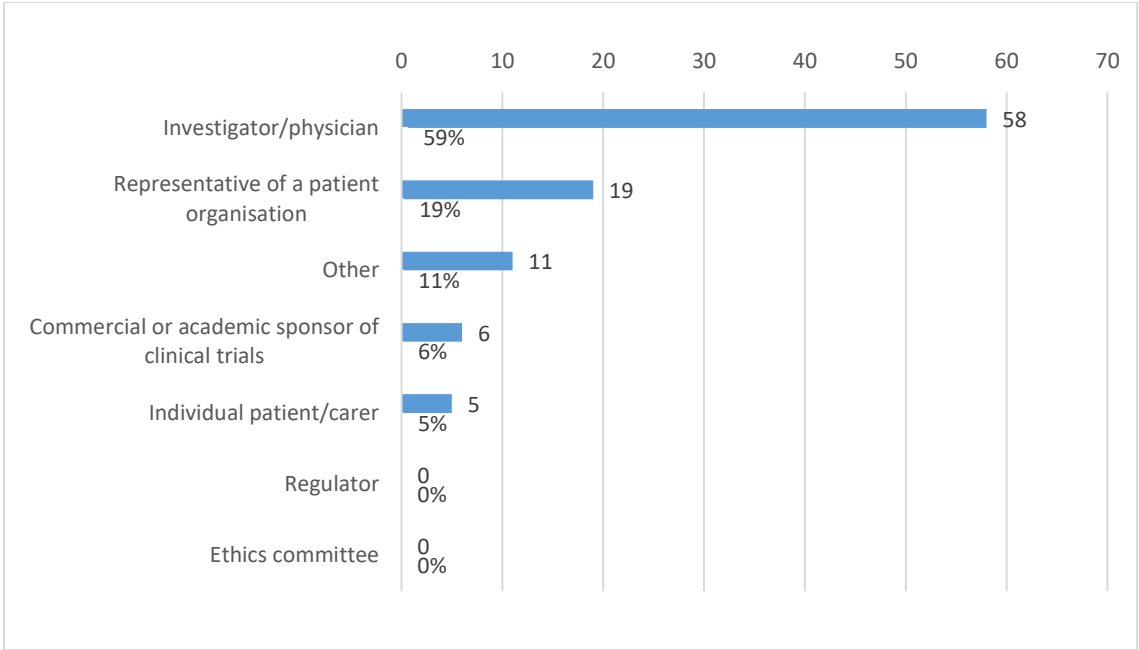
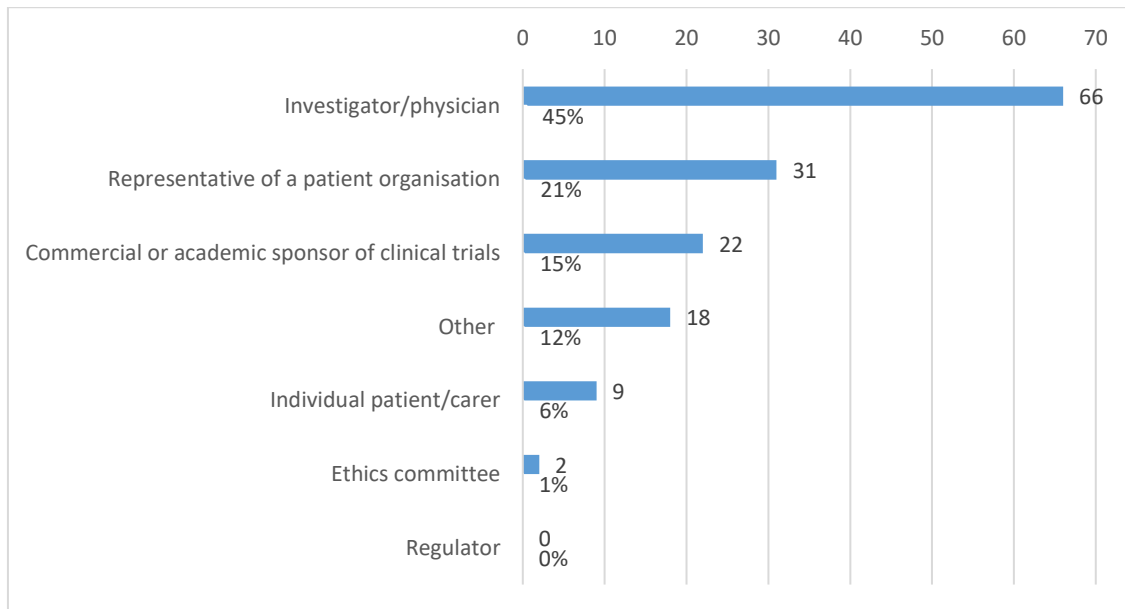


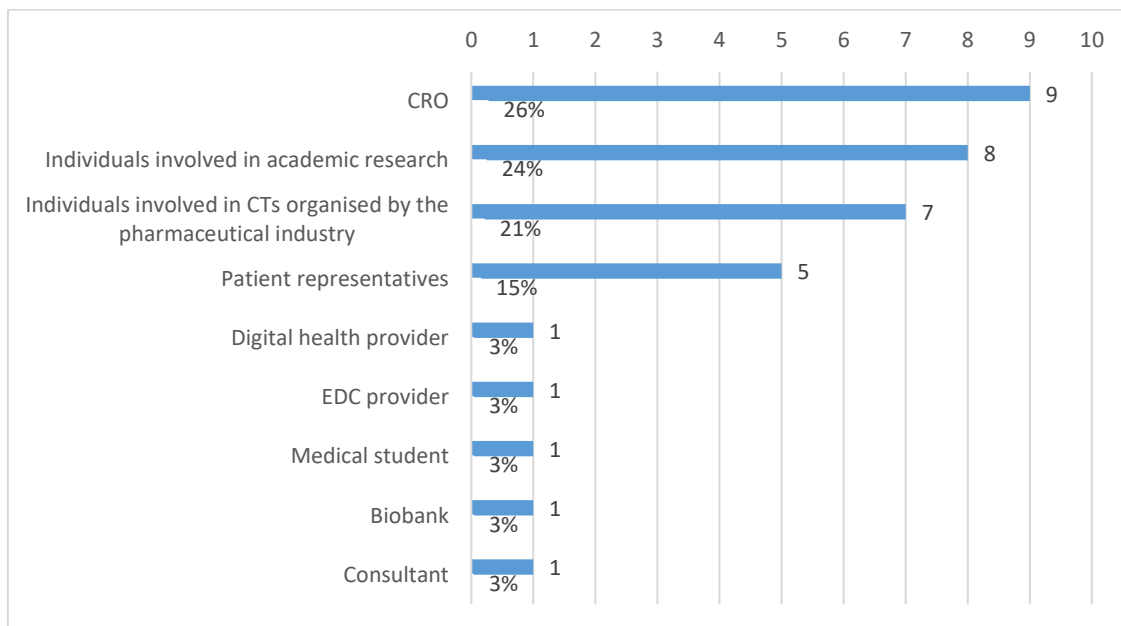
Figure 10. Distribution of stakeholder representation: Western Europe



97% of 36 answers provided under “Others” were evaluable.

The answers provided as “Other” were manually counted and grouped in meaningful categories by the research team. According to this grouping, the highest number of respondents who selected “Other” were representatives of Contract Research Organisations (CROs) (n=9), followed by individuals involved in academic research (n=8), individuals involved in the conduct of clinical trials organised by the pharmaceutical industry (n=7) and patient representatives (n=5). A detailed overview of the distribution of answers in the group of “Other” is presented in Figure 11.

Figure 11. Distribution of answers provided by respondents who chose “Other”



Question 3 was also relevant for this topic:

QUESTION 3: PLEASE ONLY ANSWER IF YOU ARE A PHYSICIAN WORKING IN THE ONCOLOGY FIELD: WHAT IS YOUR MEDICAL SPECIALTY OR INDICATION AREA?

As this question allowed an open answer, the responses were highly divergent. All answers (n=173) were grouped and manually counted by the research team. For a detailed presentation of the responses, please see Annex IV. It is of interest to report that most responding physicians were specialized in solid tumours (17%, n=29), followed by neuro-oncology (5%, n=9), breast cancer (5%, n=8), and gastrointestinal cancer (4%, n=7).

KEY RESULTS: TOPIC 2

As the Interviewees were proactively selected and invited, balanced representation concerning geographical and professional background could be achieved. The survey was broadly disseminated but with special focus on investigator networks (EORTC, ECRIN) and patient organisations (WECAN, EPF, EFGCP). This might have been the main reason for the strong representation of investigators and patients amongst the respondents, but it could also be an expression of highest interest: 396 eligible questionnaires were received. 70% (n=276) of all respondents provided answers to all 16 compulsory questions. 46% (n=183) of all respondents to the survey were investigators/physicians, primarily from solid oncology disciplines and from Western/Northern/Southern regions. 33% (n=131) were patients and patient representatives, again primarily from these three regions.

When assessing the representation of clinical trials sponsors, differentiation between commercial and academic sponsors was made in the interviews. Sponsors accounted for 14% of the total Interviewees (of which 5 participants were representatives of the pharmaceutical industry and 1 was a representative of an academic institution) and 10% (n=38) of survey participants. The low survey completion rate by academic and commercial sponsors could be in support of comments made by sponsors in interviews, namely that very few clinical researchers in sponsor organisations have been exposed to the need for dealing with cross-border patient enrolment. However, this is only an assumption and more data is required in order to prove it.

Policy experts' representation was similar to that of sponsors in the interviews (16%, n=6), closely followed by ethics committee representatives (13%, n=5 individuals). However, in the survey regulatory and ethics committee representatives did not get a meaningful representation rate (only 1% each), which could be explained with the limitations of the dissemination strategy employed by the research team.

Finally, National Contact Points were specifically targeted with the interviews. All 28 National Contact Points were invited via email by a member of the research team, however only 1 agreed to participate in the study.

Conclusions:

Comprehensive information collected in this research project represented primarily the views from investigators/physicians and patients/patient organisations in Western, Northern and Southern regions of Europe. Further investigation would be required to strengthen the input from investigators and patients from CEE countries as well as from sponsor organisations, ethics committees, and policy makers.

TOPIC 3: STUDY PARTICIPANTS' EXPERIENCE WITH CROSS-BORDER ACCESS TO CLINICAL TRIALS

This topic aimed at gaining a more concrete understanding of the level of experience of different stakeholders with cross-border access to clinical trials.

INTERVIEWS

It is important to understand the opinions and insights gathered in the course of the project by outlining the nature of Interviewees' experience with cross-border participation in clinical trials. To that end, a specific question was included in the interview guide, namely:

QUESTION 1: PLEASE DESCRIBE YOUR EXPERIENCE WITH PARTICIPATION OF PATIENTS IN A CLINICAL TRIAL THAT IS ORGANISED IN A TRIAL SITE (HOSPITAL/OTHER HEALTHCARE UNIT) OUTSIDE THE PATIENT'S HOME COUNTRY

The results outlined in this section are summarized and no details are provided. This is done in order to preserve the confidentiality of the Interviewees and to safeguard against their possible identification or the identification of other professionals and patients' Interviewees have been in contact with. The group of Interviewees is divided into two sub-groups: direct and indirect experience.

For the purposes of this report, direct experience was understood as any action personally undertaken by a participant with regard to cross-border access to clinical trials, such as, e.g., referring patients to clinical trials abroad, enrolling patients from abroad, participating in a clinical trial abroad, providing assistance to patients in finding a relevant trial abroad, providing assistance with logistical matters linked to cross-border patient participation.

Indirect experience was understood as theoretical knowledge about cross-border access to clinical trials, gathered through:

- a. discussions with experts with direct experience in the field,
- b. being contacted by patients or patient representatives with questions about cross-border participation in clinical trials, and/or
- c. being informed about cross-border access to clinical trials through any other means, e.g. reading of reports, newspaper articles, patient organisations' statements, participation in events, working groups, etc.

Out of 38 persons interviewed, 55% (n=21) had direct experience, and 45% (n=17) had indirect experience. In the group of investigators/physicians, all participants possessed direct experience. In the group of patient representatives, experience was equally distributed: five had direct experience, while six had indirect experience. Among industry representatives, two (out of five Interviewees) had direct experience. Two out of three interviewed ethics committee representatives responded on basis of their direct experience. Amongst the policy experts, indirect experience was more prevalent (five Interviewees out of six). The only National Contact Point representative who agreed to participate in the study had indirect experience as well.

In the majority of cases, Interviewees with direct and with indirect experience stated that their experience was limited. Examples of limited experience included having had only one foreign patient participating in a clinical trial during a 10 year period (as said by a physician), participants using adverbs such as "occasionally" or statements such as "we have had several requests in 6 years" to describe cross-border participation (two of the interviewed physicians), or a policy expert describing own experience as "close to zero".

In addition, the experience of Interviewees was further defined under the categories “professional” and “personal”. Professional experience was understood as one gathered in the course of the participant’s professional activities. Personal experience was understood as one gathered in the course of the private life. The majority of interviewed participants responded from the perspective of their professional experience. Five Interviewees discussed expressly their personal insight.

Some of the Interviewees had experience both as experts in the field of clinical trials (professional) and as individuals who have had to face disease either themselves, or as caretakers for loved ones (personal). The same applied to direct and indirect experience as some Interviewees possessed both.

SURVEY

Experience with cross-border access to clinical trials was investigated in:

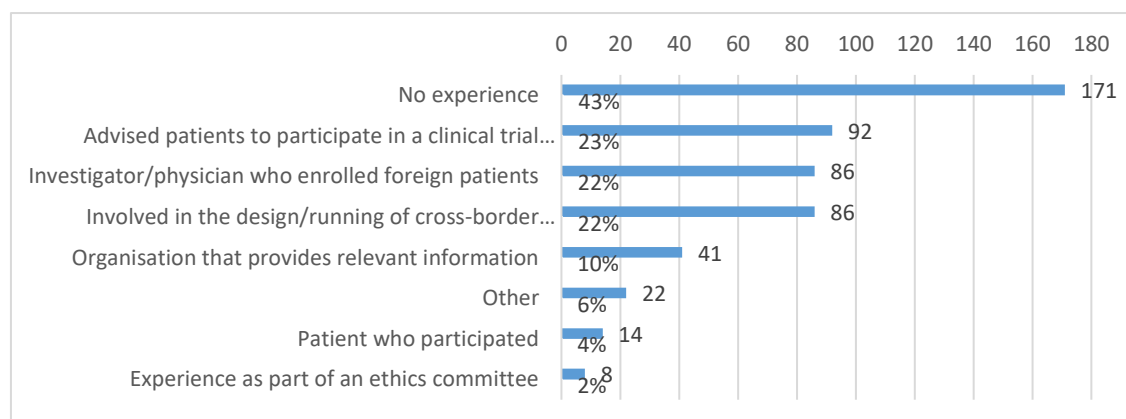
QUESTION 4: WHAT IS YOUR EXPERIENCE WITH PARTICIPATION OF PATIENTS IN A CLINICAL TRIAL THAT IS ORGANISED IN A STUDY SITE OUTSIDE THE PATIENT’S HOME COUNTRY?

This question allowed multiple answers for different types of experiences and involvement in cross-border clinical trials. Figure 12 presents an overview of the respondents’ most preferred answers, where the percentages were calculated using as a denominator the total number of individuals who responded to the question. 100% of the survey respondents answered this question with a total number of 520 responses. Most responses revealed that the respondents had been involved in one or several ways in the participation of patients in a clinical trial that was organised in a study site outside the patients’ home country. This happened by informing patients about this option (either as an individual advisor (23%, n=92) or as part of an organisation (10%, n=41), by being involved in designing or running a trial that allowed cross-border participation (22%, n=86), by being an investigator who enrolled foreign patients 22%, (n=86), or by being part of an ethics committee that reviewed clinical trials where foreign patients participated (2%, n=8). The pre-defined option “I am/was a patient in a clinical trial organised in a site outside my home country” was chosen by 4% (n=14) of the respondents only.

An important number of respondents (43%, n=171) answered that they had no experience.

The answers from respondents belonging to the “Other” category (6%, n=22) were manually grouped by the research team in two categories and referred to the fact that the participants had no experience with clinical trials abroad (n=17) or possessed some indirect experience with clinical trials abroad (n=5).

Figure 12. Experience with participation of patients in cross-border clinical trials



The following question was also relevant to the topic of experience:

QUESTION 5: AS FAR AS YOU RECALL, DO YOU KNOW ABOUT CLINICAL TRIALS THAT:

A/ EXPLICITLY FORESEE CROSS-BORDER PARTICIPATION?

B/ EXPLICITLY FORBID CROSS-BORDER PARTICIPATION?

This question allowed multiple answers. 99% (n=393) of all study participants answered Part A/, while 91% (n=363) of all study participants responded to Part B/.

42% (n=166) of the study participants on Part A/ stated knowledge about a study that explicitly allowed cross-border access to the trial, while 48% (n=187) expressed unawareness of such an option. Only 10% (n=63) respondents were aware of a clinical trial that explicitly forbid cross-border patient participation.

However, 41% (n=166) responses indicated that there is a meaningful number of respondents who know about trials that explicitly allow the cross-border participation of patients. Moreover, 17% (n=63) responses were collected for the “Yes” option of the question (Part B/) about trials that explicitly forbid cross-border participation. In the majority of cases it was reported that protocols do not address cross-border participation at all (“No” answer was selected by 48%, n=187 of respondents to Part A/, and 69%, n=250 of respondents to Part B\).

KEY RESULTS: TOPIC 3

All 38 Interviewees had direct (55%, n=21) or indirect (45%, n=17) experience with cross-border access to clinical trials, the majority of them (87%, n=33) on a professional level, only 13% (n=5) on a personal level as patient or carer.

Nearly half of the respondents of the survey had no experience but over half of them had one or several types of experience as multiple answers were possible in this question. However, only 4% (n=14) respondents reported personal experience as a patient or carer, thus supporting this result from the interviews.

The combined group of investigators/physicians (46%) and clinical trials sponsors (10%) had a significantly higher overall representation rate in the survey and this might explain the higher number of responses on experience relevant to these stakeholder groups (e.g. “enrolling patients from abroad”(22%, n=86)). The same is valid in the case of the interviews. However, patient representation in both survey and interviews was nevertheless very strong. The very low absolute number of interview and survey respondents who reported personal patient experience could be an indication of the very low rate at which cross-border participation in clinical trials currently occurs.

Conclusion:

There was a significant number of responses which clearly indicated that cross-border participation was allowed or forbidden in the protocol (42%, n=166 and 10%, n=63, respectively). In all those cases the protocol seemed to have addressed the issue in whatever way, although, in the majority of cases it was reported that protocols do not address it at all (Question 5, Part A and B, 48%, n=187 of respondents, and 69%, n=250, respectively). This showed that there is still a grey zone that needs to be addressed, e.g., in form of a recommendation that protocols should clearly address availability or not of cross-border patient participation.

TOPIC 4: STUDY PARTICIPANTS' OBSERVATIONS REGARDING FREQUENCY, INCREASE OR DECREASE IN REQUESTS FOR INCLUSION IN CLINICAL TRIALS CONDUCTED ABROAD

In this topic insight was sought on frequency and any trends in frequency of cross-border participation in clinical trials.

INTERVIEWS

This theme was explored from the viewpoint of patients seeking participation in clinical trials abroad in:

QUESTION 2: IF YOU HAVE OBSERVED AN INCREASE OR DECREASE IN THE REQUESTS FOR INCLUSION OF PATIENTS RESIDING IN YOUR COUNTRY IN CLINICAL TRIALS OPEN ABROAD IN THE PAST 3 YEARS, PLEASE PROVIDE YOUR OPINION ABOUT THE REASONS FOR THIS INCREASE/DECREASE

and from the viewpoint of countries enrolling foreign patients in:

QUESTION 3: IF YOU HAVE OBSERVED AN INCREASE OR DECREASE IN THE REQUESTS FOR INCLUSION OF FOREIGN PATIENTS IN CLINICAL TRIALS SET IN YOUR COUNTRY IN THE PAST 3 YEARS, PLEASE PROVIDE YOUR OPINION ABOUT THE REASONS FOR THIS INCREASE/DECREASE.

Also Question 5 for investigators was relevant in this context:

QUESTION 5: ACCORDING TO YOUR KNOWLEDGE, WHAT IS THE NUMBER OF FOREIGN PATIENTS PARTICIPATING IN CLINICAL TRIALS IN YOUR COUNTRY?

29% (n=11) of the Interviewees (representatives from all stakeholder groups are included in this number) indicated that they have no concrete information on frequencies or trends as no official statistics exist at national or EU level, and there was no baseline against which a relevant comparison could be made.

Other Interviewees expressed opinions about the incidence of cross-border participation in general.

Some indicated that there had not been a significant change in either direction (i.e. neither increase, nor decrease). 18% (n=7) of the Interviewees held the view that patients rarely join/express interest in joining a clinical trial conducted outside their home country. The reasons for such limited patient interest was explained with the challenges that patients face when participating in a trial abroad (see Topic 9) and with their motivations to not join a cross-border trial (see Topic 5). In terms of challenges, the most prominent ones mentioned were coverage of financial costs (more specifically, for travel and accommodation), finding the most appropriate trial for their condition, and patients' vulnerability (more specifically, unwillingness to be separated from their support system during a very challenging moment in their lives). A mentioned reason for not joining a clinical trial abroad was an example from Spain presented by an investigator: in Spain exists *"a network of hospitals, having Phase I, Phase II clinical trials in Paediatric Oncology. It resembles that of France, Germany, or UK, so patients do not forcibly have to go outside to get treatment that they can receive at home. So, I would say that at least from my hospital no patient has gone somewhere else, abroad, for getting a treatment in terms of clinical trials"*.

53% (n=20) of the study participants acknowledged with various degrees of certainty that cross-border participation in clinical trials is occurring in the EU, although in a limited manner, and that at the current moment there is an increased interest in it. However, it must be noted that the opinions of the Interviewees were admittedly subjective, as no concrete statistics regarding this topic exist. Reasons for the trend of

increasing interest could be directly explained by the motivations of patients to participate (see Topic 5) the motivations of physicians to recommend participation, and the motivations of sponsors to support recruitment of foreign patients (see Topic 6). Highlights that came up in the analysis of study participants' answers specifically to Interview Question 2 and Question 3 included:

- higher patient awareness with regard to clinical trials, coupled with better informed local physicians;
- development of medicine (e.g. therapies for rare diseases only available in clinical trials conducted abroad or new technologies only available in specialized centres abroad);
- access to treatment (regardless of disease area);
- the freedom of movement and residence for persons in the EU. A patient representative stated that *"once somebody realizes that there is a freedom of movement, there's very little that can keep them back. (...) you cannot put the spirit back into this bottle. People will move, and especially if their life and if their health depends on it."*

It was not possible to list the reasons in a descending order of importance or preference, as each of the stakeholders emphasized on a different aspect or gave equal importance to several explanations.

In addition, it must be noted that the answers provided to both Question 2 and Question 3 were similar, with Interviewees often choosing to respond a variation of the phrase *"same answer"* when asked their opinion on Question 3. In that respect, it can be concluded that there is no significant diversity between European Member States regarding the occurrence of participation in clinical trials cross-borders, and the underlying reasons for such participation. However, some degree of diversity could be observed when focusing on the most prevalent reasons to seek participation abroad, as looked from the viewpoint of different European regions. For instance, the existing inequalities between countries in respect to access to treatment would instigate higher interest in clinical trials abroad by the patients residing in Central and Eastern Europe. In the words of a policy expert, patients enrol because *"it is their only chance to access a treatment"*. Whereas for patients residing in Western Europe, the prevalent reasons were linked to treatment of rare diseases or new technologies available abroad.

Investigators' but also other stakeholders' opinion on the concrete number of foreign patients participating in their country's clinical trials was collected. The majority stated they have no information (*"we don't have actual trustworthy data"*, as commented by a patient representative). Several participants provided subjective estimations, however, all focusing on the fact that cross-border participation is extremely limited. For instance, a representative of the pharmaceutical industry talked about *"less than 1%"* of patients coming from abroad, a physician referred to *"may be 3, 4, 5 patients"* participating in trials open in the physician's country of residence, a policy expert commented *"close to zero"*, and further clarified that this is the situation on a global scale (*"it's the entire world like that"*). Only one Interviewee set forth a relatively higher number of foreign patients' participation, in comparison to the views generally expressed among stakeholders. According to an investigator, *"I can't speak for the country, but for the trials in which I am a principal investigator is approximately 10 %"*.

SURVEY

The topic of observations regarding frequency, increase or decrease in requests for inclusion in clinical trials conducted abroad was explored in Questions 6 to 11 of the survey questionnaire. Bellow follows the presentation of the answers gathered for each of these questions.

QUESTION 6: HAVE YOU OBSERVED AN INCREASE OR DECREASE IN

A/ THE REQUESTS FOR PARTICIPATION OF FOREIGN PATIENTS IN CLINICAL TRIALS

B/ THE INCLUSION OF FOREIGN PATIENTS IN CLINICAL TRIALS

Question 6A was answered by 304 survey participants, question 6B was answered by 302 respondents. In the case of requests for participation, the answers were almost equally divided among the positive (34%, n=104), the negative (33%, n=101) and the “I do not have an opinion” (33%, n=99) options (see Table 3²⁹). However, in the case of respondents’ observations concerning actual enrolment, the predominant response was negative (43%, n=130), followed by “I do not have an opinion” (34%, n=102). It was interesting to see that 23% (n=70) of the respondents observed an increase.

Table 3. Respondents’ opinion on the trend in requests and inclusion of foreign patients in CTs

<i>(Q6_A) Have you observed <u>an increase in the requests for participation of foreign patients</u> in clinical trials?</i>		<i>(Q6_B) Have you observed <u>an increase in the inclusion of foreign patients</u> in clinical trials?</i>	
<i>Yes</i>	34%, n=104	<i>Yes</i>	23% n=70
<i>No</i>	33%, n=101	<i>No</i>	43%, n=130
<i>I do not have an opinion/information on this</i>	33%, n=99	<i>I do not have an opinion/information on this</i>	34%, n=102

Furthermore, as part of the data analysis, the answers provided to Question 6 were associated with the respondents’ stakeholder group (Question 2), which lead to the following conclusions:

Investigators/physicians (78% (n=142) out of the total 183 who filled the survey) provided similar numbers of responses concerning requests for participation (“yes” (37%, n=52), “no” (43%, n=62), with 20% (n=28) of respondents being uncertain (“I do not have an opinion”). When it comes to actual inclusion of foreign patients, the majority of investigators (55%, n=78) responded that they have not observed any inclusion. A similar pattern was discovered in the responses provided by sponsors of clinical trials and by patient representatives (see Annex IV for the detailed overview of the association).

QUESTION 7: PLEASE ONLY ANSWER IF YOU ARE AN INVESTIGATOR: WHAT HAS BEEN THE HIGHEST PERCENTAGE OF FOREIGN PATIENTS YOU HAVE HAD IN ANY OF YOUR CLINICAL TRIALS?

69% (n=126) of the 183 investigators (as self-reported in Question 2) provided an answer to this question. Of them the majority of responses revealed that the percentage of foreign patients they had in any of the clinical trials was below 20% (see Table 4). More specifically, 49% (n=62) indicated a participation under 1%, and 22% (n=28) indicated a participation of 1-19%, while only 6% (n=7) of respondents reported substantial experience with a percentage interval of 20-39% of foreign participation.

²⁹ Tables 3 to 10 are originally part of Annex IV. Percentages have been additionally added where needed.

Table 4. Investigators' opinion on the participation of foreign patients in CTs

Q7 Please <i>ONLY</i> answer if you are an INVESTIGATOR: What has been the highest percentage of foreign patients you have had in any of your clinical trials?	
80-100 %	>1% (n=1)
60-79%	2% (n=3)
20-39%	6% (n=7)
1-19%	22% (n=28)
Less than 1%	49% (n=62)
I cannot provide an estimation about this	20% (n=25)

As was established above (see Topic 2), there physicians were overrepresented among the survey respondents (46% all respondents), and most probably these were physicians who were particularly interested in cross-border participation. Still only around 20% of those had considerable experience, as shown in this section. The vast majority had very little or no experience. That means that in reality cross-border participation occurs very rarely.

QUESTION 8: ACCORDING TO YOUR KNOWLEDGE, ARE THERE OFFICIAL STATISTICS PERTAINING TO THE NUMBER OF FOREIGN PATIENTS PARTICIPATING IN CLINICAL TRIALS CONDUCTED IN YOUR COUNTRY?

77% (n=304) of all survey respondents provided an answer to this question. The vast majority of answers indicated that official statistics were not available (33%, n=102) or not known (65%, n=198). Only 1% (n=4) of participants selected the answer "Yes" and shared further information in the open-ended box. However, upon evaluation, it was discovered that none of the references provided by participants was a concrete source of statistical information.

It can be concluded that cross-border participation in clinical trials is not systematically documented and researched. This might be an issue to be addressed in the future and it is included as a recommendation of this study.

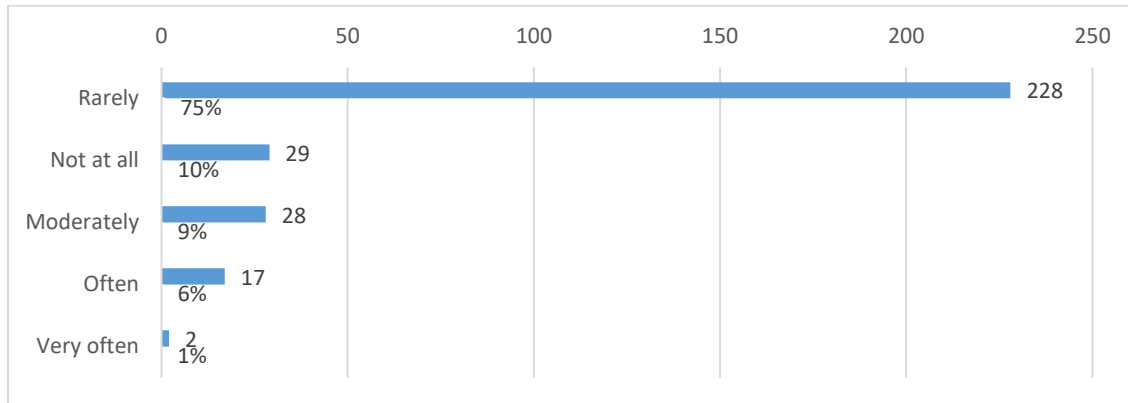
QUESTION 9: IN YOUR OPINION, HOW FREQUENTLY DO PATIENTS FROM YOUR COUNTRY PARTICIPATE IN CLINICAL TRIALS CONDUCTED ABROAD?

From the retained number of 396 questionnaires, 77% (n=304) respondents provided an answer to this question (Figure 13).³⁰ Most of those considered that participation takes place "Rarely" (75%, n=228). Only 9% (n=28) of respondents considered that patients participate "Moderately" in clinical trials conducted abroad. Only a small number of respondents considered that patients participate "Often" (6%, n=17) or

³⁰ With Question 10 respondents were additionally asked to provide a publicly available source of information that supports their answer. Most of the n=41 respondents to Question 10 referred to their personal experience, private sources of information, anecdotal evidence or no source at all (n=32.) The remaining answers that refer to public sources of data do not provide access to concrete sources of information.

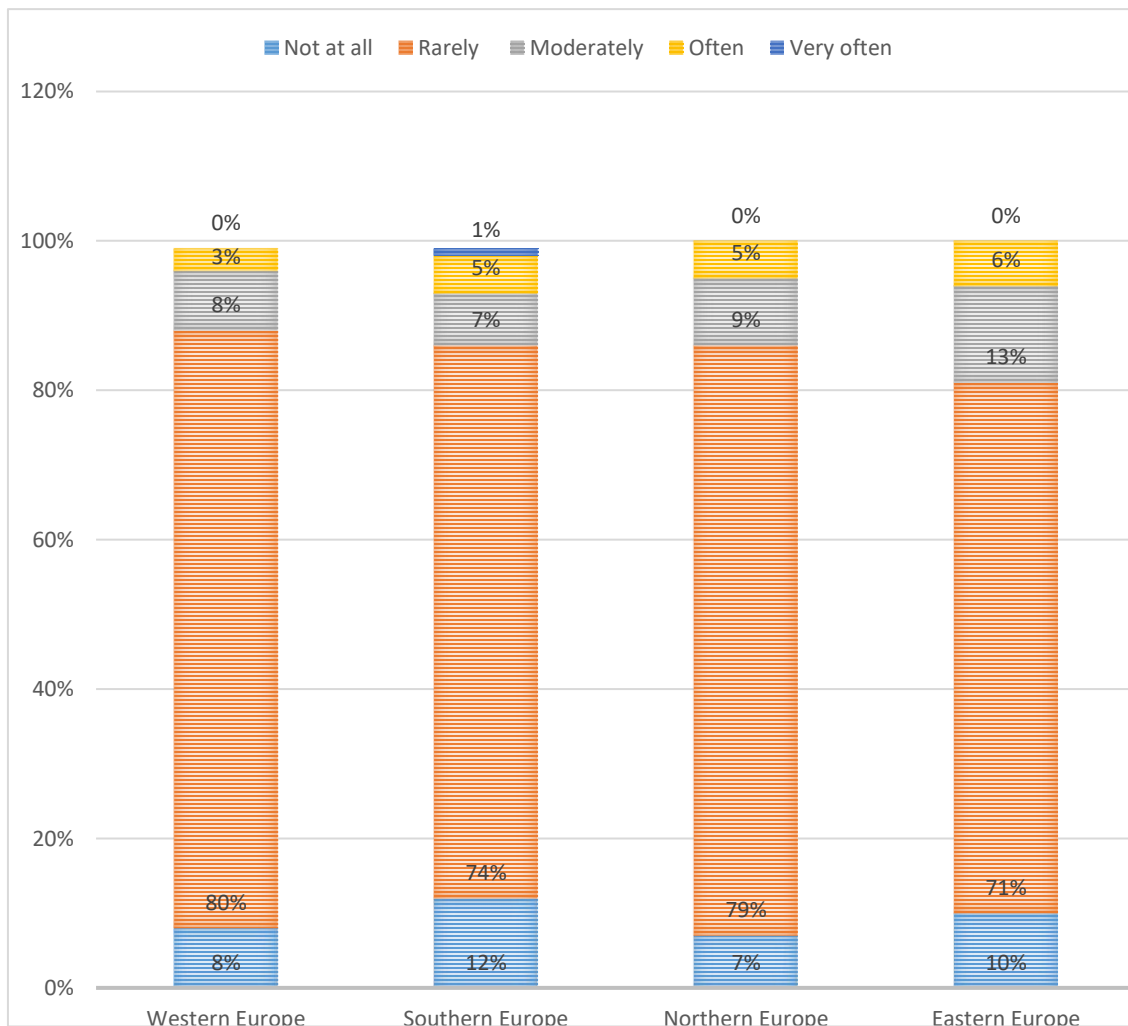
“Very often” (1%, n=2) in clinical trials conducted abroad. In the opinion of 10% (n=29) respondents, patients “Do not participate at all” in clinical trials abroad.

Figure 13. Estimated frequency of patients’ participation from own country in clinical trials abroad



In addition, Figure 14 also provides a visual presentation of the cross-tabulation performed between Question 9 and Question 1 (Countries where survey respondents are based).

Figure 14. Estimated frequency of patients’ participation (per sub-region) from own country in clinical trials abroad



The percentages of the answer “Rarely” related to the total number of responses were comparatively similar across the European regions, namely the answer was selected by 80% (n=95) of respondents from Western Europe, 75% (n=54) of respondents from Southern Europe, 79% (n=46) of respondents from Northern Europe, and 71% (n=22) of respondents from Eastern Europe.

The highest number of responses to this question occurred from Western Europe which was in line with the overall country representation in the survey. However, it can also be concluded that in absolute terms cross-border participation happens more often in Western Europe.

KEY RESULTS: TOPIC 4

Both interview and survey results showed that there was no predominant opinion on increase/decrease in interest or enrolment in cross-border clinical trials, nor was there citation of any publicly available official statistics about frequency of cross-border participation. However, the results confirmed that cross-border participation occurred, although rarely. This was established both through the interviews and by the answers provided to Question 7 and Question 9 of the survey.

Interview results regarding frequency, increase or decrease in requests for inclusion

- No opinion/no information (29%, n=11 Interviewees, representatives of all stakeholder groups).
- Neither decrease, nor increase. In general, patients rarely join/express interest to join a clinical trial conducted abroad (18%, n=7 Interviewees).
- Cross-border participation in clinical trials is occurring in very low numbers and there is an increasing interest in it (53%, n=20 Interviewees).

Survey results:

- 75% (n=228) out of a total number of 304 survey respondents confirmed that cross-border participation occurred “rarely”.
- 49% (n=62) physicians stated that the highest percentage of foreign patients they have had in any of their trials was less than 1%, 22% (n=28) reported percentages between 1% and 19%.

Conclusions:

Cross-border enrolment of patients currently occurs to a very low degree.

There is no clear trend towards increase of interest or factual enrolment, however, there is also no hint on a decrease.

There are no statistics on cross-border participation in clinical trials in any country.

TOPIC 5: MOTIVATIONS FOR PATIENTS TO PARTICIPATE OR NOT /RECOMMENDATIONS FROM PATIENTS’ ADVISORS TO PARTICIPATE OR NOT IN A CLINICAL TRIAL CONDUCTED ABROAD

With this topic information was collected on factors that are relevant for patients in making their decision on seeking access to clinical trials abroad or not.

INTERVIEWS

This theme was explored in different versions, dependent on the background of the Interviewee. In the reporting of results below “patient advisor” refers to representatives of patient organisations and treating physicians. It must be pointed out that the motivations to participate/recommend (Part 5.1) were divided in two groups. First are presented the reasons to seek cross-border access when no investigational site of a specific clinical trial is open in the patient’s home country (Part 5.1.1). Second, the reasons to seek cross-border access when an investigational site of the same clinical trial is open in the patients’ home country (Part 5.1.2). No such division was identified in the reported motivations not to participate/recommend participation in a clinical trial conducted abroad (Part 5.2).

QUESTION 7.A.: WHAT FACTORS WOULD MOTIVATE YOU, A PATIENT/CARER, TO PURSUE PARTICIPATION IN A CLINICAL TRIAL IN ANOTHER COUNTRY?

QUESTION 7.B.: WHAT FACTORS WOULD MOTIVATE YOU, A REPRESENTATIVE OF A PATIENT ORGANISATION, TO RECOMMEND TO PATIENTS FROM YOUR ORGANISATION THE PARTICIPATION IN A CLINICAL TRIAL IN ANOTHER COUNTRY?

QUESTION 7.D.: FOR WHICH REASONS WOULD YOU, A PHYSICIAN, RECOMMEND A PATIENT TO SEEK PARTICIPATION IN A CLINICAL TRIAL CONDUCTED IN ANOTHER COUNTRY?

5.1. MOTIVATIONS TO PARTICIPATE/RECOMMEND PARTICIPATION

5.1.1. WHEN NO INVESTIGATIONAL SITE OF A SPECIFIC CLINICAL TRIAL IS OPEN IN THE HOME COUNTRY OF THE PATIENT

The majority of stakeholders explained that participation in a clinical trial conducted abroad would be sought in cases where a new promising treatment (with demonstrated efficacy or high likelihood), is not available in the patient’s home country. Thus, it could be concluded that access to innovative treatment is the main reason for cross-border access.

However, it is necessary to differentiate how access to treatment was perceived by the different experts involved in the study. A policy expert spoke of “*the best treatment out there*”, whereas a patient representative referred to the cases of rare diseases where no treatment had existed before (e.g., “*the standard of care is not working*”), and the therapy that was tested in a clinical trial was the only treatment currently available. Another patient representative spoke about “*exhausting all available lines of therapies*”, thus having a situation where the patient was “*out of options*”. Lastly, access to treatment might be linked to purely financial reasons, namely a treatment not being reimbursed in the patient’s home country, hence the framework of a clinical trial presenting the only chance of receiving it.

Of high importance for patients was the opinion of their treating physician. If the treating physician perceived a clinical trial abroad as the optimal solution, patients were more likely to seek participation in it. The majority of physicians were of the opinion that they would recommend participation in clinical trials only on a strict case-by-case basis, and a preference for Phase II trials was expressed.

One policy expert expressed the opinion that a possible motivation might be the altruism of the patient, namely the willingness to contribute to science.

5.1.2. WHEN AN INVESTIGATIONAL SITE OF A SPECIFIC TRIAL IS OPEN BOTH ABROAD AND IN THE HOME COUNTRY OF THE PATIENT

Some Interviewees discussed the situation whereby even though a clinical trial site is open in the patient's home country, he or she would prefer to go abroad in order to participate in the same clinical trial. The main reason for that would be the geographical proximity. An example was given by an Ethics Committee representative: *"you have a patient that is living close to the border, and it might be easier for him or her to participate in a centre involved in the trial across the border (···) e.g., somebody who is living in Malmedy, Belgium; it might be simpler to go to Aachen than to go to Brussels"*. Another reason to seek participation abroad would be the higher trust in the foreign country's healthcare system or the foreign centre where the clinical trial is being conducted, in comparison to the patient's home country. As stated by a patient representative, *"you might even get a trial in your own country (···) but you know that the centre that is running this by far is not as good as a specialized centre for that rare disease in another country"*.

The majority of all stakeholders expressly linked both types of motivations to the precision medicine approach (currently most prominently present in the field of oncology) and rare diseases.

5.2. MOTIVATIONS NOT TO PARTICIPATE/NOT TO RECOMMEND PARTICIPATION

Reluctance to travel emerged as the major motivation to not express interest in a trial open abroad. This was explained with

- a) the vulnerable state of the patients (see Theme (5)),
- b) the high trust they have in their home country's healthcare system, and
- c) the fact that most clinical trials are available in their home country

It must be noted that this type of opinion was expressed by experts coming from Denmark and Spain.

Motivation to participate might further be affected by the ways different societies perceive the value of clinical trials in general. More specifically, the general view on clinical trials in certain EU countries might be more critical and/or distrustful than in others, which might potentially reflect on the willingness of individual foreign patients to participate in a study open abroad. However, further investigation and analysis is required on this topic in order to draw any definitive conclusions. The issue could be further linked with the cross-border access challenge to of lack of information, presented below in Theme (5).

In addition, the risk of being randomized in the placebo arm of a trial might be an additional concern for patients considering participation in a clinical trial in general, and in a cross-border trial in particular. In the words of a patient representative: *"I would try to do everything to avoid being randomised into a placebo arm, because that would be unacceptable risk"*. However, the patient did not view placebo-controlled trials as a block to going abroad, as long as there was the option to get switched to the active arm when medically required: *"I would still go ahead. I would expect some insurance, some security, for example, if it is clear there's a benefit of the investigational product, and I can get switched."*

Recommendation for participation in a placebo-controlled trial would also be linked to certain conditions, such as alleviating the patient's financial burden associated with the travel. An Ethics Committee representative stated: *"I would recommend, if the conditions for the patient would be favourable. For example, if there would be a nice compensation, or adequate compensation, for the patient to travel somewhere (...) but to my knowledge, this is not yet the case."*

SURVEY

The topics discussed above were investigated in the survey with Questions 11 and 13.

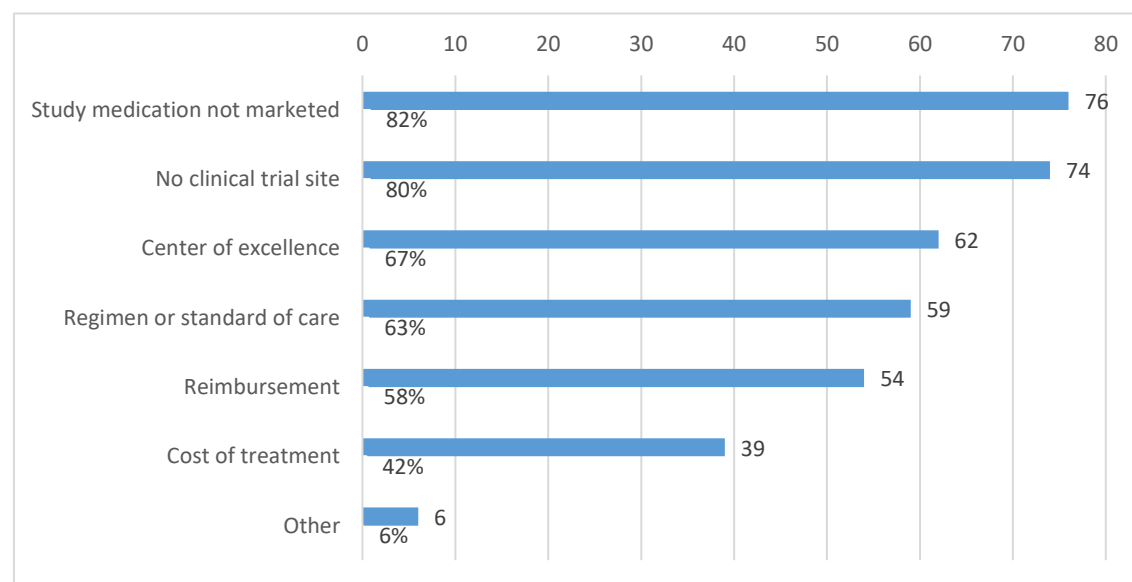
QUESTION 11: PLEASE ANSWER ONLY IF YOU ARE A PATIENT OR PATIENT REPRESENTATIVE: WHICH OF THE FOLLOWING FACTORS WOULD MOTIVATE YOU OR PATIENTS FROM YOUR PATIENT ORGANISATION TO PURSUE PARTICIPATION IN A CLINICAL TRIAL CONDUCTED IN ANOTHER COUNTRY?

Pre-defined answers for this question were available; however, the respondents had the opportunity to include a different opinion if none of the proposed options corresponded to their situation or that of patients from their organisation. The choice of multiple answers was available. 71% (n=93) of the total number of patients and patient representative (n=131) who filled the survey responded to this question.

Among the answers, first was ranked “Study medication not marketed: Access to a new treatment that is not marketed in my country of residence” (82%, n=76), followed by “No clinical trial site: Access to a new treatment that is not available in a similar clinical trial in my country of residence” (80%, n=74). The answer that collected the lowest number of responses was “Cost of treatment: Access to a new treatment that is too expensive in my home country” (42%, n=39).

Only 6% (n=6) of answers were completed in the “Other” option, and they mostly referred to the access to new treatment that works.

Figure 15. Motivations for patients to participate in a clinical trial abroad (number of responses per answer)



In addition, an association (see Table 5 below) was performed between Question 11 and Question 14 (*In which other European countries do patients from your country seek access to clinical trials?*) (see Topic 7 for more information about the results on Question 14).

Table 5. Opinion on countries where patients from own country seek access to CTs

<i>In which other European countries do patients from your country seek access to clinical trials?</i>	<i>N subjects</i>	<i>N choices</i>	<i>Study medication not marketed</i>	<i>Regimen or standard of care</i>	<i>Reimbursement</i>	<i>Cost of treatment</i>	<i>No clinical trial site</i>	<i>Centre of excellence</i>	<i>Other</i>
Eastern Europe	17	74	13 (76.5%)	15 (88.2%)	12 (70.6%)	9 (52.9%)	13 (76.5%)	12 (70.6%)	0 (0.0%)
Northern Europe	34	135	26 (76.5%)	27 (79.4%)	18 (52.9%)	14 (41.2%)	26 (76.5%)	24 (70.6%)	0 (0.0%)
Southern Europe	25	108	19 (76.0%)	21 (84.0%)	19 (76.0%)	14 (56.0%)	18 (72.0%)	17 (68.0%)	0 (0.0%)
Western Europe	62	255	52 (83.9%)	41 (66.1%)	39 (62.9%)	28 (45.2%)	50 (80.6%)	43 (69.4%)	2 (3.2%)
(Q14)Region=In your opinion in which other European countries do patients from your country seek access to clinical trials? Column (Q11)=Please answer ONLY if you are a PATIENT or PATIENT REPRESENTATIVE: Which of the following factors would motivate you or patients you're your patient organisation to pursue participation in a clinical trial conducted in another country? total number of subjects (N=93)									

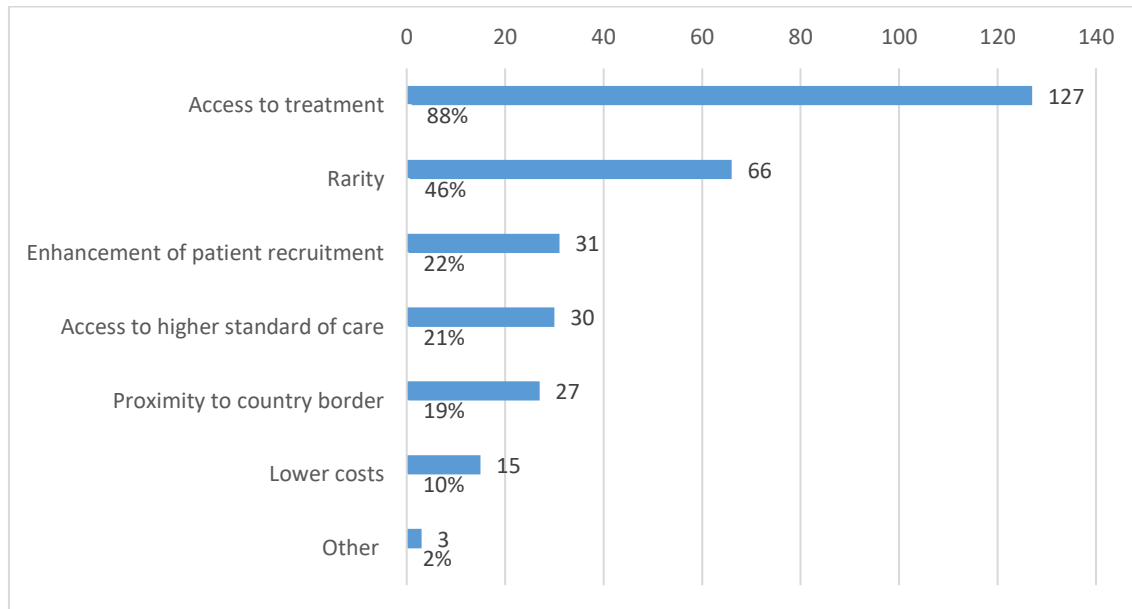
Based on the correlation presented in Table 5, a number of conclusions were made:

- The different reasons to participate in a clinical trial conducted abroad had a comparable relevance for respondents who chose Eastern Europe as a region attractive for cross-border access to clinical trials.
- The reason “Study medication not marketed” (in the home country of the respondent) had the highest ranking among the reasons which would make patients choose Southern and Western European countries for participation in a clinical trial abroad, and the second highest ranking in the case of Northern and Eastern European countries.
- “No clinical trial site” (in the home country of the respondent) was uniformly amongst the top priorities for respondents to choose any of the European countries.

QUESTION 13: PLEASE ANSWER ONLY IF YOU ARE A PHYSICIAN: FOR WHICH REASONS WOULD YOU ADVISE A PATIENT TO SEEK PARTICIPATION IN A CLINICAL TRIAL CONDUCTED IN ANOTHER COUNTRY?

79% (n=144) of the total number of respondents (n=183) who identified as investigators/physicians in Question 2 provided an answer here. The question allowed the selection of multiple answers; hence the results were presented in order of preference. A clear separation was seen between the answer “Access to treatment: Opportunity for my patient to get access to a promising investigational treatment or expensive technology” which was chosen by 88% (n=127) of the respondents to Question 13, and the rest of the answers. The second one ranked “Rarity: Incidence of patients with the protocol-required very specific in- and exclusion criteria is low” (46%, n=66), almost half of the times the first answer was selected. The remaining answers were almost equally selected by the respondents, except for “Other” that was completed by only 2% (n=3) of the respondents and emphasized on the limited number of clinical trials in Slovenia and the fact that cross border clinical trials would not be recommended.

Figure 16. Motivations for physicians to recommend participation in a clinical trial abroad (number of responses per answer)



The dominance of the answer “Access to treatment” in comparison to all other pre-defined options was interesting as the stakeholder group targeted with the survey consisted of investigators and physicians who were not investigators. Independently of that difference this was by far the most frequent answer. To the research team, this meant that investigators did not only look for getting patients into their own trials, but they also looked for opportunities for their own patients to find trials in other sites/countries.

KEY RESULTS: TOPIC 5

In the interviews the opinions of patients, representatives of patient organisations, and investigators/physicians were very much aligned and hence in the report they were presented together. What was specifically interesting in the case of the interviews as opposed to the survey, was that Interviewees also provided reasons not to participate/recommend participation. In summary:

Motivations to participate/recommend participation:

When no investigational site is open in the home country:

- Access to innovative treatment
- Patients tend to follow the opinion of their treating physician
- Willingness to contribute to science

When an investigational site of a specific clinical trial is open both abroad and in the home country of the patient:

- Geographical proximity
- Higher trust in the foreign country’s healthcare system

Note: in all cases the motivations were expressly linked to precision medicine and rare diseases.

Motivations not to participate/recommend participation:

- Reluctance to travel due to: vulnerable state of the patient; the high trust in the home country's healthcare system; the fact that most clinical trials are available in the home country.
- The general view on clinical trials might be more critical in certain EU countries
- Note on placebo-controlled trials: patients would participate, and physicians would recommend, but only under specific conditions (e.g., possibility to switch to the active treatment arm of the clinical trial)

The survey provided for a clear distinction between the opinions of patients/patient representatives and the views of physicians. The survey responses allowed us to confirm the interview insights, and vice versa, the interview results allowed us to better understand and nuance the ranking of pre-defined answers in the survey.

In the survey both patients/patient organisations representatives and physicians ranked "Access to treatment" highest, entirely in line with the interviews.

For patients, the reason reported second was "No clinical trial site". In comparison, the interviews allowed us to establish the lack of an investigational site as a separate sub-category of motivations, encompassing three distinct reasons, among which access to treatment was included.

For physicians, the reason reported second was "Rarity: incidence of patients with protocol-required very specific inclusion and exclusion criteria is low". In the interviews all of the motivations declared were expressly linked to rare diseases/precision medicine, hence to "Rarity".

Conclusions:

The primary motivation for seeking access to clinical trials abroad was the same for patients and physicians: access to innovative treatment not available in the patient's home country.

The second ranking reasons were lack of clinical trial site in the own country for patients and rarity of the patients' disease conditions for investigators.

Physical proximity of the trial site was the key reason for patients who would go abroad even if a trial site were located in their own country.

The vulnerable health condition but also the risk of getting randomised to the placebo arm were main reasons for reluctance to seek access to a clinical trial abroad for patients.

TOPIC 6: MOTIVATIONS FOR INVESTIGATORS AND SPONSORS TO RECRUIT OR NOT FOREIGN PATIENTS

In this topic information was collected on reasons for investigators but also for sponsors to perform or enable enrolment of patients from other countries into their clinical trials.

INTERVIEWS

Investigators and sponsors (i.e. commercial and academic sponsors) were specifically asked about their reasons for foreseeing the recruitment of foreign patients in clinical trials in Question 4 and Question 7.c.:

QUESTION 4: IN YOUR OPINION OR EXPERIENCE, WOULD INCREASED CROSS-BORDER CLINICAL TRIAL PARTICIPATION REDUCE PATIENT RECRUITMENT TIMELINES TO A RELEVANT EXTENT? WHY?

QUESTION 7.C.: WHAT FACTORS WOULD MOTIVATE YOU, A SPONSOR, TO FORESEE THAT YOUR INVESTIGATORS RECRUIT PATIENTS FROM ABROAD?

While some logical overlap with the motivations to participate/recommend participation (see above) was present with Question 7d for investigators, there were a few key distinctions that were specific for these stakeholder groups.

6.1. MOTIVATIONS TO RECRUIT FOREIGN PATIENTS

Faster recruitment was stated by several investigators, industry representatives, and the academic trials sponsor representative as the key reason to seek the inclusion of foreign patients in their clinical trials. This was closely followed by low recruitment rate for a given trial. Recruitment enhancement was seen particularly relevant in the context of the precision medicine approach (namely, very specific inclusion criteria) and rare diseases (as stated by an industry representative, “*in rare diseases you have no choice*”). It was also interlinked with the feasibility of opening trial centres across the EU (see Topic 14, Part 3). The majority of experts interviewed agreed that it was not possible to open a clinical trial everywhere, due to logistical, administrative, regulatory, and safety reasons (the latter especially in the case of early Phase I and II oncology trials). Finally, some of the Interviewees from these stakeholder groups focused on providing access to treatment as a motivation to foresee the recruitment of patients cross-border.

6.2. MOTIVATIONS NOT TO RECRUIT FOREIGN PATIENTS

An industry representative stressed that the majority of the patients that participate in clinical trials are recruited locally. Reasons for this include the fact that sponsors would seek enabling patients to participate in the nearest hospital possible. Furthermore, in the majority of clinical trial cases, trial subjects have to comply with strict and frequent visits to the investigational site, and this was considered as burdensome.

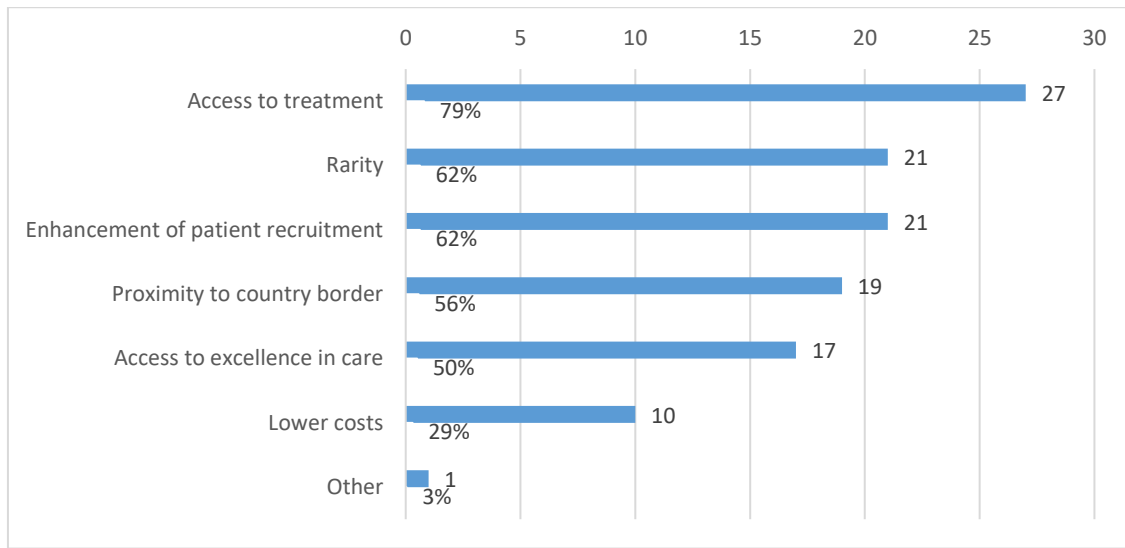
SURVEY

QUESTION 12: PLEASE ANSWER ONLY IF YOU ARE A CLINICAL TRIAL SPONSOR: WHICH FACTORS WOULD MOTIVATE YOU TO FORESEE IN YOUR CLINICAL TRIAL THAT INVESTIGATORS RECRUIT PATIENTS FROM ANOTHER COUNTRY?

89% (n=34) of the total number of respondents (n=38) who identified as sponsors in Question 2 provided an answer here. The question allowed the selection of multiple answers; hence the results were presented in order of preference. From the total of seven possible answers, four were similarly distributed, namely “Access to treatment” (79%, n=27), “Rarity” (62%, n=21), “Enhancement of patient recruitment” (62%, n=21), and “Proximity to country border” (56%, n=19).

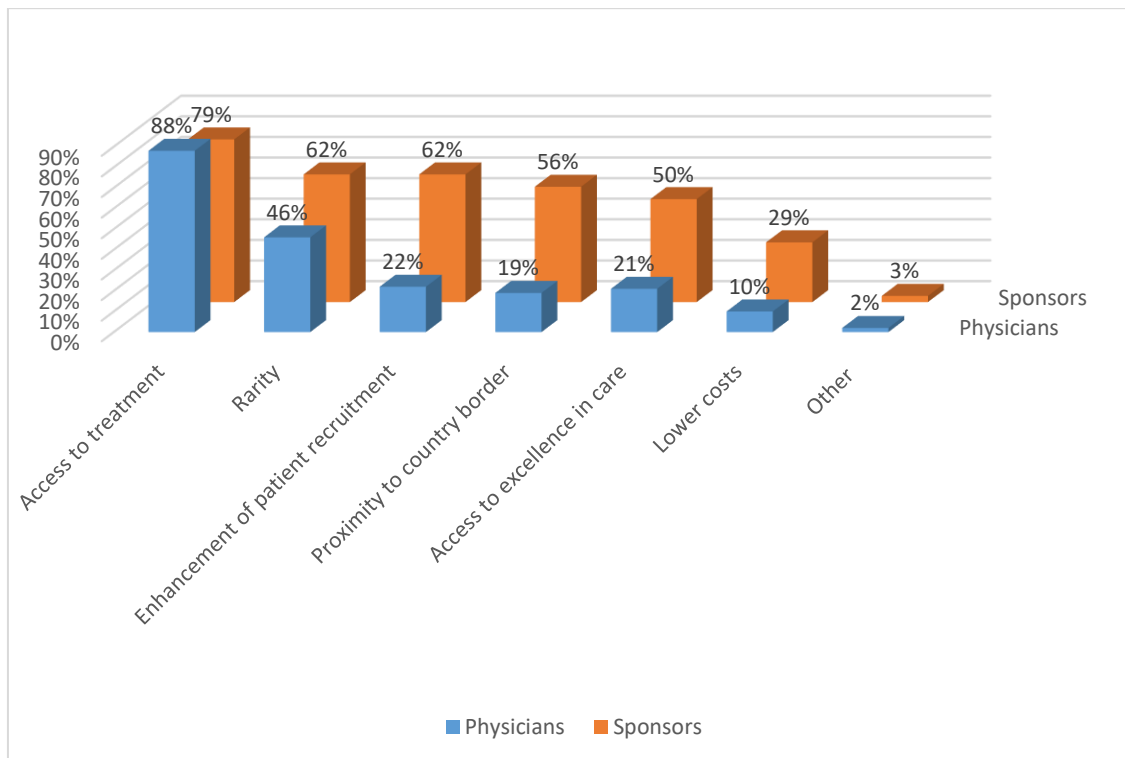
The highest pre-defined option ranked was “Access to treatment: Opportunity for a patient to get access to a promising investigational treatment or expensive technology (79%, n=27), while the lowest ranked was “Lower costs: Opportunity for a patient to get abroad cheaper or free treatment which would be costly to the patient or the healthcare system in the patient's country” (29%, n=10). There was no big variation in answers overall.

Figure 17. Motivations for sponsors to support recruitment of foreign patients



An association between Questions 12 and 13 was evaluated in order to directly compare the motivations of sponsors and physicians. A visual of this comparison is provided in Figure 18 below. For investigators the clearly dominating reason was access to treatment, followed by rarity, where in the case of sponsors there was a nearly equal dissemination of answers, with just a slight preference for access to treatment.

Figure 18. Comparison of motivations for physicians and sponsors



KEY RESULTS: TOPIC 6

In the interviews the opinions of investigators and clinical trials sponsors were collected, whereas in the survey only sponsors were asked to complete the specific question. In addition, the interviews allowed a glimpse into the motivations not to recruit foreign patients, which was not possible through the survey. In summary, according to sponsor and investigator interview participants:

Motivations to recruit foreign patients:

- Faster recruitment
- Low recruitment rates
- (Un)feasibility of opening trial centres across the EU
- To provide access to treatment

Motivations not to recruit foreign patients:

- Enabling patients to participate in the nearest hospital
- Burden of frequent visits to the site, especially for foreign patients

In the survey there was not much divergence in the number of responses gathered for each option, however a slight preference was given to providing “Access to treatment”. The next two frequently given responses were “Rarity” and “Enhancement of patient recruitment”. This was in line with the top interview results of “Faster recruitment” and “Low recruitment rates”. As shown in the comparison between the answers provided in the survey by physicians and sponsors, the motivations of both stakeholder groups were very similarly ranked in preference. However, for physicians “Access to excellence in care” (n=30) ranked higher than for sponsors. Interestingly “Lower costs” were ranked lowest by both stakeholder groups.

Conclusions:

Enabling access to treatment and faster recruitment/overcoming low recruitment conditions from rare cancers and other diseases were the key motivation for sponsors and investigators to support recruitment of patients from abroad.

Distance to the trial site and related additional burden of frequent visits were considered to be the most relevant reasons for opposing access to clinical trials in other countries.

TOPIC 7: EUROPEAN COUNTRIES ATTRACTIVE FOR PATIENTS TO SEEK PARTICIPATION IN A CLINICAL TRIAL AND REASONS WHY

This topic was included to collect information on possible differences in attractiveness of countries or regions for patients seeking access to clinical trials and underlying reasons.

INTERVIEWS

This topic was specifically explored under:

QUESTION 8: IN YOUR OPINION, IN WHICH OTHER EU MEMBER STATES DO PATIENTS FROM YOUR COUNTRY SEEK ACCESS TO CLINICAL TRIALS?

and

QUESTION 9: IN YOUR OPINION, WHAT ARE THE REASONS THAT WOULD MOTIVATE PATIENTS TO SEEK ACCESS TO CLINICAL TRIALS PRIMARILY IN THESE COUNTRIES?

The most attractive countries could not be extracted from the interviews in concrete terms. However, countries located in Western Europe were cited more frequently, namely, Belgium, Germany, The Netherlands, France, the UK, and Spain. It must be noted that none of the Interviewees supported his/her statement with publicly available statistics, as such do not exist to the best of their knowledge.

The reasons cited by Interviewees for mentioning specific countries were closely linked to the general reasons that guide the choice to participate in a clinical trial (see Topics 5 and 6 on Motivations). Moreover, according to the subjective observations of the majority of Interviewees, the most attractive countries are those with the highest number of commercially and non-commercially sponsored clinical trials.

The provided reasons for choosing certain countries are presented in a descending order of importance, to the extent such an order could be inferred through the number of mentions and references made by Interviewees. Five of the 38 interview participants stated that they had no information on the topic and refused to speculate.

1. Neighbouring countries: the geographical proximity was a very important factor for patients' selection of preferred countries.
2. Closely linked to the above follow countries where the language barrier is alleviated (e.g., Belgium when it comes to patients coming from France, The Netherlands, or Germany, and vice versa).
3. Countries where clinical trials sponsors are most likely to open sites (as no site is open in the country of residence of the patient). (Assumed) sponsor reasons for selecting a limited number of countries for opening sites have been indicated by the participants (in no particular order): - national legal and regulatory framework providing facilitation (e.g., allowing for the relatively faster opening of a clinical trial); the population of the countries being relatively larger in comparison to other countries; the hospital infrastructure and facilities being at a certain level (which is hard to describe in concrete terms based on interview data only). Additional points of view were provided by a policy expert: *"So, it's not about the country, it's where the clinical trials happen. And the clinical trials happen where the markets are. Companies, they would always go to the market where they are actually going to get reimbursement and then sell their products afterwards."*
4. Trust in the excellence of the foreign healthcare system.
5. Trust in the excellence of science in the "hosting" EU Member State. Especially when it came to oncology, participants pointed out that certain procedures, equipment, and clusters of expertise are only available in a limited number of countries and centres of excellence.
6. For reasons of cultural similarities and established frameworks for collaboration: especially prominent in the Nordic region where such frameworks have been constructed with governmental support. However, this reason could also be seen from a non-regulatory point of view, namely in the cases where a large number of a patient compatriots reside and work in a certain foreign country and are willing to provide help with logistical or other issues. In the words of a physician: *"Or maybe, there are more Lithuanians in United Kingdom or in Germany working, so somehow they find some help from there"*.
7. The advice and knowledge of the treating physician played a role: as pointed out by a patient representative, patients make the choice to seek participation in a certain country based on the insights provided by their local physicians. Hence, the knowledge and education of the treating physicians play a significant role in promoting specific countries for cross-border clinical trials access.

8. Publicity: as indicated by a patient representative, certain EU Member States advertise themselves as centres for clinical trials which might influence the decision-making process of patients: *“So I know, for example, from another project, I just happen to know that The Netherlands actively advertise their clinical trials. There are people whose job it is to advertise for clinical trials in The Netherlands. So that recruitment includes other countries, and patient communities outside of The Netherlands.”*

Finally, it is important to note the specific case of the Nordic countries. There, according to the opinion of a physician, patients are referred exclusively to clinical trials open within their own country or neighbouring Nordic countries, and refer patients farer away only in cases where the treatment provided in the trial is based on the genetic profile of patients.

SURVEY

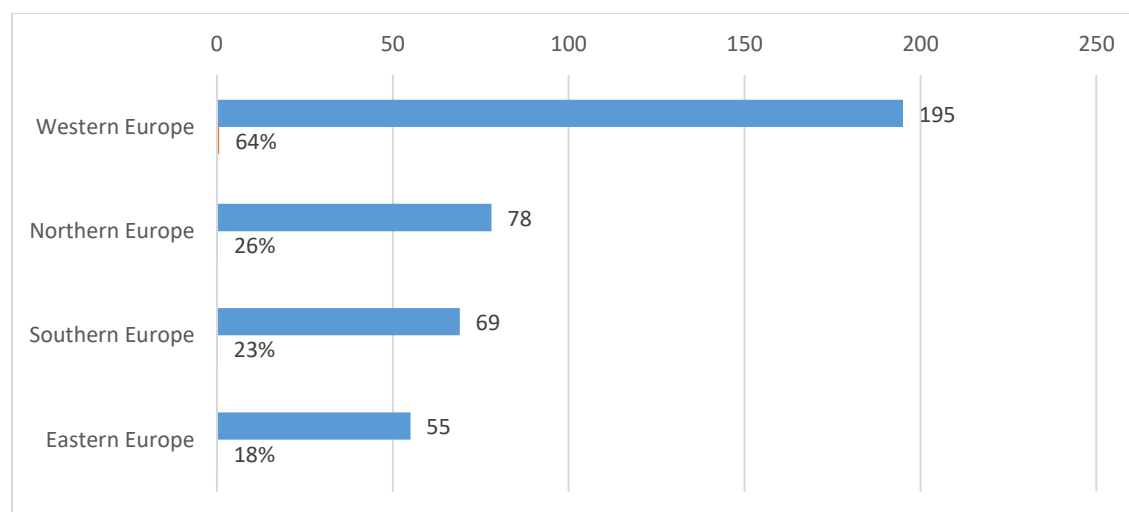
The topic was explored with:

QUESTION 14: IN YOUR OPINION, IN WHICH OTHER EUROPEAN COUNTRIES DO PATIENTS FROM YOUR COUNTRY SEEK ACCESS TO CLINICAL TRIALS?

More than one answer could be selected. 77% (n=304) out of the total of 396 survey respondents answered it with a total of 744 responses. The option “I do not have opinion” was also provided and gathered 31% (n=95) of responses.

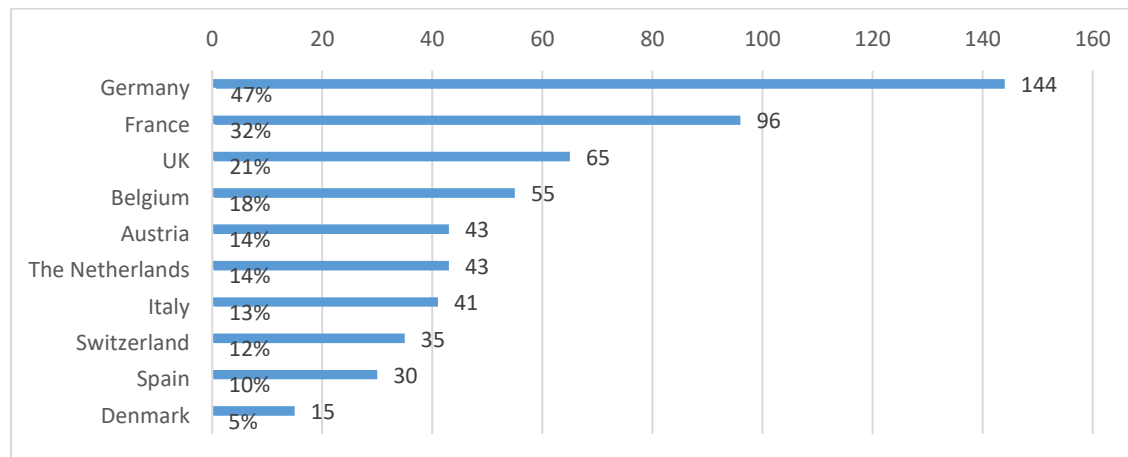
In Figure 19 below the results were grouped in the order of preference expressed by the respondents, calculated on the number of times countries from each European region were selected. As the pre-defined answers included the possibility to select countries not part of the EU (e.g. Armenia, Turkey), responses for these countries are not accounted for in Figure 19. A clear preference for Western Europe was reported. The results were also grouped based on country income. High-income countries were ranked overwhelmingly higher (70%, n=209). Upper-middle-income and lower-middle-income countries were hardly selected (5% (n=15) and less than 1% (n=2), respectively).

Figure 19. European countries where foreign patients seek access to CTs



In terms of individual countries within the regions presented in the figure above, the following ten countries were mostly selected by the respondents: Germany, France, United Kingdom, Belgium, Austria, Netherlands, Italy, Switzerland, Spain and Denmark. The corresponding number of answers for each country is included in Figure 20 below.

Figure 20. Most attractive countries for foreign patients seeking access to a clinical trial



An association with Question 1 (countries where the survey respondents were based, organised by region) was performed (see Table 6)³¹. As the results show, respondents based in all European regions indicated a preference for trial participation in Western Europe. Only respondents from Northern Europe rated the Northern countries similarly to the Western European countries, however the preference was still for Western Europe.

Table 6. European countries where patients from own country seek access to CTs

<i>Frequency</i>	<i>Q14. In your opinion in which other European countries do patients from your country seek access to clinical trials?</i>						
<i>Q1 In which country are you based?</i>	<i>N subjects</i>	<i>N choices</i>	<i>Eastern Europe</i>	<i>Northern Europe</i>	<i>Southern Europe</i>	<i>Western Europe</i>	<i>No opinion</i>
Eastern Europe	31	63	14 (45.2%)	6 (19.4%)	13 (41.9%)	24 (77.4%)	6 (19.4%)
Northern Europe	58	89	5 (8.6%)	24 (41.4%)	6 (10.3%)	34 (58.6%)	20 (34.5%)
Southern Europe	73	142	18 (24.7%)	26 (35.6%)	28 (38.4%)	49 (67.1%)	21 (28.8%)
Western Europe	119	166	14 (11.8%)	20 (16.8%)	14 (11.8%)	76 (63.9%)	42 (35.3%)
Total number of subjects (N=304)							

Finally, with Question 16 survey participants were asked to provide a publicly available source of information that supported their answer to Question 14. Of 22 respondents, 31% (n=7) indicated that the information came from personal experience and 23% (n=5) shared that they do not have a source.³²

³¹ Per row, the percentages were calculated with the number of subjects as denominator. Since Q14 was not mutually exclusive, these percentages did not add up to 100.

³² See Annex IV for the full list of answers gathered for Question 16.

KEY RESULTS: TOPIC 7

In the interviews the most attractive countries were not presented in concrete terms, however countries located in Western Europe were cited more frequently (Belgium, Germany, The Netherlands, France, the UK, and Spain). Moreover, the interviews allowed to explore the reasons why these countries were perceived attractive.

In summary:

- Neighbouring countries
- Countries where the language barrier is alleviated
- Countries where clinical trials sponsors are most likely to open sites, as no site is open in the country of residence of the patient
- Trust in the excellence of the foreign healthcare system
- Trust in the excellence of science of the “hosting” country
- For reasons of cultural similarities and established frameworks for collaboration
- The advice and knowledge of the treating physician
- Publicity

The results from the survey provided a strong confirmation for the insights gathered through the interviews, namely the opinion that countries located in Western Europe were most attractive (64%). In particular, all of the six countries that were most frequently mentioned in the interviews were also found in the top 10 ranking of countries reported in accordance with survey responses: 1) Germany, 2) France, 3) UK, 4) Belgium, 6) The Netherlands, and 9) Spain.

In addition, both interviews and survey, showed that currently there are no publicly available sources of information/statistics about this topic.

Conclusions:

Western European countries, in particular Germany, France, UK, Belgium, The Netherlands and Spain, are most attractive for foreign patients seeking access to clinical trials.

Most important reasons stated were proximity of the site, reduced language barrier and likelihood of hosting sites even if in studies with small number of sites.

TOPIC 8: EUROPEAN COUNTRIES OF ORIGIN FOR PATIENTS SEEKING PARTICIPATION IN A CLINICAL TRIAL CONDUCTED ABROAD AND REASONS WHY

This topic was included to learn more about the countries of origin of patients looking for cross-border access to clinical trials and their reasons.

INTERVIEWS

This theme was explored specifically under:

QUESTION 10: IN YOUR OPINION, WHAT ARE THE EU MEMBER STATES FROM WHICH PATIENTS ARE MOST LIKELY TO SEEK ACCESS TO CLINICAL TRIALS CONDUCTED IN YOUR COUNTRY?

and

QUESTION 11: IN YOUR OPINION, WHAT ARE THE REASONS THAT WOULD MOTIVATE PATIENTS FROM THESE COUNTRIES TO SEEK ACCESS TO CLINICAL TRIALS SET IN YOUR COUNTRY?

It was not possible to concretely extract those countries from the interviews that were of highest interest to patients seeking access to clinical trials abroad. Interviewees made some broad statements based on personal and subjective observations, not on statistics. However, EU Member States located in Central and Eastern Europe (CEE) were more frequently mentioned.

Yet, a clear priority list emerged regarding the reasons why patients from certain countries would seek cross-border access to clinical trials, summarized as follows:

1. Neighbouring countries: when a clinical trial site was open in short distance across the border and was thus objectively closer to the residence of a patient (in comparison to a site open in the home country which was located objectively farer away), or when a site in a neighbouring country provided access to experimental therapy that was not yet available in the patient's country of residence, then people were likely to participate abroad. This reason was especially prominent in the case of Belgium, France, and The Netherlands.
2. When the healthcare system in a given country was perceived by its residents as less developed in comparison to other EU Member States' systems. CEE, Portugal, and Italy were most often cited in relation to this reason. However, a physician presented a deviating opinion: patients that come from countries with less-developed healthcare systems would not primarily enrol in a clinical trial. They would rather seek treatment in the "*private environment*", as part of the standard clinical practice.
3. Countries where less clinical trials are opened. In this context the most frequently mentioned countries were CEE countries (e.g., Bulgaria, Romania) and Greece. None of the Interviewees who indicated this reason had access to concrete numbers of trials open in specific countries, hence the answers must be perceived as personal speculations based on professional experience and observations.
4. Countries where a new promising treatment was currently not available. This reason was applicable to all EU Member States, regardless of their geographical location. A physician's answer "*it is widely distributed across Europe*" was among the confirmations that the reasons to seek participation in a trial abroad was not confined to one single part of the EU.

SURVEY

The topic was investigated with:

QUESTION 15: IN YOUR OPINION, FROM WHICH OTHER EUROPEAN COUNTRIES DO PATIENTS MOST LIKELY SEEK ACCESS TO CLINICAL TRIALS CONDUCTED IN YOUR COUNTRY?

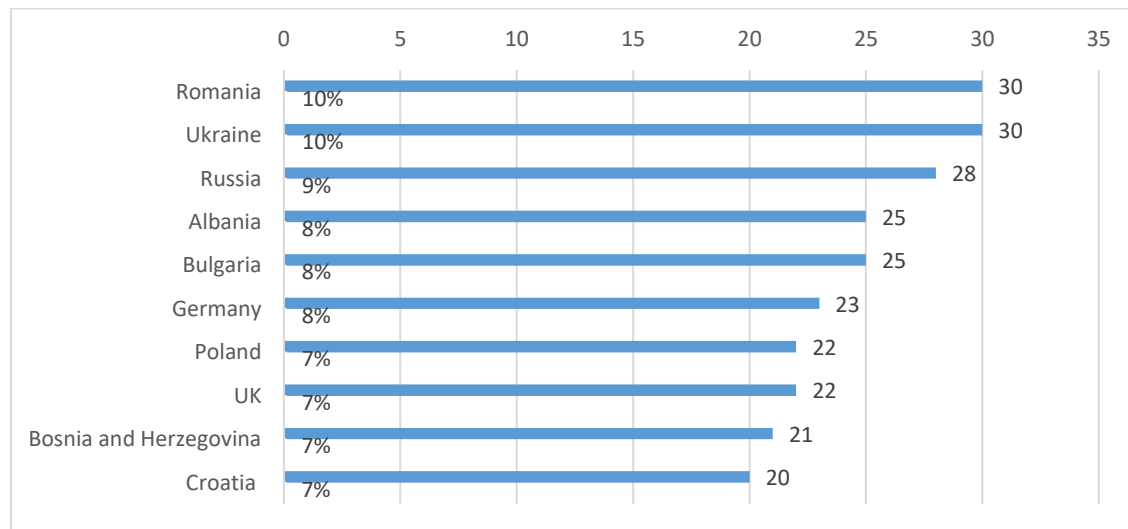
More than one answer could be selected. 77% (n=304) out of all survey respondents (n=396) answered this question. Of those who responded, 44% (n=132) selected “I do not have an opinion”. Note that there were also subjects who chose one or more countries or indicated no opinion. As a result, the number of subjects choosing other was higher than the number of subjects not choosing any country.

In Figure 21 below the results were grouped in the order of preference expressed by the respondents and show the ten countries that received the highest number of responses. With the exception of Germany and the UK, the figure presents mainly Eastern and Southern European countries. Northern countries were not registered among the first ten countries from which patients are likely to seek access to a clinical trial abroad.

Based on the sub-regions grouping of results, 30% (n=90) of responses indicated Southern Europe first, followed by Eastern Europe (29%, n=87), Western Europe (21%, n=63), and Northern Europe (14%, n=44).

The results were also grouped based on country income. High-income countries were ranked first (45%, n=137), followed by upper-middle-income (30%, n=92) and lower-middle-income countries (10%, n=31).

Figure 21. First ten countries of origin of patients seeking participation in a clinical trial abroad



Question 16 (presented above in Topic 7) also applied to Question 15. As shown above, the majority of survey respondents indicated that their knowledge came from personal experience or did not have any source of information.

KEY RESULTS: TOPIC 8

In the interviews EU Member States located in Central and Eastern Europe were more frequently mentioned as countries of origin of patients seeking access to clinical trials abroad than other European regions.

A clear priority list emerged regarding the reasons why patients from certain countries would seek cross-border access to clinical trials.

In summary:

- Neighbouring countries
- When the healthcare system in the country of residence of the patient was perceived as less developed in comparison to other EU Member States' systems
- Countries where less clinical trials were conducted
- Countries where a new promising treatment was currently not available

The results from the survey provided a strong confirmation for the insights gathered through the interviews, namely the opinion that residents of countries located in Central and Eastern Europe were most likely to seek treatment abroad. It was interesting to observe that also Germany and UK were in the top 10 countries of origin for patients seeking participation in a clinical trial abroad.

In addition, both interviews and survey showed that there are no publicly available sources of information/statistics about this topic.

Conclusions:

Patients from Southern and Eastern European countries were rated as most frequently seeking access to clinical trials abroad but also Germany and UK were amongst the top 10 countries in this topic.

According to the interviews, the main reasons for patients from these countries participating in clinical trials abroad was the cross-border proximity of the site or availability of new treatments, but also the perception that the own healthcare system was less developed or fewer clinical trials take place.

TOPIC 9: CHALLENGES TO PARTICIPATE IN OR ORGANISE CROSS-BORDER CLINICAL TRIALS

This research project also aimed at gaining a better understanding of the practical challenges of cross-border access to clinical trials for the different stakeholders. Results are presented under this topic.

INTERVIEWS

This topic was investigated under:

QUESTION 12: IN YOUR VIEW, WHAT ARE THE CHALLENGES FOR PATIENTS FROM YOUR COUNTRY GOING ABROAD TO PARTICIPATE IN CLINICAL TRIALS OPEN ABROAD?

and

QUESTION 13: IN YOUR VIEW, WHAT ARE THE CHALLENGES FOR PATIENTS COMING INTO YOUR COUNTRY TO PARTICIPATE IN A CLINICAL TRIAL?

However, numerous other times during the interviews, participants commented on challenges and expressed further opinions, as the topic was inextricably linked to several of the major themes investigated

in the research project (such as, e.g., increase or decrease in requests for inclusion in clinical trials conducted abroad, motivations or hindering forces for participation).

The concrete challenges are presented in a descending order of importance that was established based on the frequency with which participants brought them up. Regarding the first four challenges (costs coverage, language barrier, lack of information, and procedural challenges), the number of references made to each of them by all stakeholders was comparable, hence it could be concluded that they were deemed equally important.

No differentiation in respect to individual EU Member States was made, as it was largely shown that the high-level issues were the same cross-countries. However, national particularities that potentially affect tackling the challenges were shown to exist (e.g., differences in average wage). Therefore, wherever such particularities were deemed meaningful for the purposes of the report, they are explicitly stated. To illustrate with the words of an academic sponsor representative, *“I don’t think there are radical differences. Then it depends in which country you are going, and each country will have its own specificities. There are certain things that will be easy and more organised, and other things that would be more difficult. (···) But again, the hosting country, that might change. So, I guess if a French patient would come to Belgium, financially it would be less problematic than if a Romanian patient would come to Belgium, because of the differences and the costs, like the daily living costs - food costs and this kind of stuff”*.

Finally, it must be stated that in addition to the challenges that patients face, several Interviewees spontaneously brought up the barriers for organising clinical trials that accept foreign patient. Most of those hurdles closely mirrored the challenges for patients, therefore we chose to present them below together, adding a visual indicator to specify that the information related to the sponsor/investigator perspective.

1. COSTS COVERAGE

During the course of the study several Interviewees pointed out that only *“rich patients”* can afford participation in a clinical trial abroad. Representatives of all stakeholder groups unanimously identified costs coverage as the biggest challenge that patients face when they seek cross-border access to clinical trials.

The financial burden coverage issue pertained to two sub-topics. On the one hand, costs associated with joining the clinical trial abroad. This included travel expenses, coverage of accommodation, coverage of care (either the costs associated with a family member accompanying the patient, or the costs for hiring a carer in the host country). In addition, where the experimental treatment was an add-on to baseline standard therapy, the costs of the baseline therapy/standard of care therapy was in most cases allocated to the patient as well, as such standard treatment costs are not covered by the social security system of the host country. In the words of one physician, *“not always they have reimbursement of all the clinical procedures in those clinical trials. Maybe if there is something the standard of care, in the countries that the trial is running, so then for our patients it’s not reimbursed”*. Moreover, as pointed out by another physician, *“My hospital may require a guarantee of a certain sum of money in case something happens to that patient”*.

On the other hand, there were costs associated with loss of income, e.g. the patient and/or the patient’s carer leaving their employment in order to be able to travel.

To illustrate further the hurdle that potential costs bring to patients, two more quotes were relevant. First, as stated by an Ethics Committee representative, *“Even 5000 Euros, or 1000 Euros is enough to make the patient afraid to do anything”*. Second, as pointed out by a patient representative, *“we had people who basically use the entire family savings to go on a clinical study”*.

Practical recommendations from interviews to overcome challenges:**Cost coverage as challenge for organising clinical trials that recruit foreign patients:**

An important aspect to plan and solve between sponsor and investigators enabling foreign patients' inclusion in a clinical trial are the type, size and allocation rules for additional resources and related budget to cover the costs of enrolment of those patients. This also includes the allocation of responsibilities for calculating and managing this additional budget comprising aspects like travel and accommodation expenses but also translation costs, school costs, standard healthcare costs, etc.

2. LANGUAGE BARRIER

The language issue was the second most prevalent challenge stated by representatives of all stakeholder groups. *"Many patients only speak their mother language and no other languages"* (Physician).

Language knowledge bears huge importance when it comes to communication with hospital staff and day-to-day living in the host country. As stated by an Ethics Committee representative, *"being in a clinical trial it's not just going for the holiday. There might be things that go wrong and so on, so I need being assured that I can communicate with the people there, running the trial and taking care, care of me, about me"*.

Language issues create also additional costs associated with translation services.

In addition, language could also be a barrier in relation to all documentation associated with joining a clinical trial, particularly the understanding and acceptance of informed consent for participation in a trial. *"Patients need to have information in their own language in order to be able to sign"* (industry representative). Each EU Member State has its own ethical requirements regarding informed consent. It emerged that some have stricter rules than others. For instance, in Germany *"if you can't read the informed consent, you can't go on a trial. We have been negotiating with them to at least include an English informed consent, just like routinely, that every trial has at least a German and an English one, because that would open it up to many more"* (patient representative). Whereas in Belgium, informed consent in English did not appear to be an issue.

However, language can also play an important role in decision-making whether or not to join a clinical trial abroad. For instance, when it comes to border regions that share the same or a similar language (e.g., as is the case in the Nordics, or with Belgium, France, Germany, and The Netherlands), patients would be more inclined to participate in a cross-border clinical trial. In the words of a physician, *"Norway, Sweden and Denmark have a very similar language, so when I talk in Norwegian, I could talk with them in my mother tongue"*. Moreover, language also plays a role when it comes to identifying the EU countries that would be most attractive for foreign patients, e.g., in the case of Belgium where there are three official languages (French, Dutch, and German), *"the fact it's multilingual is also a very good aspect for patients coming to Belgium. I think that's an advantage."* (Patient representative).

Practical recommendation from interviews to overcome challenges:**Language barrier as a challenge for organising clinical trials that recruit foreign patients**

As Interviewees pointed out, language issues can arise and need to be dealt with in different areas ranging from basic conversation on the patients' health conditions to the informed consent process, to adverse event reporting, validation of questionnaires and other patient reported outcomes as well as emergency communication with relatives.

Definition and availability of the required level of translator support, often subject to ethics committee requirements, need to be enabled.

3. LACK OF INFORMATION

The majority of Interviewees were of the opinion that the lack of well-structured and easily accessible information about the availability and elements of clinical trials is among the biggest challenges to patients seeking to participate in clinical trials cross-borders.

The lack of information comprised three crucial points:

- Firstly, information about ongoing clinical trials, eligibility criteria, and location of clinical trial sites (see also the discussed below Procedural challenges). Interviewees explained that the majority of patients learn about clinical trials primarily through their treating physicians. However, as shown below, it is possible that the treating physicians themselves might not be aware of suitable ongoing studies or might be unwilling to refer their patients to trials. In addition, it was reported, that most patients are not aware of the EU clinical trials register and clinicaltrials.gov databases, or do not find them user-friendly. Hence, the major responsibility of providing information to patients falls on patient organisations and patient advocacy groups. However, it must be noted that such groups, due to lack of financial and time-resources, are not always best positioned to gather and disseminate knowledge.
- Secondly, information about the value of clinical trials, i.e. more efforts seems to be needed in order to familiarise patients with what a clinical trials involves and how it could be beneficial (in the words of a patient representative, *“you know, certain patient populations don’t even understand what a clinical trials is. So, I think, the first thing is to explain to patients that a clinical trial is not about being a guinea pig, which still, unfortunately, is the kind of popular notion in many cases of clinical trials”,* and another patient representative, *“there is also a high degree of suspicion” [towards clinical trials in general]*).
- Thirdly, specifically in the case of cross-border clinical trials, information for all involved stakeholders about options and best practices when joining a trial abroad (e.g., legal and regulatory rules that have to be taken into account, information about where and how to find appropriate help for logistical issues, etc).

Representatives of both commercial and non-commercial clinical trials sponsors shared that patients regularly attempt to contact them directly, in order to inquire about possibilities for joining a trial. However, pursuant to ICH GCP standards and applicable legislation the sponsor is not allowed to know the identity of participants in his clinical trials.

Practical recommendations from interviews to overcome challenges:

Lack of information

As Interviewees recommended, efforts should be made

- to make methodology and value of clinical trials more broadly known to patient organisations, physicians and the public at large
- to provide easy to find information or even proactive information for treating physicians and related patient communities about clinical trials, their in- and exclusion criteria, study conditions and locations
- to create guidance on best practices for cross-border access to clinical trials

4. PROCEDURAL CHALLENGES

The procedural challenges associated with cross-border access to clinical trials constituted the most complex issues that came out in the interviews. The procedural barriers are manifold, and mainly linked to national legal requirements, or lack of a clearly defined regulatory path and infrastructure for joining clinical trials abroad. All sub-challenges that emerged under this topic will require separate in-depth country-by-country investigation, in order to find the most optimal solutions.

4.1. REIMBURSEMENT CONSTRAINTS (INSURANCE)

This point pertained, on the one hand, to the uncertainty related to who will or can be responsible for the reimbursement of costs incurred by the patient who participates in a trial abroad. As delineated in the introduction, such reimbursement issues are only solved at EU level in the case of receiving cross-border healthcare. Pursuant to Article 7 of Directive 2011/24/EU, healthcare costs occurring abroad have to be covered by the patient's own country healthcare system up to that Member State's coverage level. However, costs associated with clinical trials do not fall under the scope of this rule and is thus legally unresolved on European level.

On the other hand, the topic of reimbursement constraints pertains further to specific legislation enacted in Member States. Three pertinent examples emerged in the course of the interviews:

- In the case of France, one of the requirements for joining a clinical trial conducted in the country is that patients are affiliated with the French social security system (it was been brought up by a French physician and a Belgian physician who tried to send patients for clinical trials to France). The reverse situation, namely a French resident attempting to join a trial open outside of France, is equally complicated. From the analysis of the interviews performed it seems that local insurance companies in France would refuse reimbursement.
- In the case of Slovakia, pursuant to Act No 362/2011 on medicines and medical devices, patients must request the permission from their insurance company prior to joining a foreign clinical trial, or otherwise stand at risk of being fined for the amount of 200 to 10 000 Euros. An Ethics Committee representative aptly illustrated and provided further information on the issue: *"The health insurance company would give permission, if this is clearly a therapeutic trial, when the drug is not available, for any reason in Slovakia, and where there is a reasonable hope, that the patient could be saved. Then, I see, well, under these justifications, I think the health insurance company could agree, but this would be a fight. This is another hard one for the patient"*.
- In the case of Spain, it is required that patients who wish to access treatment abroad (regardless of whether it is provided in the framework of a clinical trial, or not) have to apply and obtain the S2 form (as established under (EC) regulation No. 883/2004)³³. However, obtaining the S2 form is practically impossible, as regional health authorities would deny approval. Concrete example has been provided by a physician: *"we tried to send patients to France, to [name of institute redacted] for early clinical trials, and it was systematically denied by our regional health system, based on the same grounds that early clinical trials are not approved in therapy and they were not going to fund that"*. Another example shared by a physician shed light on the practical way patients and their carers would be able to solve the issue of reimbursement: *"We did send a couple of patients to Italy for a leukaemia trial and then that could happen because, first (...) the Italian site was not very restrictive on what they asked, and then in the end because it was the parents that moved and went there and once they were there, sort of they sent the bill to the regional healthcare system"*. The same opinion was echoed by a policy expert: *"In order to participate, you will have to find a way to have a local insurance, so that*

³³ Portable Document S2 (PD S2) on 'Entitlement to scheduled treatment' certifies the entitlement to planned health treatment in a Member State other than the competent Member State of the insured person, based on the procedures determined by EU rules on the coordination of social security systems: Regulation (EC) No 883/2004 and Regulation (EC) No 987/2009

they can even pay attention on you being a volunteer for this clinical trial and run a screening visit with you. Otherwise, I don't think they even allow to do that."

However, having patients change their place of residence in order to subscribe to a foreign health insurance system is a serious additional burden that combines the financial coverage of costs challenge, and the described below vulnerability challenge. It is neither sustainable, nor an ethically sound solution for the facilitation of cross-border access to clinical trials.

Practical recommendations from interviews to overcome challenges:

Reimbursement constraints

The uncertainty about rules, flexibilities and best practices in the two involved healthcare systems are a major obstacle to frequent cross-border patient enrolment and are the reason for much inefficiency, stress and frustration on patients', investigators' and sponsors' side.

Efforts should be made to clarify the conditions for healthcare and travel cost coverage of patients participating in clinical trials abroad, especially between neighbouring countries' healthcare systems.

An overview over the different national conditions should be elaborated on EU level and provided to investigators, patient organisations and sponsors.

4.2. NAVIGATING THE FOREIGN HEALTHCARE SYSTEM

There was agreement between the stakeholders that it is a challenge for patients to understand a foreign healthcare system and to find out about the transition conditions from the own national healthcare system to the foreign one. Included here are logistical hurdles, such as, in the words of a policy expert, *"knowing who to contact, or how to get information"*.

Practical recommendations from interviews to overcome challenges:

Navigating the foreign healthcare system

There is a need for easy to find information in simple language that explains a Member State's healthcare cost coverage conditions for patients in clinical trials from abroad.

4.3. THE INVESTIGATIONAL SITE NOT WILLING TO RECRUIT FOREIGN PATIENTS

Several Interviewees pointed out that frequently the sites would not be willing to accept patients coming from abroad. One physician specified that *"I don't think that the site, at least in the early phase studies, will want to have foreign patients"*, while a patient representative emphasized that *"there are a lot of hospitals that are not open at all to get patients from abroad"*.

The two main reasons cited by Interviewees were:

- Financial concerns: could be linked with the reimbursement constraints challenge, described above.
- Administrative burden: e.g., the additional burden associated with processing relevant documentation of the foreign patient (*"it will be of course a lot of paperwork"*, as stated by a patient representative).

It was mentioned that in industry-sponsored trials this challenge was sometimes alleviated during the stage of planning the trial. Namely, by organising discussions with the investigators, and by foreseeing appropriate safeguards, such as allocation of additional financial resources to cover for the increased administrative workload.

Practical recommendations from interviews to overcome challenges:

Sites' unwillingness to recruit foreign patients

During the feasibility assessment the sponsor should explore whether foreign patients would be accepted at that site, especially in clinical trials with high likelihood of foreign patient recruitment.

During study preparation the sponsor and investigator should clarify the hospital's conditions for accepting patients in clinical trials whose healthcare costs are covered by a foreign healthcare system.

4.4. LACK OF TREATING PHYSICIANS' MOTIVATION TO REFER PATIENTS TO CLINICAL TRIALS

Some interviews revealed a lack of motivation of local treating physicians to refer patients to clinical trials in other hospitals. There was no concrete data emerging from this exploratory study regarding the extent to which the issue is widespread. Financial considerations seemed to be the most frequent reason for this phenomenon. Hospitals/physicians receive their fees based on the number of patients treated and/or the services provided. Therefore, there is no incentive to refer patients to other institutions. As expressed by an industry representative: *"I am just going to say it - I think, the physicians in some of the countries want to keep their patients base. So, I am not as sure in all countries in Europe, but in the pharmaceutical world, when we view hospitals, some hospitals don't want to give up their patients to other clinical sites, because that part of their treatment of that patient rolls into the viability on the financial side of that hospital"*.

Another reason brought up by Interviewees was the unwillingness of physicians to recognise gaps in their own knowledge: *"In real world practice with all the egos around in medicine, I would say that's not the case, because usually what we see even within the country, that's not cross-borders, is that physicians that are aware about the clinical trial, they are not even telling patients that the study is open, because they don't want to lose a customer or they are not convinced, because they don't know anything about it or they just can't admit that they don't know enough about it"* (Patient representative).

It must be noted that this challenge was not specific for cross-border participation in clinical trials but was applicable to the conduct of clinical trials in general.

Practical recommendations from interviews to overcome challenges:

Treating physicians' motivation to refer patients to clinical trials:

Efforts should be made to generally inform physicians better about the benefits of clinical trials for their patients and the role they can and should play in the ongoing and long-term care of these patients.

4.5. LACK OF AN APPROPRIATE SYSTEM FOR PATIENT REFERRAL AND FOR ASSESSMENT WHETHER A CLINICAL TRIAL IS THE BEST OPTION IN A GIVEN CASE

Mainly patient representatives and physicians brought attention to the fact that at the current moment there is a lack of an appropriate system for patient referral to a suitable clinical trial. Patients often seem to be searching for the most suitable trial on their own, or with the help of patient organisations. The "EU Clinical

Trials Register” and “clinicaltrials.gov” clinical trial databases were reported to be difficult to navigate for patients and treating physicians. Physicians commented that they refer patients on a case-by-case basis, with no specific system existing for further facilitation of the process.

Linked to this issue was the need for assessment whether participation in a clinical trial is in fact the optimal solution in a given case. This is a medical assessment that is even difficult to make for a treating physician as knowledge about suitable studies is not easily available and especially not detailed information on in- and exclusion criteria as well as the features of the treatment investigated in the trial. Patients try to find trials and assess their conditions: *“The first big step is always, is this trial my best option? You spend a lot of time on that, so basically you look at the situation, you think about your options, what can you access without a trial? What can you only access in a trial? So, it’s a combination; that decision process is quite challenging”* (patient representative).

**Practical recommendations from interviews to overcome challenges:
Assessment of suitability of a clinical trial as treatment options**

Understanding of the available clinical trials options in the patient’s country or abroad and pre-assessment of a patient’s suitability for a particular trial should be made jointly by investigator and treating physician. A role in optimised patient referral was proposed for the European Research Networks (ERN), established by the Cross-border Healthcare Directive for different areas of indications, as an easy to approach collegial source of expertise,

4.6. ELIGIBILITY CRITERIA ASSESSMENT

The uncertainty about a patient’s suitability for the trial was identified as a major hurdle to cross-border participation in clinical trials. As shared by a number of study participants from almost all stakeholder groups (excluding ethics committee representatives and the national contact point representative), the concept of strict eligibility criteria is often not easily understandable for patients willing to access a trial cross-border. Interviewees reported that even when published (e.g., on clinicaltrials.gov or the EU Clinical Trials Register), it can still be challenging for the patients to properly assess themselves whether or not they meet the criteria: *“the eligibility criteria, they were published, they were everywhere but in the end, he found out that the company was actually defining the eligibility criteria as such that he was not, he was doing too well for that study. So, they wanted to exclude the still well performing patients, because that would have watered down the therapeutic effect.”* (Patient representative)

Another patient representative expressed the opinion that the quality of published eligibility criteria varies, which in itself presents a burden: *“Unfortunately, if you look on clinicaltrials.gov, the submissions there are... let’s put it that way: very variable quality. So, some of them are very well-written, others are a disaster, and you think like, whom do they put there to do this? I mean, sometimes you see that there are contradictions between inclusion-exclusion criteria.”*

In addition, assessing eligibility often involves the performance of diagnostic tests. This means that the patient has to travel to the trial site just to check whether he/she fulfils the inclusion and exclusion criteria with a high chance of not meeting them. Hence, already at the stage of eligibility assessment the burden of costs and logistical hurdles (e.g., finding accommodation) are present. A second possible scenario that emerged from the interviews was presented in the words of a physician: *“in many countries the local sites and investigators do expect that the diagnostic tests that had to be done within the framework of the trial, would have to be done in the home country of the patient, like CT scan, which is a nightmare, because they*

want us to do the CT scans over here, while we are not involved in the actual experimental treatment of the patient, and actually by this we are charging the national health insurance for tests that are done in the context of clinical trials which should actually be covered by the sponsor of the study.” This refers one more time to the challenge of cost coverage (see topic 4.1). Furthermore, in the case of a precision medicine approach, it is possible that the specific diagnostic tests required are not available in the home country of the patient, or are not covered by the public health insurance system, which makes them hardly accessible: “The problem is that we do not provide these gene tests on a regularly basis in the public, the fact is, some patients have purchased it from the private health services, but of course, that’s not something that every patient has the possibility of doing, so. But we are working on developing or building up a structure for providing such gene tests within the public sector, so it’s going to be better in the future, I guess.” (Policy expert).

**Practical recommendations from interviews to overcome challenges:
Eligibility criteria assessment**

Efforts should be made to increase the acceptance level of clinical trials amongst physicians so that patients can more easily discuss the option of a clinical trial with the treating physician.

Efforts should be made to facilitate communication between investigator and treating physician about the suitability of the patient and the coverage of cost of tests required in this pre-assessment.

4.7. FOLLOW-UP CARE

Another hurdle from a procedural point of view was linked to follow-up care for patients that have participated in a cross-border clinical trial.

Relevant issues with the follow-up of patients, potentially over several years and especially in oncology trials, was brought-up by Interviewees from most stakeholder groups but for different reasons.

Firstly, it was unclear how best to allocate responsibility for follow-up care. Normally, the healthcare system of the patient’s home country would have to monitor him/her once the clinical trials has finished or if there is long-term follow-up. However, it is possible that the home country does not possess an equal level of scientific expertise and/or specialized equipment available as the country where the trial had been performed. A policy expert even expressed the opinion that follow-up care has to be performed in all cases in the host country; however, this would also mean additional financial and logistical burden for the patient (e.g., having to relocate long-term to another country).

Generation of follow-up data for a clinical trial by the patient’s home country physician raises the question whether every physician/hospital performing this data generation, needs to be considered as clinical trial site with the related need for study approval by competent authority and ethics committee, national liability insurance, monitoring and national pharmacovigilance obligations. According to a Policy expert the current EU’ s regulatory clinical trial infrastructure is not enabling a pragmatic approach to such long-term third-party follow-up, neither on a national nor on a cross-border basis.

Thirdly, also follow-up care further brings up the question of reimbursement and allocation of financial coverage responsibilities. According to a patient representative, the home country health insurance system might refuse to fund follow-up care services for patients who had access to experimental treatment abroad. None of the Interviewees provided a concrete answer on how coverage of follow-up care could be regulated.

However, an industry representative expressed the opinion that the sponsor has a “*certain moral obligation*” towards the patient regarding follow-up care.

More specifically, physicians raised the need for accepting a certain degree of moral and ethical responsibility for the patient in form of a need for organising the follow-up care. Collaboration between the investigational site and the treating physician was identified as necessary. Several challenges to such collaboration were reported. Namely:

- The organisation and maintenance of communication between the two parties;
- Access to information and relevant training;
- Data generation according to the clinical trial protocol and delivery of the collected data to the study centre;
- Access to the electronic health record of the patient;
- The possibility that the standard drug for follow-up might not be available in the patient’s home country;
- The possibility that follow-up procedures might be in conflict with the patient’s home country healthcare rules.

Practical recommendations from interviews to overcome challenges:

Follow-up care

Investigators, sponsors, regulators and national healthcare system representatives should define a pragmatic framework for treating physician contribution to data collection in national and transnational clinical trials.

4.8. LEGAL AND REGULATORY REQUIREMENTS

Three legal and regulatory topics were considered as particularly relevant in the interviews:

- Strict regulatory rules and the need for safety surveillance in the conduct of clinical trials in general, and especially in early Phase clinical trials in vulnerable populations, require that all study procedures are performed at the investigational site, preventing the possibility of having at least part of the study supervision done in the patient’s home country.
- Lack of clarity about legally required roles, responsibilities and communication channels between Principal Investigator and treating physician in cross-border clinical trials create an environment of uncertainties and risks for physicians and patients that increase the burden and reduce the willingness to engage in such relevant options.
- Data protection rules (also explored in Theme 9): Physicians, Industry and Ethics Committee representatives reported that the application of the European General Data Protection Regulation (GDPR) constitutes an additional obstacle to the recruitment of foreign patients. More specifically, it seems it presents a challenge with respect to the eligibility assessment of the patient, prior to joining a cross-border trial (namely, when it comes to data sharing). In the words of a physician, “*Because, when the patient is on a trial, we get the information on-site, because we take blood samples and scans and imaging and electro-cardiograms, all the things, that we need, in order to find out if the patient is eligible. But if you have a cross-border patient, you would only invite a patient to our site, if you knew beforehand that this patient is eligible, if we could see this in the*

documents... . Another physician pointed to a lack of a proper systems for sharing information of patient data between Member States, which had been circumvented in their own clinical practice by assessing patients' eligibility on the phone, i.e. in a discussion with the treating physician in the home country by phone.

Practical recommendations from interviews to overcome challenges:

Legal and regulatory requirements

Rules, roles, responsibilities and communication in the collaboration between investigator and treating physician in cross-border clinical trial participation in the EU should be jointly defined by the involved stakeholders and published, e.g., in a guideline.

4.9. OBSTACLES PRESENTED BY ETHICS COMMITTEES

The interviews revealed that ethics committees have different requirements in different countries concerning the limitations in acceptable language of communication, specifically with respect to Informed Consent (as explained above, Topic 9: Part 2 Language barrier).

Ethics committees are responsible for protecting the patients in a clinical trial and therefore they are also reviewing the cost coverage conditions in the clinical trial; typically, they review the conditions of the liability insurance. But when there is the option of foreign patient enrolment they would need to review the conditions for reliable cost coverage for the patient in all aspects of the trial, in particular how can be ensured that also the standard healthcare costs of foreign patients and their follow-up healthcare costs back home are covered.

Finally, several participants commented on the lack of harmonisation of ethical frameworks in Europe and the burden this creates for enrolling foreign patients. It does not seem that the near future would present a solution to this issue. However, several participants expressed the view that enhanced information and communication with the relevant ethics committees of the investigators might help to ease the process of including foreign patients in clinical trials.

Practical recommendations from interviews to overcome challenges:

Obstacles presented by Ethics Committees

An ethical debate should be enabled between ethics committees from different Member States, investigators and patients on conditions for optimal protection of patients in cross-border clinical trials.

5. VULNERABILITY OF THE PATIENTS

Patients seeking access to cross-border clinical trials are mostly in vulnerable conditions due to their disease. The complexity of cross-border trial participation increases their vulnerability for several reasons as pointed out by most of the Interviewees.

- First, enrolling in a clinical trial abroad necessarily means having to go through a difficult decision-making process in many even existential aspects, e.g. employment and family issues. As already mentioned above, the patient and/or his carer might have to resign from work in order to be able to travel long-term. Moreover, it might be the case that the patient has to travel alone (i.e. without the support of his/her close ones), or has to accept family separation (i.e., one family member accompanies the patient, while others have to stay back home). The patient might have to accept

that the family invests all savings to enable his/her study participation. The choices that have to be made present a massive psychological burden in already psychologically and physically challenging times for the patient and his/her family. An apt illustration of such a situation was presented by an academic sponsor representative: *There is a challenge that the kind of cost constraints which exist are making that you do need to make choices. So, for instance, in the case of the leukaemia kid, they didn't have enough resources for the whole family to travel, so the Dad went with the kid, and Mum had to stay here because she had a baby to take care of and I think there the situation of the kid at the end of life, probably, with the whole family being split apart – I find it really tough.*"

- Second, vulnerability of the patient due to lack of moral and physical support from the familiar environment had to be stated as a separate point. Having to go through an experimental treatment in a mostly life-threatening condition, in a foreign country, far away from the loved ones, adds additional psychological burden.
- Third, the physical fragility of the patient. As pointed out by a patient representative: *"Obviously with some of these conditions, the affected person could be extremely frail, so the demands of visiting a remote centre in another country can actually be a disincentive to participating. And especially when you're dealing with children, very often there are other children in the family and you have a job... all those things which make difficult to...hop over to Berlin, or Stockholm, or wherever, for a bit, or on a regular basis."*

Practical recommendations from interviews to overcome challenges:

Vulnerability of the patients

The level of vulnerability and the personal burden of participation in a cross-border trial should be carefully and comprehensively assessed and weight against the benefit/risk balance of the envisaged clinical trial.

6. TRAVEL DISTANCE

All stakeholder groups emphasized the role that travel distance between the site and the patient's country of residence plays for patients' willingness to participate in a clinical trial abroad. Neighbouring countries see higher numbers of patients seeking to join a study cross-borders, whereas longer distances constitute a disincentive. The challenge of travel is closely linked to the cost's coverage, as the expenses for transport and accommodation are in most cases proportional to the distance between two countries. In addition, travel is also associated with the vulnerability of the patient. As stated by one physician, *"That's if you have six-month life expectance, I don't think you should use most of the time on travelling around for participation in clinical trial, unless it's a high probability for a long lasting response"*.

Practical recommendations from interviews to overcome challenges:

Travel distance

Clinical trials should seek reduction of patients' travel to the site by improving the options for remote data collection, e.g. enabling assessments made in the patients' home through electronic means, reduction of frequency and greater flexibility concerning visits at the site, etc.

7. CULTURAL BARRIERS

Patient and industry representatives brought-up cultural barriers as a possible challenge, however, not many concrete examples of such barriers were given. It can be broadly concluded that the Interviewees

meant general cultural differences between nations, either in the way people would perceive clinical trials, or in the way people would behave in any given social context, with the latter playing a role in the vulnerability of patients traveling abroad.

It is deemed relevant to include under the topic of cultural barriers an observation made by an industry representative regarding generational differences in the way cross-border access to clinical trials is perceived: *“I would guess, younger persons or a mother or father with a young kid, I just wonder if there could be a demographic relationship, who goes and who doesn’t go. Because if you are 80, maybe you are not looking to go through a very hard regimen in a clinical trial, showing up every week for a clinical trial”*.

8. BREXIT AND OTHER POLITICAL CONSTRAINTS

A challenge unique to patients aiming to join a trial open in the UK, or, alternatively, to UK patients attempting to join a study open outside of their home country, pertained to be particularly challenging and burdensome due to the ongoing uncertainty imposed by the political situation of the UK’s withdrawal from the EU (“Brexit”). A UK-based patient representative described the additional limitation of cross-border trial options due to this political situation.

The inequalities in political and healthcare systems in Europe were addressed in a subtle way by a number of Interviewees but one patient representative expressed it boldly: *“it really depends on where you are within Europe, within the European Union, how much access you will have to this possibility”* [referring to the possibility to join a clinical trial conducted abroad].

SURVEY

In the survey this topic was explored in a two-fold way. First, the opinions of survey respondents who have not tried to participate (or who have not tried to help a patient participate) in a clinical trial abroad were gathered, thus providing a theoretical insight into the challenges for cross-border access to clinical trials (Question 17). Second, the views of study respondents with practical experience were collected (Question 18). Below the results to both questions are presented separately, followed by presenting their correlation.³⁴

**QUESTION 17: PLEASE ANSWER THE FOLLOWING QUESTION IF YOU HAVE NOT TRIED YOURSELF TO GET ACCESS TO A TRIAL IN A DIFFERENT COUNTRY OR IF YOU HAVE NOT TRIED TO HELP A PATIENT TO GET ACCESS:
IN YOUR OPINION, DO THE FOLLOWING FACTORS PRESENT A CHALLENGE FOR THE CROSS-BORDER ACCESS TO CLINICAL TRIALS?**

53% (n=209) of all survey respondents (n=396) answered this question. Respondents were provided with a set of 13 pre-defined answers and could rate each of them by choosing “Agree”, “Disagree”, or “Neither agree nor disagree”. Not all of the 209 survey respondents selected an opinion for each of the provided challenges. Percentages showed below were calculated by using as denominator the number of individuals who rated each particular challenge.

A higher preference for “Disagree” was registered for only 2 of the challenges, namely:

³⁴ For detailed overview of percentages and numbers, see Annex IV

- “The patient’s lack of trust in the investigator proposing the clinical trial” (53% (n=106) of the respondents disagreed that this is a challenge, while 32% (n=63) stayed neutral and only 15% (n=30) agreed with the statement)
- “The patient’s lack of trust into the foreign country’s healthcare system” (44% (n=88) “Disagree”, 36% (n=72) neutral, 20% (n=39) “Agree”)

Only for one option study participants chose to stay predominantly neutral (42%, n=84), namely “Transport of the investigational medicinal product to the patient’s country of residence”, but it must be noted that 36% (n=71) agreed that this is a challenge.

Respondents predominantly agreed that all other 10 pre-defined answers describe challenges that patients would meet when trying to participate in cross-border clinical trials. In Figure 22 below these barriers are listed in a descending order of preference, based on the percentage associated with the option “Agree”. Figure 23 gives an overview of the results where the relationship between the options “Agree”, “Neither Agree nor Disagree”, and “Disagree” can be observed.

Figure 22. Challenges for the cross-border access to clinical trials (respondents without personal experience)

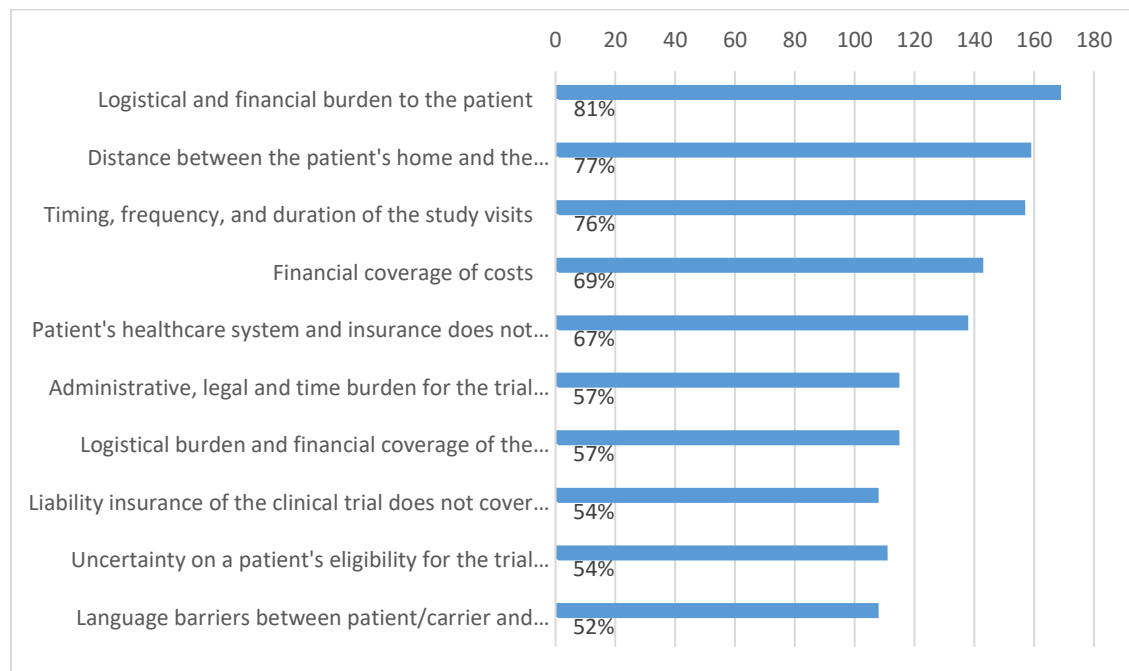
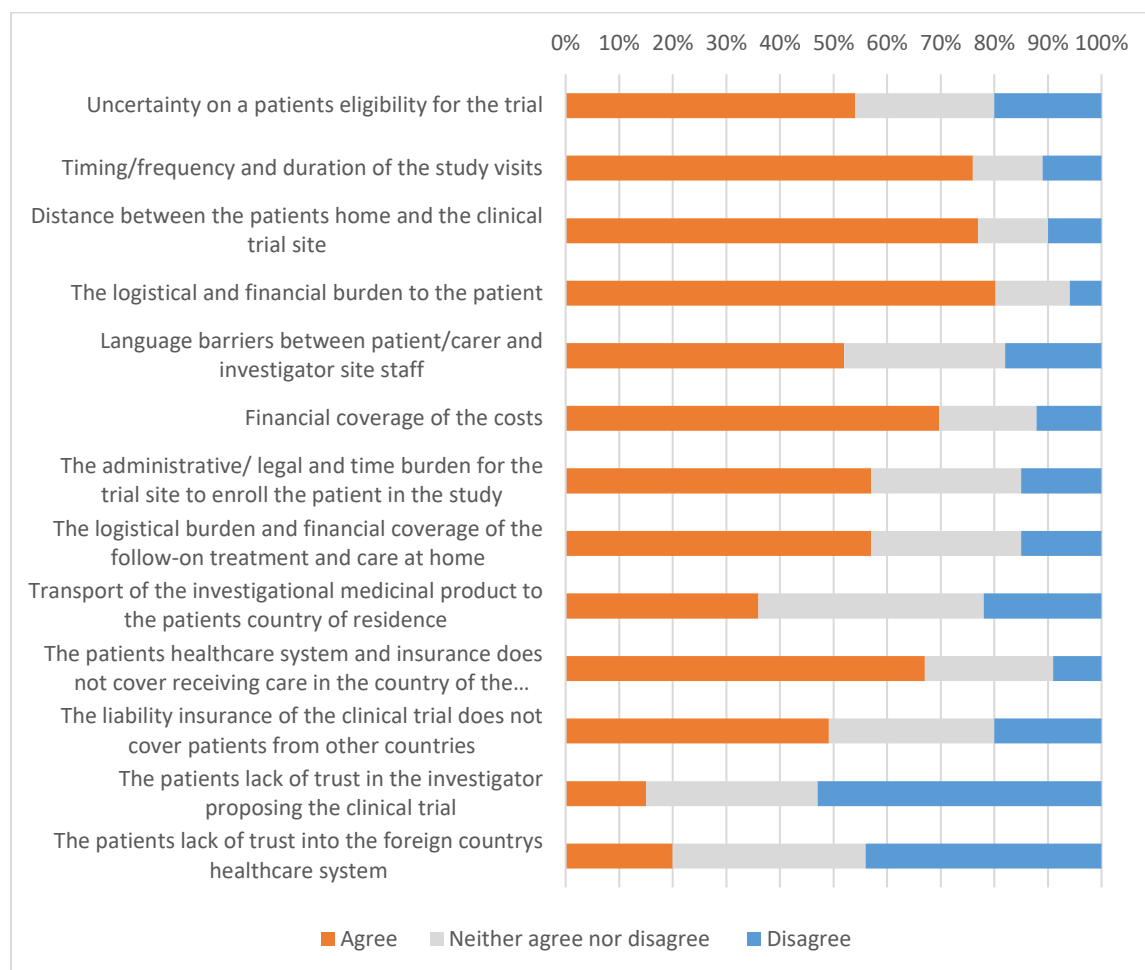


Figure 23. Complete overview of answers to Question 17



In addition, an open-ended option “Other” allowed study respondents to share challenges not included in the pre-defined list. Only 2% (n=5) of individuals chose to use this option and the majority of answers repeated the challenges specified under Question 17. Two provided additional insight, namely: “Acceptance of such by ethics committee, availability of all patient documents in several languages and skills by local ethics to review, approve and release such documents, different legal systems and requirements by the ethics and authorities” and “Psychological/emotional Support of the carers (immediate family)” [original spelling not changed].

QUESTION 18: IF YOU HAVE TRIED/MANAGED FOR YOURSELF TO ACCESS A CLINICAL TRIAL IN A DIFFERENT COUNTRY OR HELPED A PATIENT TO ENROL IN A CLINICAL TRIAL IN A DIFFERENT COUNTRY, WHAT WERE THE BARRIERS THAT YOU ENCOUNTERED?

34% (n=133) of all 396 survey respondents provided an answer to this question, hence self-declaring they possess practical experience with cross-border participation in clinical trials. They were provided with the same set of 13 pre-defined answers as the respondents to Question 17 and could also rate each option by choosing “Agree”, “Disagree”, or “Neither agree nor disagree”.

The theoretical and practical view on the challenges were similar to a large extent.

As in the case of Question 17, here too, a higher preference for “Disagree” was registered for only 2 of the challenges, namely:

- “The patient’s lack of trust in the investigator proposing the clinical trial” (57% (n=68) of the respondents disagreed that this is a challenge, while 33% (n=39) stayed neutral and only 10% (n=12) agreed with the statement)
- “The patient’s lack of trust into the foreign country’s healthcare system” (57% (n=68) “Disagree”, 31% (n=37) neutral, 12% (n=15) “Agree”)

Study participants chose to stay predominantly neutral (47%, n=56) for the same option as in Question 17 above, namely: “Transport of the investigational medicinal product to the patient’s country of residence”. The percentage of people who agreed that this is a challenge (26%, n=31) was almost the same as of those who disagreed (27%, n=32).

The respondents predominantly agreed that the 10 other pre-defined options are challenges (see Figure 24). In addition, Figure 25 gives an overview of the results where the relationship between the options “Agree”, “Neither Agree nor Disagree”, and “Disagree” can be observed.

Figure 24. Challenges for the cross-border access to clinical trials (respondents with personal experience)

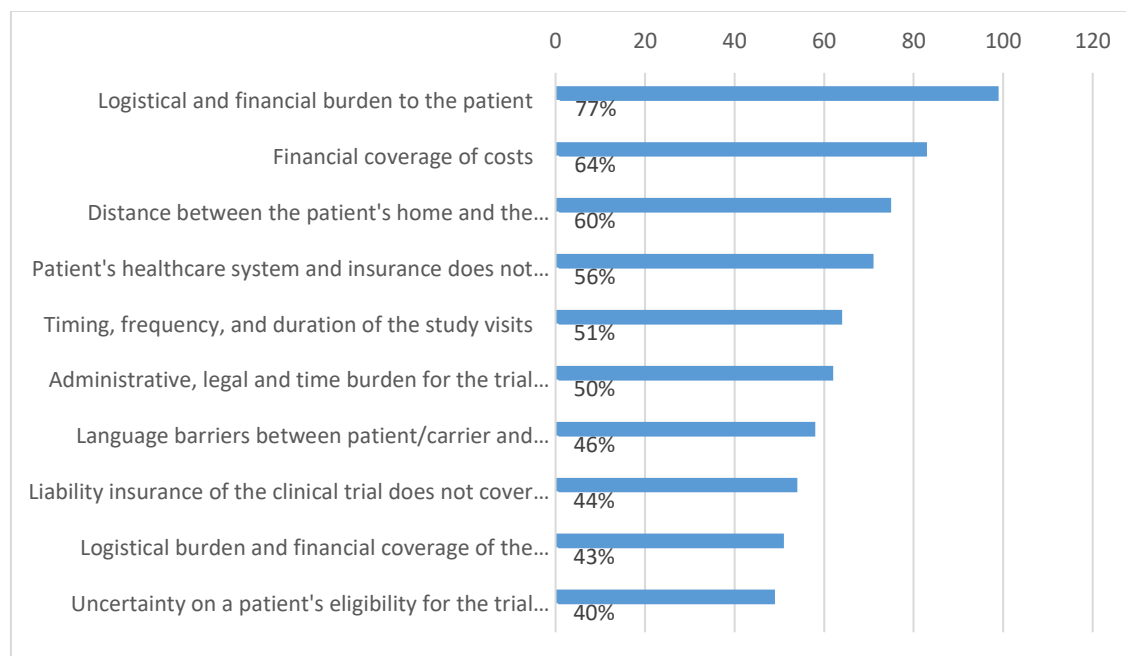
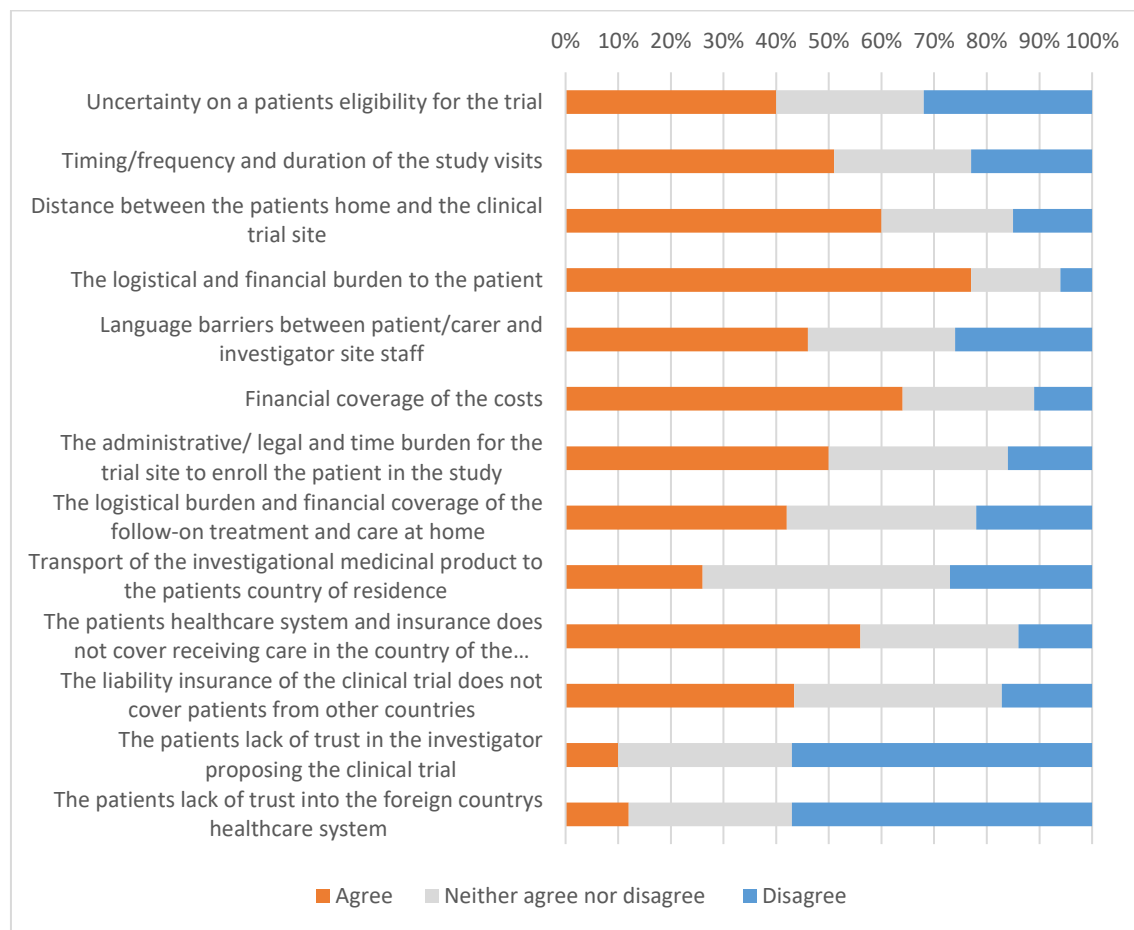


Figure 25. Complete overview of answers to Question 18



Here as well an open-ended box “Other” allowed respondents to share additional challenges they had faced when trying to participate in a trial abroad. 10% (n=13) of individuals provided an answer. Insights that differ from the pre-defined options included psychological burden for the patient (e.g., loss of employment and not being together with their carer), the patient’s home country healthcare system not being able to ensure appropriate follow-up, and obstacles created for the sponsor from ethics committees: *“The different language is a key factor to consider from the ethical perspective. Ethics committees require most of the times that a certified translator be present during the study visits to ensure an appropriate informed consent process and that GCP is followed during the trial (safety information given to the patient, etc). This poses the patient referral across countries almost impossible from the practical point. Additionally, even if the patient has a good understanding of the foreign language evidences are required by ethics committees which is most of the times not feasible to have. Additionally even when the certificate/evidence need is waived the informed consent form must be available in the native patient language; because informed consent forms require ethics committee review (GCP) even if we prepare one at full speed the ethics committee approval can take 30 days or more; most of the times the patient needs to start treatment and cannot cope to wait. From the sponsor perspective this piece is the one that really prevents cross-border”* [original spelling not changed].

COMPARISON BETWEEN THE THEORETICAL BARRIERS (QUESTION 17) AND THE CHALLENGES THAT PATIENTS ACTUALLY ENCOUNTERED WHEN TRYING TO ACCESS A CLINICAL TRIAL ABROAD (QUESTION 18)

The theoretical and practical perspectives were aligned when it came to disagreeing that “The patient’s lack of trust in the investigator proposing the clinical trial” and “The patient’s lack of trust into the foreign country’s healthcare system” are barriers to cross-border access to clinical trials and to staying neutral with regard to “Transport of the investigational medicinal product to the patient’s country of residence”.

The theoretical and practical perspectives were also in alignment with respect to what is the biggest hurdle, namely “The logistical and financial burden to the patient” (classified the highest according to the order of preference established in both sets of results). Agreement with respect “Distance between the patient’s home and the clinical trial site” (ranked third in Question 18 with 60 % “Agree” and second in Question 17 with 77 % “Agree”) was also shown.

It was observed that the relative percentages for the option “Agree” in comparison to choosing “Disagree” or “Neither agree nor disagree” were overall higher in the results to the theoretical Question 17 compared to Question 18. For instance, the challenge “The administrative, legal and time burden for the trial site to enrol the patient in the study” which was positioned on the 6th place in the order of preference for both questions, was assigned this place with 57 % for “Agree” in the case of Question 17 and 50 % for “Agree” in the case of Question 18.

KEY RESULTS: TOPIC 9

The interviews provided an in-depth look not only into the challenges that patients face when seeking to participate in a clinical trial abroad, but also into the challenges that investigators and sponsor have to address when setting forth to recruit foreign patients. In summary:

Challenges to participate in or organise cross-border clinical trials that recruit foreign patients

- Costs coverage (*also challenge for organising*)
- Language barrier (*also challenge for organising*)
- Lack of information
- Procedural challenges:
 - reimbursement constrains (*also challenge for organising*)
 - investigational site not willing to recruit foreign patients
 - lack of treating physicians’ motivation to refer patients to a clinical trial (*also challenge for organising*)
 - navigating the foreign healthcare system
 - lack of an appropriate system for patient referral
 - eligibility criteria assessment
 - follow-up care (*also challenge for organising*)

Specific procedural challenges for organising clinical trials that recruit foreign patients

- legal and regulatory procedure
- obstacles presented by ethics committees
- Vulnerability of the patients
- Travel distance
- Cultural barriers
- Brexit and other political constrains

In comparison, the survey contained responses addressing both patients and the organisation of foreign patients' recruitment (e.g., "The administrative, legal and time burden for the trial site to enrol the patient in the study"). However, unlike the interviews, it compared the theoretical opinion of participants who have not tried to access a trial abroad to the view of individuals who have tried or managed to access a trial abroad and showed that they were in alignment.

Overall, the barriers mentioned in the interviews were confirmed by the study results. In particular, the logistical and financial burden to the patient was unanimously ranked highest. Additional important insights that came solely from the interviews included: a detailed look into the procedural challenges, the lack of information, the vulnerability of patients, cultural barriers, and Brexit and other political constraints. Specifically, in the case of lack of information, the interviews highlighted that this was among the biggest constraints for regular cross-border access to clinical trials.

Interestingly, the language barrier (which was the challenge most frequently mentioned by Interviewees, only second to cost coverage) was ranked the lowest in the results of the theoretical Question 17 and only 7th (out of 10 challenges) in the results of the practical Question 18.

Conclusion:

As shown by both survey and interviews, the barriers to cross-border access to clinical trials are numerous and touch upon very divergent fields. A principle improvement of the situation would require the development of a comprehensive framework.

TOPIC 10: STUDY PARTICIPANTS' OPINIONS ON THE STATEMENT "CROSS-BORDER ACCESS TO CLINICAL TRIALS IS NEEDED OR NOT NEEDED"

This research project aimed also at investigating whether the different stakeholders consider cross-border access to clinical trials as an option relevant to have or not.

INTERVIEWS

The topic was explored under

QUESTION 15: FOR THE FOLLOWING STATEMENT, PLEASE COMPLETE THE PHRASE WITH YOUR OPINION ON CROSS-BORDER PARTICIPATION IN CLINICAL TRIALS IN EUROPE:

CROSS-BORDER PARTICIPATION IN CLINICAL TRIALS IN EUROPE IS NEEDED/NOT NEEDED BECAUSE...

The majority of participants (from all stakeholder groups) agreed that cross-border access is needed. In the words of a physician: *"There is a need for the Member States to collaborate and for the citizens to have access to everything that is visible in the European Union. This is exactly the meaning for me of European Union: to be together to help ourselves and to work together"*. However, also according to the majority, in an ideal situation, patients would not have to travel in order to access experimental treatment.

The reasons why it is needed were to a large extent similar to the ones presented in Topics 5 and 6.

Caution was raised regarding the possibility that if cross-border access to clinical trials were regulated and facilitated across the EU it might be "wrongly diverted" (an academic sponsor representative). In particular:

“It is very easy to say our clinical trial is only open in these three huge centres, and actually the economic incentive can be potentially not only for the clinical trial sponsor, but actually for the centres as well, and so there is also a kind of risk that some centres will almost make their business out of it, because of course their income is somehow related to the number of patients, whether paid by sponsor or even by healthcare system”. A possible precaution measure would be to establish certain limitations (“it is needed in very specific situations”). For more information about the stakeholders’ views regarding limitations, see Topic 11 below.

In addition, a number of participants provided a counter-argument to the idea that cross-border access is needed: more specifically, they stated that the main aim should be to bring the clinical trials closer to the patient, either by opening sites in more countries, or by facilitating the regulation of remote/decentralized clinical trials (as directly expressed by 3 of the physicians, 2 of the pharmaceutical industry representatives, 1 of the Ethics Committee representatives, and 1 of the policy experts. Regarding the opening of clinical trials across the EU, in the words of a physician: *“regulatory procedures between countries are very different: they can be extremely slow in some countries, and then what we see as a consequence of that, is some pharmaceutical companies not willing to open their trial in some countries, which is going to deeply affect then patients from that country; the ethics committee approvals are still extremely different from one to the other, and that is again, detrimental for patients, because I think if you live in a country where the system is effective and fast, you will have better chances to access very important drugs”.*

Some participants provided a more nuanced opinion by speaking of the need to find a suitable equilibrium for action that would include both facilitating cross-border access to clinical trials, on the one hand, and opening sites in more EU Member states, on the other hand. As described by a physician: [cross-border access] *“it’s absolutely needed, absolutely. But, it’s not the entire solution to the problem, it’s part of the solution, but it’s only one part of the solution. We need additional measures and solutions.* In the words of a policy expert: *“I think that both increased multi-centre trials are needed and also an increased exchange of patients between the different countries”.* According to a patient representative: *“when the framework is more harmonised for clinical studies, crossing borders only happens if patients are really desperate to take the extra load and I don’t think the numbers are so high”.*

Finally, the answer provided by one industry representative provided a further detailed overview of the issues at stake and the high complexity of the question whether or not cross-border access is needed: *“I am going to say, from whose perspective? If it’s a patient that can’t get access to a drug, that could provide a lifetime of survival, then of course it’s needed. But I think what I would like to say here is that there is no easy answer to that question. Are we making general statements? I don’t think there can be a very easy general statement as to whether it’s needed. I think the way it’s done presently is by not using cross-border collaboration, it’s more done by opening sites in that country. And that becomes a financial issue as well, so could that be improved upon? Potentially, yes. I am not sure that I know the answer as to whether it’s needed or not. I think we look from to you as the academic, and you as the patient advocates, to tell us if it’s needed. We can tell you how much funding we have to support it in a clinical trial setting and then I think you need to make a hard judgement, like a budget, it’s like, well, how much do you put towards supporting this type of effort versus, opening sites in that country?” (...)* *“I think real discussion for me is whether you want cross-border clinical trials versus opening sites in each individual country. An then, comparing the merits of it, the pros and cons, but doing it objectively, because the way I would see it is that any cooperative group, that, has the ability to work in many countries would favour cross-border collaboration, right?”*

SURVEY

The topic was explored under:

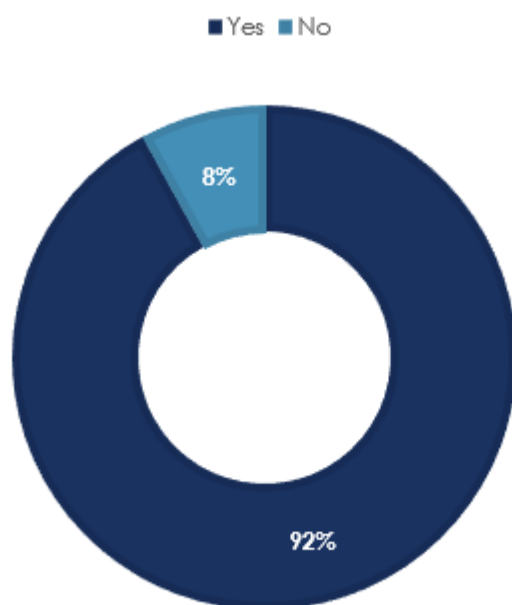
QUESTION 19: PLEASE INDICATE WHAT DO YOU THINK ABOUT THE FOLLOWING STATEMENT:

CROSS-BORDER PARTICIPATION TO CLINICAL TRIALS IN EUROPE IS NEEDED.

Study participants could choose between two options: “I agree” or “I disagree”.

77% (n=304) of the survey participants responded to this question. Of them, 92 % (n=279) agreed with the statement and only 8 % (n=25) disagreed (see Figure 26).

Figure 26. Cross-border participation in clinical trials: needed or not



Disagreement came from 25 study participants, of which 84% were from Western European countries. The majority of negative answers were from the UK (25%, n=6), France (16%, n=4), Spain (12%, n=3), Germany (8%, n=2), The Netherlands (8%, n=2), and Portugal (8%, n=2). In addition, only three stakeholder groups were represented in the negative answer, namely investigators/physicians (60%, n=15), commercial or academic sponsors of clinical trials (20%, n=5), and Ethics Committee (4%, n=1).

The reasons why study participants agreed or disagreed with the statement “Cross-border participation in clinical trials is needed” were explored in Question 20 and 21 respectively.

QUESTION 20: IF YOU AGREED IN QUESTION 19, PLEASE SELECT THE REASON(S) FOR WHICH, IN YOUR VIEW, CROSS-BORDER PARTICIPATION IN CLINICAL TRIALS IS NEEDED IN EUROPE

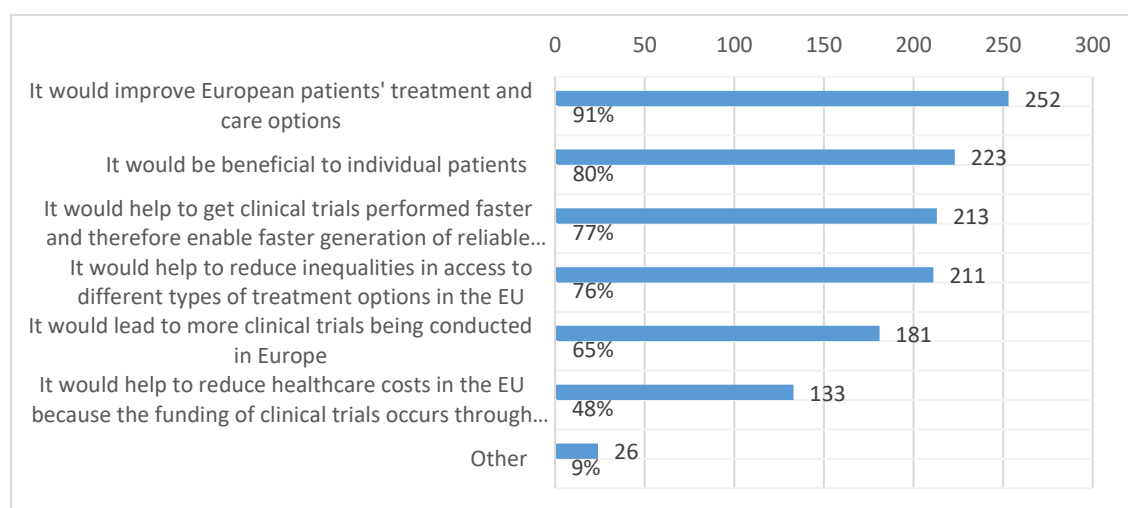
70% (n=278) of all 396 study respondents answered this question.

Question 20 had 6 pre-defined answers and provided the option “Other” in case respondents wanted to share additional reasons. Study participants could select more than one answer. In Figure 27 below the answers are shown in a descending order of preference based on the number of responses each of them received.

“It would improve European patients’ treatment and care options” received the highest number of responses (91%, n=252). The reasons ranked second, third and fourth deemed equally important to study participants, as the number of responses assigned to them was almost the same:

- It would be beneficial to individual patients (e.g., by prolonging their life, providing them with better quality of life, or curing them) (80%, n=223)
- It would help to get clinical trials performed faster and therefore enable faster generation of reliable data (77%, n=213)
- It would help to reduce inequalities in access to different types of treatment options in the EU (76%, n=211)

Figure 27. Reasons for which cross border participation in clinical trials is needed in Europe



9% (n=24) of respondents selected the “Other” option. The answers provided mostly emphasised on the importance of cross-border access to clinical trials in the case of rare cancers and orphan diseases (37%, n=9). Other answers focussed on the access of patients and ensuring a balanced participation from small countries and countries in Eastern Europe (21%, n=5) or concerned the opportunity of an increased number of participants in clinical trials, reduced costs, and the image advantage for the European Union.

The answers provided to Question 20 were correlated with the answers to Question 1 in order to understand whether there was a difference in opinion between survey respondents from different countries (see Table 7). Respondents from all four European regions were in agreement that the most important reason for needing cross-border access to clinical trials was “It would improve European patients’ treatment and care options” (in the case of Eastern Europe, this answer received the same number of responses as “It would be beneficial to individual patients”). However, there were differences in the ranking of the other pre-defined answers. For instance, while for study respondents from Western Europe the second most important reason “It would be beneficial to individual patients” (76%, n=84), for respondents from Southern Europe second came “It would help to reduce inequalities in access to different types of treatment options in the EU” (85%, n=58) and only fourth in the general ranking) and for respondents from Northern Europe second came “It

would help to get clinical trials performed faster and therefore enable faster generation of reliable data” (86% (n=44) and third in the general ranking).

Table 7. Distribution of answers based on the country of affiliation of those who agreed that cross-border participation in clinical trials is needed in Europe

<i>Country</i>	<i>N Subjects</i>	<i>N Choices</i>	<i>It would improve European patients' treatment and care options</i>	<i>It would help to reduce inequalities in access to different types of treatment options in the EU</i>	<i>It would lead to more clinical trials being conducted in Europe</i>	<i>It would be beneficial to individual patients</i>	<i>It would help to get clinical trials performed faster and therefore enable faster generation of reliable data</i>
Eastern Europe	29	121	28 (96.6%)	24 (82.8%)	18 (62.1%)	28 (96.6%)	23 (79.3%)
Northern Europe	51	214	48 (94.1%)	43 (84.3%)	37 (72.5%)	42 (82.4%)	44 (86.3%)
Southern Europe	68	263	63 (92.6%)	58 (85.3%)	43 (63.2%)	51 (75.0%)	48 (70.6%)
Western Europe	110	407	98 (89.1%)	73 (66.4%)	69 (62.7%)	84 (76.4%)	83 (75.5%)
Row (Q1 region)=Country Column (Q20)=If you agreed in Question 19 please select the reason(s) for which in your view cross-border participation in clinical trials is needed in Europe Total number of subjects (N=278)							

QUESTION 21: IF YOU DISAGREED IN QUESTION 19, PLEASE SELECT THE REASON(S) FOR WHICH, IN YOUR VIEW, CROSS-BORDER PARTICIPATION IN CLINICAL TRIALS IS NOT NEEDED IN EUROPE

9% (n=34) study respondents answered this question. Note, however, that only 6% (n=25) selected “I disagree” to Question 19.

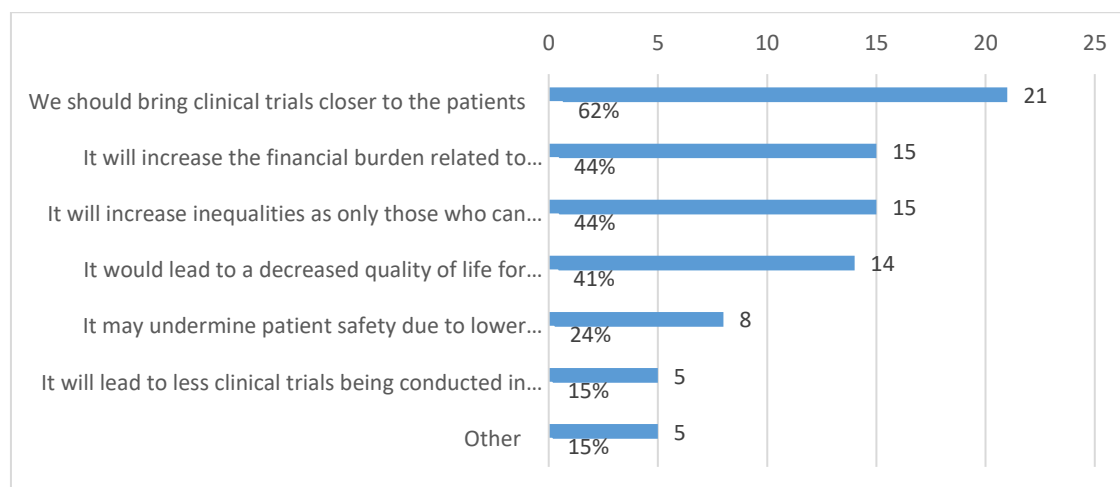
Question 21 had 6 pre-defined answers and provided the option “Other” in case respondents wanted to share additional reasons. Study participants could select more than one answer. In Figure 28 below the answers are presented in a descending order of preference based on the number of responses each of them received.

“We should work to bring clinical trials closer to the patients (i.e. more sites opening in more EU countries), instead of having patients travel in order to participate in clinical trials” received the highest number of responses (62%, n=21). Study participants equally ranked the reasons in second, third and fourth position, as the number of responses was almost the same:

- It will increase the financial burden related to receiving healthcare (e.g. due to the additional costs for travel and accommodation) (44%, n=15)
- It will increase inequalities as only those who can afford to travel will be able to access clinical trials abroad (44%, n=15)
- It would lead to a decreased quality of life for individual patients (for reasons such as being away from their family, anxiety linked to being treated in a foreign setting, etc.) (41%, n=14)

Only 15% (n=5) of the individuals who responded to this question thought that cross-border access to clinical trial is not needed because it will lead to less clinical trials being conducted in Europe.

Figure 28. Reasons for which cross-border participation in CTs is not needed in Europe



15% (n=5) OF respondents selected the “Other” option. The answers included the opinion that a fair distribution of clinical trials throughout all EU Member States will facilitate better access; the opinion that it is impossible to reconcile the disparate healthcare systems; the opinion that the language barrier would prevent doctors to communicate safely with patients from other countries.

The answers provided to Question 21 were correlated with the answers to Question 1, in order to understand whether there was a difference in opinion between survey respondents from different countries (see Table 8). Respondents from all four European regions were in agreement about the most important reason for not needing cross-border access to clinical trials (“We should work to bring clinical trials closer to the patients”). One of the reasons ranked second in the general ranking (“It will increase the financial burden related to receiving healthcare”), was also put second in the rankings of respondents from Southern and Western Europe, however, no respondent from Eastern Europe selected it at all.

Table 8. Reasons for which cross border participation in CTs is not needed in Europe

Country	N subjects	N choices	It will increase the financial burden related to receiving healthcare	It will increase inequalities as only those who can afford to travel will be able to access clinical trials abroad	It will lead to less clinical trials being conducted in Europe	It would lead to a decreased quality of life for individual patients	It may undermine patient safety due to lower standards of care in other countries than the country of residence	We should work to bring clinical trials closer to the patients	Other
Eastern Europe	2	5	0 (0.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	2 (100.0%)	0 (0.0%)
Northern Europe	7	24	4 (57.1%)	4 (57.1%)	1 (14.3%)	5 (71.4%)	3 (42.9%)	5 (71.4%)	2 (28.6%)
Southern Europe	5	11	3 (60.0%)	2 (40.0%)	0 (0.0%)	1 (20.0%)	1 (20.0%)	4 (80.0%)	0 (0.0%)
Western Europe	9	36	7 (77.8%)	7 (77.8%)	2 (22.2%)	6 (66.7%)	4 (44.4%)	8 (88.9%)	2 (22.2%)
Western Asia	1	5	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
South-America	1	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)

Row (Q1region)=Country
Column (Q21)=If you disagreed in Question 19 please select the reason(s) for which in your view cross-border participation in clinical trials is not needed in Europe
total number of subjects (N=25)

Per row, the percentages are calculated with the number of subjects as denominator. Since Q21 is not mutual exclusive, these percentages do not add up to 100.

KEY RESULTS: TOPIC 10

In the interviews, the majority of participants agreed with the statement that “Cross-border access to clinical trials is needed”. This was strongly confirmed by 92% (n=279) of the survey participants who responded to the question.

The interviews provided reflections on this statement. In summary:

- In an ideal situation, patients would not have to travel in order to access experimental treatment
- Cautions were raised that if facilitated, cross-border access might be wrongly diverted
- A counter-argument to the statement “Cross-border access to clinical trials is needed was provided, namely that the main aim of key stakeholders should be to bring clinical trials closer to the patient and thus alleviate the need for cross-border access
- According to some, the most suitable course of action would be achieving both aiming to facilitate cross-border participation AND opening sites in more EU Member States

The survey data provided information on the countries of residence of the stakeholder groups that disagreed with the statement. The majority of such answers come from the UK, France, Spain, Germany and Portugal. All of these countries (with the exception of Portugal) were shown to be among the countries that are most attractive for patients seeking to participate in a clinical trial abroad (see Topic 7). In addition, the majority of negative responses came from Investigators/Physicians and Sponsors, but none was from a patient.

In the interviews there was overlap with motivations stated in Topics 5 and 6 concerning the existing need for cross-border access to clinical trials. According to the survey results, the most important reason was because “It would improve European patients’ treatment and care options”. On the other hand, the survey data about reasons why it was not needed provided confirmation to one of the main points raised in the interviews, namely, “We should work to bring clinical trials closer to the patient (i.e. more sites opening in more EU countries), instead of having patients travel in order to participate in clinical trials”.

Conclusions:

92% of all research participants in the interviews and survey underlined the need for cross-border access to clinical trials because this improves European patients’ treatment and care options, but also because it would allow to perform clinical trials faster and reduce inequalities.

The small number of negative responses, (all from investigators/physicians, sponsors and Ethics Committee, none from patients) came from Western European countries and focused on preference for broader distribution of sites, stronger efforts to bring the trials to the patients’ home but also on the fear that this option increases burden and inequalities.

TOPIC 11: STUDY PARTICIPANTS’ OPINIONS REGARDING WHETHER CROSS-BORDER ACCESS TO CLINICAL TRIALS SHOULD BE LIMITED

To provide a more detailed view on the scope of the need for cross-border access to clinical trials the opinion on possible limitations of this option was investigated.

INTERVIEWS

The topic was explored with:

QUESTION 16: IN YOUR OPINION SHOULD CROSS-BORDER PARTICIPATION TO CLINICAL TRIALS BE LIMITED?

and

QUESTION 17: WHY SHOULD IT/SHOULD IT NOT BE LIMITED?

The number of references made to limitations and no limitations was almost equal, with a very slight preference expressed for no limitations, however, patient representatives were primarily in favour of no limitations at all.

Certain limitations were proposed primarily by physicians. It was argued that the opportunity for cross-border access should be regulated and facilitated for early phase clinical trials, for rare diseases, for trials where gene testing is involved (precision medicine). In the words of a physician, *“it is only for quite specific subgroups that a cross-border invitation will be a benefit for the patient”*.

Another proposed limitation, not linked to disease area, was proposed by a physician: *“if the trial is open somewhere in the country, where the patient is, then prioritise this patient to this city in his own country, rather than travelling away for this”*.

Other limitations included facilitation on a case-by-case basis only (whereby first an expert opinion by a group of physicians would have to be provided); facilitation for neighbouring countries on the basis of bilateral agreements; facilitation only in cases where there is no treatment available in the home country of the patient.

Finally, an Ethics Committee representative and a patient representative expressed the opinion that while there is no need for externally imposed limitations, the cross-border access to clinical trials would inevitably go through a kind of “self-regulation”. Namely, in the words of a patient representative, *“I somehow doubt that people would go to that length for something that is not really important. So, I would believe that there is a self-regulation in place: you only do it when you’re desperate”*.

SURVEY

QUESTION 22: IN YOUR VIEW, SHOULD CROSS-BORDER ACCESS TO CLINICAL TRIALS BE LIMITED?

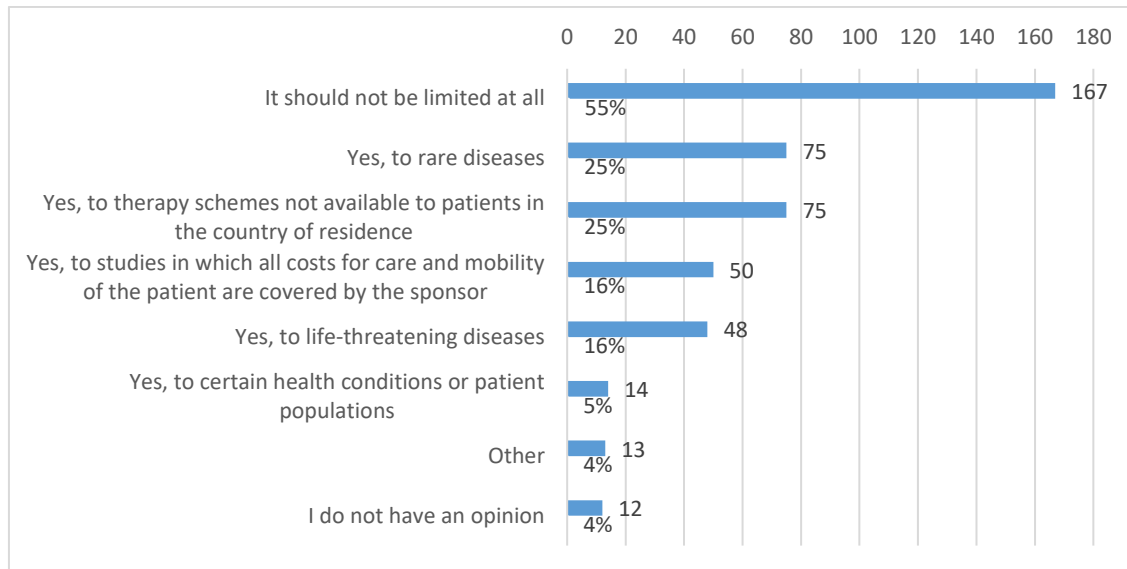
The question provided seven pre-defined answers: “No limitation”, five options for limitations, “No opinion” as well as the option “Other”. Study respondents could select multiple answers.

77% (n=304) of all survey respondents answered this question. In Figure 29 the answers are shown in a descending order of preference based on the number of responses received. The opinion that cross-border access to clinical trials “should not be limited at all” received a significant number of responses (55%, n=167). However, when the responses on limitation options were combined, a higher preference for imposing limits on cross-border access was observed (total n=262 of selections made for the various positive answers). Among the concrete suggestions for limitations, the answers “Yes, to rare diseases” and “Yes, to therapy schemes not available to patients in the country of residence” collected an equal number of responses (25%, n=75). The least frequent answer selected was “No opinion” (4%, n=12).

Answers were provided under the “Other” option (4%, n=13) as well. Some of them were in agreement with the pre-defined answers to this Question 22. Others included the following comments:

- “Any limitation is a tacit expression of inequality across the EU”
- “It should evolve, starting with rare and threatening diseases but eventually become applicable to all”
- “No, but should be the exception. Only for cases well documented and justified.”
- “This has to be considered case-by-case basis depending on balance between benefits and risks to trial participants”
- “When a patient is living in Rosenheim/Bavaria, what is the difference between Munich and Vienna? Why should he go to Munich, when his healing process would be better in Vienna?”

Figure 29. Opinion on the limitation of cross border access to clinical trials



KEY RESULTS: TOPIC 11

Overall in the interviews, a very slight preference for no limitations was reported, however, no patient respondent was in favour of any limitations, whereas primarily physicians expressed support to limitation to specific situations. Study participants’ opinions included that cross-border access to clinical trials should be limited to:

- Early phase clinical trials
- Rare diseases
- Precision medicine clinical trials
- Clinical trials that do not have an open site in the patient’s home country
- Neighbouring countries
- Cases where no treatment is available in the patient’s home country

Two of the Interviewees were of the opinion that cross-border participation in clinical trials would “self-regulate”.

In the survey, there was a strong support for no limitations (55%, n=167), but the combined number of responses for different limitations was higher (n=262). The ranking of pre-defined options in the survey closely resembled the limitations that were shared by Interviewees, namely that cross-border access should be limited to:

- Rare diseases (55%, n=75)
- Therapy schemes not available to the patients in the country of residence (55%, n=75)
- Life-threatening diseases (16%, n=48).

The Interviewees did not discuss the limiting option offered in the survey “Studies in which the costs for care and mobility of the patient are covered by the sponsor” (16%, n=50).

Conclusions:

No limitation was clearly preferred in the survey, however, considerations on offered limitation options and comments made in the interviews gave a more balanced view. Limitation to rare diseases or when there is no suitable treatment option in the patient’s country could thus be considered.

TOPIC 12: STUDY PARTICIPANTS’ OPINIONS ABOUT ALLOCATION OF RESPONSIBILITY REGARDING LOGISTICS

Handling the logistics of cross-border clinical trial participation is one of the major challenges reported by patients and investigators. This topic aimed at learning about opinions on who should take responsibility for managing the logistics.

INTERVIEWS

This theme was specifically explored under:

QUESTION 18: “IN YOUR OPINION WHO SHOULD BE ORGANISING THE LOGISTICS OF STUDY PARTICIPATION OF PATIENTS COMING FROM ABROAD?”

Study participants gave highly divergent answers to this question; hence it was hard to provide an order of preference regarding the options listed below. However, reference should be made to the survey (see below) where the results provided a concrete basis for prioritisation.

The question of logistical support inevitably touched upon the issue of allocation of responsibility for cost coverage as a significant number of the solutions proposed concerned the involvement of a third party (e.g., a CRO or a special navigator) which would require remuneration for these services.

By the term “logistics” Interviewees understood several issues, namely:

a/ provision of relevant information regarding the organisation of the cross-border participation (e.g., in the words of an academic sponsor representative, “*It’s not about the travel, but it’s about what does it mean to go abroad, what documents you will be asked when you arrive*”);

b/ psychological support for the patient and their family;

c/ all other relevant support, e.g., finding suitable accommodation abroad, navigating the foreign healthcare system, etc.

There was a general agreement among the stakeholders that the burden of organising logistics should not be left to the patients (in the words of an industry representative, “*we need to put the patient’s interest at the centre*”).

Following solution frameworks for allocating responsibility for managing the logistics were proposed in the interviews:

I. Variations on a joint support approach

- **Joint support provided by both involved countries.**

For instance, in respect to the patient's home country: *"the one that refers could already instruct the patient about different things they need to think about, I mean "you need to do this with your insurance," standard check list, like some travel agencies do"* (an academic sponsor representative). In respect to the host country responsibility, the same participant stressed that for routine healthcare there are already institutions *"which more and more organise this thing (...)– for instance in Belgium, I know several institutions that build buildings, specifically for kids, for instance – they built a house where parents can stay. So it's not a hotel – there are costs – but it's a house where they stay. And so they can see the kids, when kids can go out, they can also go there. So it's like a notion about patients have family around them"*.

Several participants expressed that responsibility should be allocated specifically to the hospitals at which the patient is treated in both the home and the host country. However, it was also acknowledged that the hospitals already face a high number of challenges and are struggling to provide support in general, e.g. in the words of a physician: *"one would wish that the hospitals could provide that support. So, ideally, the hospital should be able to help with that. I think there are, I understand that the public hospitals have a lot of need and they do need to provide psychosocial support for their own patients, which they are still not providing in full"*.

- **Joint support provided by both countries in collaboration with the ERNs.**

A role for the ERNs was strongly supported. In the words of an academic sponsor representative, they should be *"the actual privileged hubs for clinical research"*. However, Interviewees also acknowledged that at the current moment the ERNs do not have the required resources that would allow active participation in cross-border clinical trials. In the words of a physician: *"I would definitely think that this is the role of the ERN, if you provide means. To strengthen that, currently, we absolutely do not have any means to do that, and that's a pity."*

- **Joint support provided by the home country in collaboration with other interested stakeholders (e.g. patient organisations, CROs).**

According to a physician, the first point of contact for patients should be *"a single point of call"* at the treating hospital, while all subsequent steps from a logistical point of view should be covered in collaboration with patient organisations. According to an industry representative, *the collaboration must be even broader, involving all interested stakeholders: "Certainly, I would expect that the National Contact Points would take even more responsibility in facilitating, that there is a public recognition that this is an issue that needs to be tackled jointly. I see a need to involve, also to train and equip CROs in this area as well and to expect companies to be more inclusive and to involve, and to make an effort to involve patients from other countries"*.

II. Support provided solely by the patient's home country

For example, one physician said: *"ideally it should be the country where this patient lives and takes care of all this stuff for the patient. That would be the ideal thing. That somebody or some group from the government takes it's --this responsibility"*. Another physician further spoke about the Norwegian experience at the current moment. In particular, he expressed support for the *"centralised"* system that involves setting up a so called *"foreign office"* in the treating hospitals which organises the travel and accommodation and takes care of the insurance guarantee that the receiving hospital might require.

According to them, *“I think it has to be a sort of official way to send the patients, it should not be up to each responsible clinician to find those studies and send patients”*.

In addition, some participants were in favour of allocating the logistical support to the patient’s home country National Contact Point, specifically when it comes to provision of relevant information. However, it was discovered that NCPs are not motivated to take upon such role. According to a patient representative, they are *“resistant to this, because they say it’s not their job”*.

It is relevant to provide here the comments from the only NCP that agreed to an interview. This person confirmed that patients sometimes seek information from them in relation to clinical trials, with a focus on advanced therapy medicinal products (ATMPs). However, this study participant was of the opinion that the responsibility for organising logistical support should be allocated to the sponsor of the clinical trial. All other existing NCP in the EU did not respond to the interview invitation or declined the invitation because they neither have experience nor responsibility in clinical trials.

III. Support organised by the sponsor

Some participants (NCP representative, six of the patient representatives, one policy expert, and one physician) stated that responsibility should be allocated to the sponsor, without going into further details as to the way the logistics would be organised in practice. Several arguments were put forward. According to a patient representative: *“I think if you want to have patients in the study, you have to take the responsibility to keep the patients in the study”*. This sentiment was echoed in the view of another patient representative according to whom the sponsors have *“the highest interest in it to work”*. The main focus in the justification of a third patient representative was with respect to the fact that sponsors are *“more present in these locations or have a higher degree of influence than CROs do”*.

According to other participants (Ethics Committee representative, patient representative, policy expert) the support should be provided by a CRO financed by the sponsor.

IV. Support organised by a “special navigator”

Several participants talked about the need to establish the support by a “special navigator”. As illustrated by a patient representative: *“I would love to see every patient who can access a cross-border clinical trial to have some sort of navigator. You know, a specifically defined person and appointed person from their multidisciplinary team in their original treating hospital, who can actually manage this process for them”*.

Several opinions were expressed about who should finance such a navigator. According to a patient representative, financing could be provided either by the healthcare system in the patient’s home country, or by the sponsor.

One policy expert saw a role for “committees of clinical trial navigators” in each country. In their view, such committees should be working in close collaboration with patient organisations, educated by the patients’ advocacy groups.

V. Support organised at EU level

A final proposal that emerged from the interviews suggested that logistics should be organised at EU level, especially when it comes to academic trials. However, almost none of the Interviewees who spoke about this possibility suggested any specific details for implementing the idea in practice.

One physician supported the idea that in the cases of industry-sponsored trials, the sponsor should be responsible, while in the case of academic trials the logistics could be organised on a central EU level by the EORTC, or an organisation similar to EORTC.

The same idea was expressed by another physician: *“In the EU an EORTC-organised group, that could probably be good”*, and further supported by an industry representative: *“of course, it should be managed at the European level, but which part of Europe and or what type of European organisation should do that, would it be EORTC, I mean, I don’t know”*.

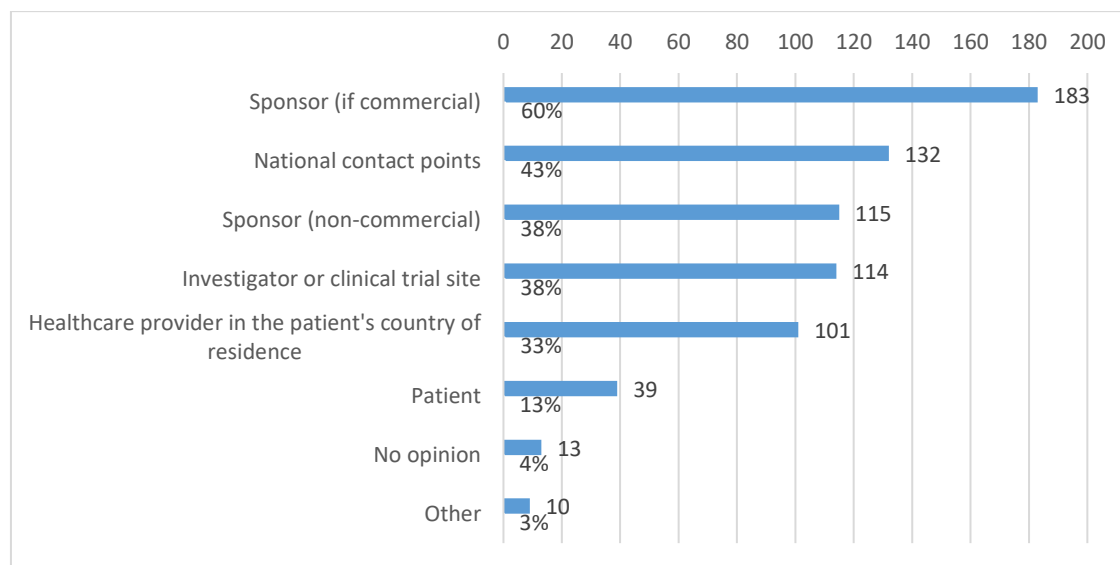
SURVEY

QUESTION 23: IN YOUR VIEW, WHO SHOULD ORGANISE THE LOGISTICS OF CLINICAL TRIAL PARTICIPATION OF PATIENTS COMING FROM ANOTHER COUNTRY?

The question had seven pre-defined answers (including “I do not have an opinion”) and provided the option “Other”. Study respondents could select multiple answers.

77% (n=304) of all survey respondents answered this question. In Figure 30 below the answers are shown in a descending order of preference based on the number of responses each of them received. Highest ranked was the commercial sponsor (60%, n=183), followed by National Contact Points (43%, n=132). Non-commercial sponsors only came at third place (38%, n=115) and received almost the same number of responses as investigators/clinical trial sites (38%, n=114). There was an agreement among respondents that the burden of organising logistics should not be allocated to the patients (only 13% (n=39) of responses were provided for this option).

Figure 30. Opinion on the responsibility to organise the logistics of clinical trial participation abroad



Of the responses, only 3% (n=10) were recorded for the “**Other**” option. The proposed solutions included:

- All stakeholders should be responsible
- This matter should be regulated on EU level
- Patient organisations should be responsible

- The referring physician together with the accepting site
- The European Reference Networks should be responsible

The correlation between the answers to Question 23 and the results of Question 2 (stakeholder groups of the study respondents) was investigated (see Table 9).

The correlation showed that there was a slight divergence in the preferences of the main stakeholder groups represented in the survey.

- Both investigators/physicians and sponsors ranked first “The sponsor (in case it is a commercial one)” (64%, n=91 and 63%, n=22 respectively). Sponsors’ second most preferred choice was “The sponsor (in case it is a non-commercial one)” (49%, n=17), whereas investigators’ second most preferred choice was “National Contact Points” (60%, n=60).
- Individual patients/carers selected most frequently “The investigator or clinical trial site” (58%, n=15), closely followed by the commercial sponsor (54%, n=14).
- Representatives of patient organisations selected mostly “National Contact Points” (67%, n=47), followed by the commercial sponsor (51%, n=36).

Table 9. Opinion on the responsibility for logistics of clinical trial participation correlated with affiliation to a stakeholder group of respondents

Q2 To which stakeholder group do you belong?	N subjects	N choices	The patient	The investigator or clinical trial site	The sponsor (in case it is a commercial one)	The sponsor (in case it is a non-commercial one)	The official National Contact Point	The relevant healthcare provider in the patients country of residence	I do not have an opinion	Other (please specify)
Other (please specify)	25	52	3 (12.0%)	8 (32.0%)	17 (68.0%)	10 (40.0%)	7 (28.0%)	7 (28.0%)	0 (0.0%)	0 (0.0%)
Representative of a patient organisation	70	191	13 (18.6%)	32 (45.7%)	36 (51.4%)	24 (34.3%)	47 (67.1%)	31 (44.3%)	3 (4.3%)	5 (7.1%)
Individual patient/carer	26	68	9 (34.6%)	15 (57.7%)	14 (53.8%)	10 (38.5%)	5 (19.2%)	12 (46.2%)	2 (7.7%)	1 (3.8%)
Investigator/physician	142	308	12 (8.5%)	43 (30.3%)	91 (64.1%)	51 (35.9%)	60 (42.3%)	42 (29.6%)	6 (4.2%)	3 (2.1%)
Commercial or academic sponsor of clinical trials	35	74	0 (0.0%)	14 (40.0%)	22 (62.9%)	17 (48.6%)	11 (31.4%)	8 (22.9%)	2 (5.7%)	0 (0.0%)
Ethics committee	3	9	2 (66.7%)	0 (0.0%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	1 (33.3%)	0 (0.0%)	0 (0.0%)
Regulator	3	4	0 (0.0%)	2 (66.7%)	1 (33.3%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Row (Q2)=Q2 To which stakeholder group do you belong?

Column (Q23)=In your view who should organise the logistics of clinical trial participation of patients coming from another country
total number of subjects (N=304)

Per row, the percentages are calculated with the number of subjects as denominator. Since Q23 is not mutual exclusive, these percentages do not add up to 100.

KEY RESULTS: TOPIC 12

In the interviews, five frameworks were proposed. However, no concrete terms for organisation were suggested. In summary:

1. Variations on joint support:
 - Provided by the home and host country
 - Provided by the home and host country, with a role for the European Reference Networks
 - Provided by the home and host country, with a role for other stakeholders (patient organisations, CROs)
2. Support provided solely by the patient’s home country (e.g., through a “foreign office” in hospitals (see Topic 14, Part 2) or National Contact Points)

3. Support by the sponsor directly or indirectly (a CRO financed by the sponsor)
4. Support by a special navigator (financed either by the patient's home country healthcare system, or by the sponsor)
5. Support organised at EU level

In the survey a very high degree of preference for the commercial sponsor (60%, n=183) was received, followed by the National Contact Points (43%, n=132). However, during the course of the interviews it was established that the NCPs would not be suitable actors for provision of logistical support, due to their lack of expertise in clinical trials, their general reluctance to take up this role, and the lack of resources attributed to them. Organisation by the non-commercial sponsor and the investigator/clinical trial site received almost the same number of responses (38%, n=115 and n=114, respectively).

In both interviews and survey there was a strong support for the opinion that the patient should not carry the burden of organising logistics.

Conclusions:

The results from the survey clearly indicated that the commercial sponsor should be mainly responsible for handling the logistics of cross-border clinical trial participation. However, also the trial site, National Contact Points or ERNs were proposed, also in the interviews. There was broad agreement that the management of the logistics should be not left to the patients.

TOPIC 13: STUDY PARTICIPANTS' OPINIONS ABOUT ALLOCATION OF RESPONSIBILITY FOR COSTS COVERAGE

Equally relevant to the question of responsibility for handling of the logistics was the question about the responsibility for coverage of the costs of cross-border access to clinical trials.

INTERVIEWS

As shown in Topic 9, study participants perceived costs coverage as the biggest challenge in cross-border access to clinical trials. With *Question 19*, we sought to gather the respondents' opinions concerning the allocation of responsibility for costs coverage:

QUESTION 19: "IN YOUR OPINION WHO SHOULD COVER THE COSTS FOR STUDY PARTICIPATION OF PATIENTS COMING FROM ABROAD?"

Pursuant to Article 88 of the Clinical Trials Regulation, the investigational medicinal product is provided free of charge to the clinical trials subjects and the costs for all trial-related activities have to be covered by the sponsor. General healthcare costs outside the trial are covered by the national healthcare system. Accessing a clinical trial abroad creates additional costs in several aspects, namely, receiving medication that is not part of the investigational therapy, additional healthcare services required to manage disease-related issues outside the clinical trial, travel and accommodation costs for patient and carer, etc.

Out of 38 Interviewees, two industry representatives declined to provide an opinion on this question, stating that they do not know.

Among all other participants, there was a general agreement that it is unethical to leave the burden of these additional costs to the patients and that such burden would further exacerbate social inequalities, as it would mean that only wealthy people have the opportunity to join a clinical trial abroad.

Several possible solution frameworks were identified during the course of the interviews. They are presented in detail below. No specific order of preference was followed in this overview, as due to the qualitative character of the research and the diversity in answers given, it was not feasible to establish such an order. However, the responses to the survey (see below) provided more generalisable conclusions on the question of preference.

In the majority of cases study participants suggested more than one possible solution, depending on whether the clinical trial was funded by a commercial or a non-commercial sponsor. In addition, due to the fact that the majority of Interviewees did not have regulatory expertise, the proposed solutions were not detailed in terms of regulatory or economical specificities. Hence, further economical assessment and investigation into the intricacies of national social security systems was deemed beneficial.

I. The sponsor (regardless of whether commercial or non-commercial) should cover the entirety of additional costs

This solution was mainly supported by patient representatives. However, several policy experts, physicians, the National Contact Point representative, and an Ethics Committee representative were also in favour of it.

Several arguments were put forward as to the question why the sponsor (commercial or non-commercial) should be responsible for all additional costs (instead of, for instance, allocating some of the costs to the social security system of the patient's country of residence).

- According to a patient representative, *“The need to do clinical trials, to generate new therapies, is obviously important, but research should not disrupt the – or should not put an undue burden on – the healthcare system (...) by taking resources that obviously are scarce across the board”*. This sentiment was echoed by another patient representative: *“because I know the Eastern European reality, that health system here will never be able to pay for costs of sending their patients abroad for a clinical trial. If it is up to the sending country, because of the economic differences within Europe, it is not going to be possible”*.
- A patient representative was of the opinion that any other financial coverage framework would be *“impossibly complicated”*. More specifically, *“why it becomes complicated is because how treatments are reimbursed or financed is very different across the countries in Europe. Technically speaking, the only way how it seems feasible, is if it is done by one peer, and that one peer should be the sponsor”, “to avoid that money has to be channelled through too many intermediaries, which is an increased risk”*.
- Finally, according to a policy expert: *“Whether that’s a CRO, whether it’s a research organisation or whether that’s pharmaceutical really directly, they should sponsor it, because they have the duty of care. So, this is really my profound view: you are putting patients through your treatment on your product, you make sure they get looked after.”*

A potential risk was identified by an industry representative when a commercial sponsor covers all additional costs: *“this could be [used] against us, if, for example, the trial doesn’t go well, or something happens with the side effects, etc. I already see the headlines that we were using people as guinea-pigs and that we incentivised them to participate in a trial which in the end ended not very well for them”*.

II. Responsibility for coverage of additional costs should be allocated differently based on whether the sponsor is commercial or non-commercial

According to some of the study participants (a group comprised of physicians (primarily), patient representatives, a policy expert, and an Ethics Committee representative), the allocation of financial responsibility should take into account whether the study is an industry-sponsored or an academia-initiated one.

- When the sponsor is commercial, he should be entirely responsible for the coverage of any additional costs.
- When the sponsor is non-commercial, the coverage of costs associated with the cross-border access to the clinical trial should be the responsibility of the patients' home country because the funding for non-commercial clinical trials is generally limited, as most of these Interviewees argued.

By 'home country' Interviewees understood the healthcare system or the social security system to which patients are subjects, or the government of that Member State. In the words of an Ethics Committee representative, *"Logically it should be the healthcare system in the country of the patient. Because they would cover that cost if the patient was not moving to another country"*. According to a patient representative, *"For academic trials, it's much more difficult – they would need to ensure that there is some kind of arrangement with the home country and with the care the patient would receive in that country, but I have no idea how that could happen"*. Another example in relation to this particular view was provided by a physician: *"if it's academic I think it should be the insurance or the public health insurance from the referring country"*. Another physician suggested that each Member State could allocate a specific budget for such purposes.

Currently, based on information gathered through the interviews, such a model is already in place in Denmark and Norway. According to a physician: *"they say that the hospital or the region where they come from, will have to pay for the costs when they go to another site for experimental treatment. And that would be the same thing in Norway. So mostly they are referred from university hospitals, then the university hospital, they stand obliged to cover the costs"*.

III. Combined model for costs responsibility (regardless of whether the sponsor is a commercial or a non-commercial one).

Several possible models for cost-sharing were proposed:

- Support should be provided by the patients' home country.

Participants expressed the opinion that a way to structure this model would be by following the same principles as the ones established with the Cross-border Healthcare Directive. However, the existing differences between Member States' health insurance coverage would bring another question, namely who should be responsible for the expenses that go beyond what the home country's system is able to cover. A possible solution is presented in the final point of this section, namely by setting up a specialized European fund.

- Support should be provided by the country where the clinical trial is taking place.

Only one participant (a patient representative) expressed this opinion. The Interviewee further provided ideas on how the system could be structured, namely by establishing a set of criteria for the patients who would have to prove their financial status. Furthermore, *"any kind of arrangement for coverage of these extra expenses would have to have built in some kind of a super highway, so that patients could get through"*

this kind of validation process of their financial status as quickly as possible". However, no other participant supported this view.

- Support should be provided by a specifically designated European fund (either in full, or in part, as an addition to what the patients' home country can reimburse). An academic sponsor representative provided a more detailed suggestion as to how such a fund could be set up. In particular, the patient's home country should reimburse the incurred expenses to the level it can, while the difference should be allocated to a "*compensation fund*". Resources for such a fund might be collected in the following manner: "*from certain research funds that Europe has; Europe can also think about the kind of mechanism that Italy tried to put in place, which consists of putting aside a certain percentage of money that industry pays when running clinical trials in terms of fees, or whatsoever. So, it becomes a kind of diverted tax, in a way. So if you imagine the volume of all industrial clinical trials, when you think about it in terms of fees, but also in terms of the fees they pay to the European Medicinal Agency when they want to register the drug, you can for instance add, I don't know, a 2% tax, and the money will automatically go to this fund. So, in a way, it's a tax, but it may eventually return to the same industry*".

An example of a similar model was reported in the work of the European Patients Forum (EPF). As shared by a patient representative, EPF planned to create a "*funding pool*" in order to assist patients seeking healthcare abroad, however not in the context of a clinical trial. However, this idea was never realised in practice.

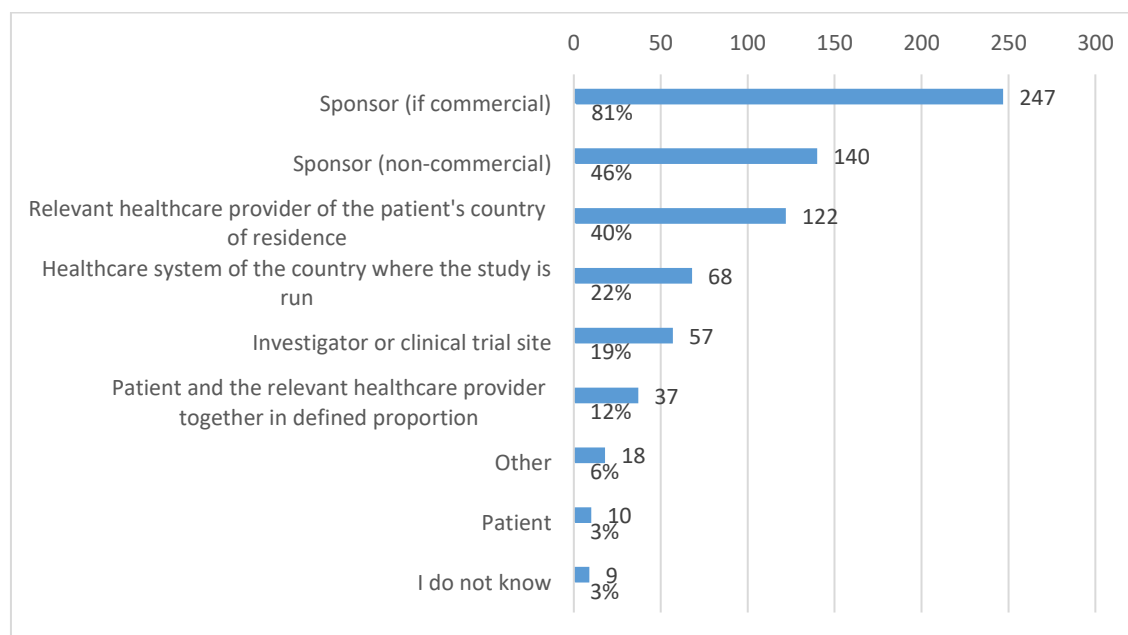
SURVEY

QUESTION 24: IN YOUR VIEW, WHO SHOULD COVER THE COSTS FOR CLINICAL TRIAL PARTICIPATION OF PATIENTS COMING FROM ANOTHER COUNTRY, E.G. INVESTIGATIONAL MEDICINAL PRODUCT, BASELINE TREATMENT, HOSPITAL STAY, TRAVEL, FOLLOW-ON CARE AT HOME?

The question had eight pre-defined answers (including "I do not know") and provided the option "Other". Study respondents could select multiple answers; hence the number of responses was larger than the number of involved subjects.

77% (n=304) of all survey respondents answered this question. In Figure 31 below the answers are shown in a descending order of preference based on the number of responses each of them received. Highest ranked for cost coverage responsibility was the commercial sponsor (81%, n=247), followed by the non-commercial sponsor (46%, n=140). Similarly to the question about logistics, there was an agreement among respondents that the burden of organising logistics should not be allocated to the patients (only 3% (n=10) of responses were provided for this option, almost the same number as for the option "I do not know", 3% (n=9)). The answer ranked third was "The relevant healthcare provider of the patients' country of residence" (40%, n=122).

Figure 31. Opinion related to the responsibility for cost coverage in cross-border clinical trial participation



6% (n=18) of the responses were provided under the “Other” option. Some of them echoed the solution frameworks discussed in the interviews, e.g.:

- “Shared costs between sponsor and healthcare provider/insurer in home country”; “Sponsor and local insurance together: sponsor to cover study costs, as they would do for local patients, insurance for the normal other costs of healthcare”; “The healthcare provider in both countries together with the healthcare insurance company”
- “EU specific funding”

Others stressed that the responsibility should not be allocated to the patient.

The correlation between the answers to Question 24 and the results of Question 2 (stakeholder groups of the study respondents) was evaluated (see Table 10).

Based on the correlation, it was observed that the four main stakeholder groups represented in the survey were in agreement that the commercial sponsor should be responsible for the coverage of costs (representative of a patient organisation 70%, n=49, individual patient carer 77%, n=20, investigator/physician 83%, n=118, sponsor 80%, n=30).

However, the answer ranked second diverged among the study representatives from different stakeholder groups:

- Individual patients/carers provided the second highest number of responses to “Investigator or clinical trial site” (58%, n=15) and the non-commercial sponsor (58%, n=15).
- Representatives of patient organisations and sponsors selected second “The relevant healthcare provider of the patients’ country of residence” (43%, n=30 and 51%, n=18, respectively).
- Investigators/physicians put second “The sponsor (in case it is a non-commercial one)” (43%, n=61).

Table 10. Responsibility for covering the costs of clinical trial participation abroad according to stakeholder group

Q2 To which stakeholder group do you belong?	N subjects	N choices	The patient	The investigator or clinical trial site	The sponsor (in case it is a commercial one)	The sponsor (in case it is a non-commercial one)	The relevant healthcare provider of the patients country of residence	The healthcare system of the country where the study is run	The patient and the relevant healthcare provider together in a defined proportion	I do not know	Other
Other (please specify)	25	52	0 (0.0%)	3 (12.0%)	24 (96.0%)	15 (60.0%)	5 (20.0%)	2 (8.0%)	2 (8.0%)	0 (0.0%)	1 (4.0%)
Representative of a patient organisation	70	176	2 (2.9%)	20 (28.6%)	49 (70.0%)	28 (40.0%)	30 (42.9%)	21 (30.0%)	15 (21.4%)	3 (4.3%)	8 (11.4%)
Individual patient/carer	26	79	1 (3.8%)	15 (57.7%)	20 (76.9%)	15 (57.7%)	13 (50.0%)	10 (38.5%)	3 (11.5%)	0 (0.0%)	2 (7.7%)
Investigator/physician	142	313	6 (4.2%)	16 (11.3%)	118 (83.1%)	61 (43.0%)	56 (39.4%)	27 (19.0%)	17 (12.0%)	6 (4.2%)	6 (4.2%)
Commercial or academic sponsor of clinical trials	35	76	1 (2.9%)	3 (8.6%)	30 (85.7%)	15 (42.9%)	18 (51.4%)	8 (22.9%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
Ethics committee	3	6	0 (0.0%)	0 (0.0%)	3 (100.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Regulator	3	6	0 (0.0%)	0 (0.0%)	3 (100.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

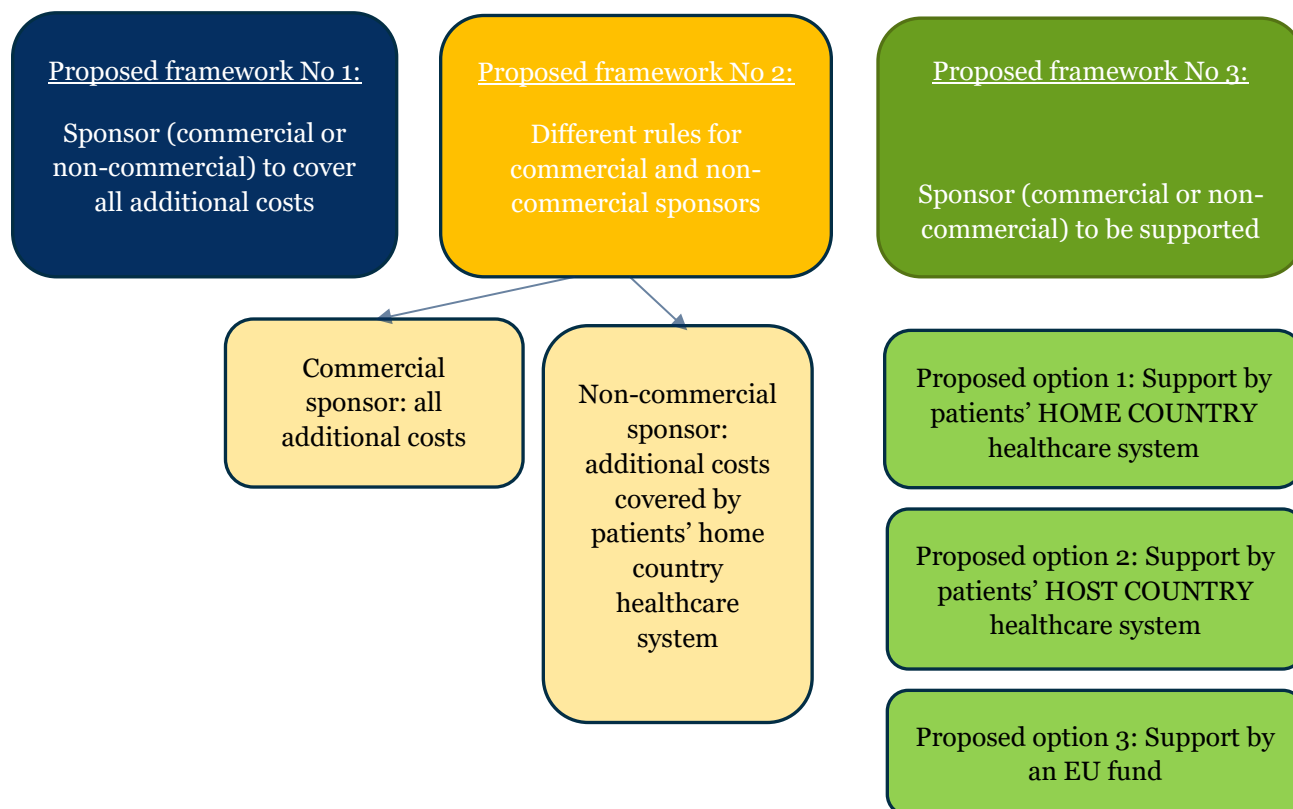
Row (Q2)=Q2 To which stakeholder group do you belong?

Column (Q24)=In your view who should cover the costs for clinical trial participation of patients coming from another country
total number of subjects (N=304)

Per row, the percentages are calculated with the number of subjects as denominator. Since Q24 is not mutual exclusive, these percentages do not add up to 100.

KEY RESULTS: TOPIC 13

In the interviews three main solution frameworks were proposed and allowed for a more subtle presentation of ideas for costs-sharing than the survey:



In comparison, the survey results showed a clear preference for the commercial sponsor (81%, n=247). Non-commercial sponsors were ranked immediately after (46%, n=140), closely followed by the relevant healthcare provider of the patient's country of residence (40%, n=122).

Support for the responsibility of the host country (which was a solution brought up by only one of the Interviewees) was preferred to some extent in the survey, namely, by the responses gathered for "Healthcare system of the country where the study is run" (22%, n=68) and for "The investigator or clinical trial site" (19%, n=57).

Conclusions:

There was broad agreement among the study participants that the cost coverage should not be left to the patient.

For commercially sponsored trials the vast majority of respondents saw the sponsor in the responsibility for covering the costs, although some supported the coverage of only those costs that are not covered by the patient's home country.

For academic studies cost coverage responsibility was seen quite divergently, including versions that foresaw the responsibility of the academic sponsor, the site and/or the patient's home country healthcare system.

TOPIC 14: SPECIFIC TOPICS FROM THE INTERVIEWS: REGULATORY AND ORGANISATIONAL ENVIRONMENT FOR CROSS-BORDER ACCESS TO CLINICAL TRIALS

Due to the expertise of the Interviewees additional specific ideas and recommendations concerning the regulatory and organisational environment for cross-border access to clinical trials were proposed by the Interviewees which are presented in this topic.

1. STUDY PARTICIPANTS' OPINIONS ON THE CURRENT (EU AND NATIONAL) LEGISLATION

The stakeholders' opinion concerning legal issues were specifically collected under:

QUESTION 14: DO YOU KNOW WHETHER CROSS-BORDER ACCESS TO CLINICAL TRIALS IS PART OF THE CURRENT EU LEGISLATION ON CROSS-BORDER HEALTHCARE (THE DIRECTIVE 2011/24/EU ON PATIENTS' RIGHTS IN CROSS-BORDER HEALTHCARE)?

and

21. HOW DO YOU PERCEIVE THE CURRENT NATIONAL LEGISLATION IN YOUR COUNTRY OF RESIDENCE IN TERMS OF CROSS-BORDER ACCESS TO CLINICAL TRIALS?

22. FOLLOW-UP QUESTION WHATEVER THE RESPONSE ON THE QUESTION ABOVE: WHY?

23. WHEN YOU THINK OF CURRENT EU LEGISLATION DO YOU CONSIDER IT PRESENTS AN OBSTACLE TO CROSS-BORDER ACCESS TO CLINICAL TRIALS, OR IT PROVIDES A BASIS FOR FACILITATION?

24. FOLLOW-UP QUESTION WHATEVER THE RESPONSE ON THE QUESTION ABOVE: WHY?

However, participants' answers to *Question 20: In your opinion which actions would facilitate cross-border participation in clinical trials?* often included reflections on the legislation, as well.

The majority of participants had only anecdotal impressions of their applicable legislation. Although the stakeholders' views were very valuable for assessing how the applicable legislation was currently perceived and understood by the legal subjects, they could not be directly used to generate a critical analysis of the EU and national legal frameworks or normative claims. Further detailed legal analysis of the legal instruments identified through the interviews was deemed necessary.

1.1. THE CROSS-BORDER HEALTHCARE DIRECTIVE

The Cross-border Healthcare Directive constituted the basis for the initiation of this exploratory research project. Therefore, it was deemed meaningful to test the extent to which representatives of the different stakeholder groups were aware of this specific piece of legislation, and how they perceived it in connection to cross-border access to clinical trials.

13 of the 38 participants were not aware of the Directive and its application. The other Interviewees had a general idea about the scope of application of the Directive (i.e., that clinical trials are excluded from its scope) and of the fact that the Directive established a mechanism for reimbursement of costs incurred by patients treated outside their country of residence.

The question why clinical trials were excluded from the scope of the Directive was answered by representatives of the stakeholder groups Ethics Committees, industry, and patients. None of the Interviewees were involved in the political discussions held at the EU Parliament, the EU Commission, and the EU Council prior to the adoption of the Directive, hence their views represented only personal assumptions. Moreover, most of the Interviewees refused to comment, stating they did not have any knowledge on the topic.

Two reasons for exclusion of clinical trials from the scope of the Directive emerged from the interviews:

- The legal and political complexity of clinical trials was feared to hamper adoption of the Directive. An Ethics Committee representative provided an overview of the reasons that make the topic politically sensitive: *"First of all, what if something happens to the patient? So, there is the problem of insurance of the patient. Then, there is the problem of the treatment of the patient, coming back to his or her own country, if something went wrong. If the patient is healed, well, wonderful. If not, what? And especially, if patient claims, that well, he was or she was expecting being healed and not, and that this is injury made to him, you know? So, and I am not listing more and more scenarios, that could really go very wrong. And also, if there is injury to the patient, just unexpected adverse effect, then who will pay indemnity and how this will be done in a trans-border manner and so on? And I am not sure, if there are appropriate agreements in place between the countries on these issues"*.
- A need for including clinical trials was simply being overlooked during the political debate. In the words of a patient representative, *"My gut feeling is that they didn't think about it"*.

Criticism on the Directive's rationale was raised by one patient representative, according to whom: *"The problem is always that the home country always says [they will] reimburse up to what it would cost here. So that already precludes a lot from it, so they don't cover a real cost, and the next thing is that you still have to organise all the rest yourself. Unless you have an agreement in place between different countries – we share expensive facilities, it requires quite a bit of effort on the side of the patient"*. A policy expert further indicated that *"The spirit of the Directive is – although nobody will publicly say this – people from richer Member States can go to Member States with a lower GDP, but not the opposite around"*. In the interviews, it was pointed out several times that changing the scope of the Cross-border Healthcare Directive

to include clinical trials would not provide a sufficiently viable solution for the facilitation of cross-border access to clinical trials.

Finally, an industry representative and a patient representative expressed their opinion that the Directive should not be amended (“*re-opened*”) in order to have clinical trials included in its scope. Their arguments were mainly based on the perceived lack of political will in the current political climate to legislate in this field.

1.2. CURRENT EU LAW IN GENERAL

All study participants were asked whether they perceived the current EU legislation as a facilitator, or as an obstacle to cross-border access to clinical trials. No specific legislative acts were cited; hence the Interviewees had a broad discretion in their choice to which frameworks to refer. The majority made a reference either to the EU Clinical Trials Regulation (Regulation No 536/2014), the GDPR, or to EU law *in abstracto*.

Summary of the study participants’ opinions:

- EU law seen as an obstacle to cross-border access to clinical trials (primarily by patient representatives, physicians, one industry representative, and one policy expert).

First, the most frequently raised obstacle for cross-border collaboration was the need for compliance with data protection rules, and in particular with the EU GDPR. Several issues were identified:

a/ Difficulties were reported in the patient suitability assessment step in respect to access to data and sharing of data. For instance, according to a physician: *“Another issue is how to share patient data within the GDPR. We don’t have a real platform for sharing a patient data, so it’s over the phone”*.

b/ GDPR was seen as a hurdle for the conduct of pan-European clinical trials, i.e. opening investigational sites in several countries.

c/ GDPR was seen as a hurdle for EU-non-EU collaboration without further specifications provided

Second, EU law was cited as an obstacle due to the lack of a specific legal framework and regulatory infrastructure for cross-border participation in clinical trials. Although cross-border participation is not explicitly forbidden, some of the Interviewees expressed that they *“don’t feel that it’s promoted, so maybe more could be done”* (in the words of a patient representative).

Third, the divergences between the main regulations applicable to research (namely, the Clinical Trials Regulation, the In-vitro Diagnostics Regulation, the Medical Devices Regulation, and GDPR) were cited as a further challenge for both opening clinical trials on a pan-EU level (and thus creates an obstacle for conducting research multi-nationally and having investigational sites closer to the patients), and for recruiting foreign patients.

One physician specifically indicated that the main issue lies in the division of competences between the EU and its Member States: *“It’s not the legislation; it’s the fact that healthcare is not European business, but is a national responsibility, so there is a lot of disparity between the different healthcare systems. We are making Europe way too complex: we should unify, we should uniform things to provide easy access to all patients in all Member States in a very similar way, using the same administrative steps and preparatory steps. So, we are far away from an ideal system”*.

- EU law seen as a potential facilitator to cross-border access to clinical trials: (primarily by physicians and the academic sponsor representative).

Several Interviewees were of the opinion that harmonisation in the relevant legal domains could be achieved if there were the political will. For instance, in the words of the academic sponsor representative, *“I think Europe has basically all pillars to work on this; not to invent something new; but to produce an add-on on the four regulations at the same time. I am not sure how far there is a similar need in case of In-vitro diagnostics and devices as such; but the problem comes also from the fact that frequently when you do have a clinical trial, there is also device and also diagnostic, so even if maybe the device and in vitro diagnostic regulations would spontaneously need the cross-border movement – little bit less than the drug regulation - but they will be impacted because of those projects which spread over several regulations, so it needs to be considered as well”*. Moreover, specifically to the Cross-border Healthcare Directive and its potential for the facilitation of cross-border access to clinical trials, a national example emerged. In the case of Denmark, the Directive and (EC) regulation No. 883/2004 were implemented in such a way that the S2 form can be used for the reimbursement of costs incurred during participation in a clinical trial.

- Neutral stance with respect to EU law (neither facilitator, nor an obstacle): (by policy experts, physicians, and the National Contact Point representative. They expressed their inexperience with the legal matter and refused to take a position).

1.3. NATIONAL LAWS

Finally, the Interviewees discussed to what extent they were familiar with national legislation that clarifies the conditions for cross-border access to clinical trials. The majority of participants referred to the legislation *in abstracto* and did not cite any concrete pieces of legislation.

- Neutral stance with respect to national legislation (neither facilitator, nor an obstacle): the majority of participants from all stakeholder groups said that they were not familiar with any national legislation on this topic, hence they could not provide an informed opinion.

Phrases such as *“To be honest, I cannot answer the question, I don’t know the German legislation enough”* (patient representative), *“I don’t know the legislation in Belgium”* (patient representative), *“Honestly, I don’t know what to answer”* (patient representative), *“I don’t think we have done anything”* (physician) have been frequently used. Whenever Interviewees made assumptions about their national legislation based on their professional experience, they generally expressed that it seemed to be *“a blind spot”* (National Contact Point representative): it does not forbid cross-border participation in clinical trials, but it does not regulate it in any way either.

An Ethics Committee representative pointed out that there seems to be a *“blurry area”* in legislation when it comes to clinical practice and research that should potentially be solved: *“But also, it think that there are some conceptual biases, that prevent us from having a lot of discussion on this. And this is really like this niche divide between therapy and research. Because, in my perception, in the last 10 years that has been a little bit a blurry area, where it is quite unclear, if you are still only in a research realm or already in a therapeutic realm”*.

- National legislation seen as a barrier to cross-border access to clinical trials (according to physicians, two of the policy experts, one of the industry representatives, one of the Ethics Committee representatives, one of the patient representatives, and the academic sponsor of clinical trials representatives).

The situation in several countries was commented by different stakeholder representatives, showing the different national conditions perceived as weaknesses.

The Belgian legislation was referred to as “very opaque” and further discussed as *“I was looking on this legislation from the perspective of reimbursement of the clinical trial, standard of care, procedures within clinical trials: it’s not the legislation that is very easily accessible to someone outside Belgium and to understand what’s applicable”*.

In Slovakia, the national legislation applicable to the conduct of clinical trials was perceived among the reasons for not having as much investigational sites open in the country as in other EU Member States: *“First of all, I think we are still not doing as many trials, as we could in Slovakia. And this is because of the legislation in 2011 and later, the legislation was made a little bit, well, complicated at that time. It was since that time already amended many times, so it is now okay already, for a couple of years, I would say. But this development in 2011 till about, well, I would say, 2016, where, well it was quite tricky, and some companies left”*.

French legislation was referred to as a *“nightmare described by Kafka”*.

Spanish legislation was seen as setting out a *“difficult process”* when it comes to joining a clinical trial abroad and *“dreadful”*.

In Central and Eastern European countries in general, laws were described as *“awful”*. More specifically, Bulgarian legislation was seen, on the one hand, as *“not working well”*, and on the other hand, the lack of appropriate system for logistical support in the country was brought up as a weakness that further exacerbates the legal challenges: *“First of all, people don’t know that this exists, in the first place. And when they find out, they have no idea, what’s the procedure after that. They have no idea, who do they need to contact, what is the type of documents. There is entire medical tourism industry already, helping these patients, like, take advantage from the cross-border legislation and I am not saying this is a bad thing, I mean, it’s good that at least, there are people, who are consulting these patients and helping them out, but I think that there should be an easier way for people to know, that they can benefit from a treatment somewhere else, and what would be the route for that. So, clear path, clear procedures”*. Regarding Romania, specific attention had been brought to the fact that *“even the running of trials (...) is really difficult and it has a lot of legislative - and especially - just bureaucratic challenges. I think the speed with which approvals are obtained is actually one of the biggest factors, because if the approval, you know, eventually, will get approved, it’s not fast enough for many trials to be run here. So, by the time, approval starts getting, actually trials would be already like in 2 year delay in Romania, compared to other sites in Western Europe, so it doesn’t seem to motivate the sponsors to set up trials in Romania. So that much I know about the legislative framework”*.

- National legislation seen as facilitator to cross-border access to clinical trials.

An alternative view on Belgian legislation was presented by a physician, who commented that the legal framework is *“relatively liberal and good”*. And *“It’s a bit of an administrative nightmare once in a while, but much less than in other countries”*.

Denmark was cited as a prominent example of a country where the national legislation is already providing facilitation for cross-border participation in clinical trials, especially, when referring patients with rare diseases to clinical trials conducted abroad.

2. CURRENT ACTIONS, INITIATIVES, OR PROJECTS THAT FACILITATE CROSS-BORDER ACCESS TO CLINICAL TRIALS

Below follows a list of current actions, initiatives, or projects that were specifically mentioned by study participants as facilitating cross-border access to clinical trials:

1. **Patient organisations and patient advocacy groups** sometimes provide information and guidance for cross-border access to clinical trials. This does not happen in a systematic way and is organised on a voluntary basis.
2. **FindMeCure:** an online platform targeted at patients and described as “the Google for Clinical Trials”. In their words: “*We help you find, weigh and understand treatments in development.*” More information at: <https://www.findmecure.com/>
3. **Nordic Network for Early Cancer Trials (Nordic NECT):** the network is designed to promote patient access to new investigational drugs and access to Phase I and early Phase II programmes in the Nordic countries (Norway, Denmark, Finland, and Sweden). Among its objectives is “*work for a bilateral agreement between the Nordic countries allowing for inclusion of patients in early clinical trial protocols across the borders*”. More information at: <https://nordicnect.org/index.php/about-us>
4. **Nordic Trial Alliance:** its objective is to enhance Nordic country cooperation on multi-centre clinical trials. The Nordic Trial Alliance was specifically brought up by a policy expert. More information at: <https://nta.nordforsk.org/>
5. **European Clinical Research Infrastructure Network (ECRIN), and NorECRIN** in particular. More information at: <https://www.ecriin.org/>
6. **Bi-lateral agreements for collaboration of University Hospitals** in the case of neighbouring countries (e.g., between the university hospitals in Aachen and Maastricht).
7. **National implementation of the Cross-border Healthcare Directive** in Denmark that allows the possibility to use the S2 form for expenses incurred when a patient participated in a clinical trial.
8. **“Foreign office”/Office for treatment abroad,** (so called by Interviewees), established in university hospitals in Norway. Physicians and a policy expert reported that in Norway, specifically for rare diseases and children, these offices provide practical assistance for participation in a clinical trial conducted in another Nordic country (not in other European countries). The costs, including travel expenses, were reported to be jointly guaranteed by the hospital and the governmental health authorities. These offices have been in operation, according to the study participants, since approximately 2017, and 1-2 patients are sent abroad per year.
9. **Multidisciplinary national tumour board/expert panel (in operation in Denmark and Norway).** In operation since approximately 2017-2018, the national expert panels provide a new assessment of treatment options for patients who have exhausted all standard of care options. Their mandate is, among other things, to assess whether adequate treatment is provided to the patient. Furthermore, they assess whether there are relevant clinical trials for the patient in their home country (preferably) or abroad. In Norway the establishment of the expert panel was initiated in 2018 by the Ministry of Health and followed the Danish example.
10. **Ethics Committee requirements regarding Informed Consent forms in Denmark** allow easy acceptance of foreign patients.

11. **A joint Nordic electronic information portal on Ethics Committee approvals:** currently in development by the Nordic Council of Ministers for Health and Social Affairs, the Nordic Committee on Health and Social Affairs, the Nordic Committees for Education and Research. Part of a three-year priority project *Nordic research collaboration for better health* (2017-2019) and its Pillar 1: Consider opportunities to make it easier to obtain ethical approval for Nordic research projects.
12. **The Slovak EFPIA member association AIFP created a specialised website on clinical trials** which provides the possibility for online consultations, practical information about clinical trials in general, reference to the Slovak database for clinical trials (run by the Slovak Institute for Drug Control). However, this website has information only about clinical trials running in Slovakia.

3. BACKGROUND INFORMATION: HOW SPONSORS SELECT COUNTRIES IN WHICH TO OPEN CLINICAL TRIALS

Some of the study participants provided their insight on issues that are indirectly linked to the topic of cross-border access to clinical trials. In particular, how sponsors select countries in which to open a trial.

Several considerations were brought up:

- **Costs:** the more investigational sites are open, the more costs for the sponsor. However, it was reported that a balance is sought in all cases because more investigational sites means also faster recruitment and faster results.
- The procedure for **opening a clinical trial site** is lengthier or more complex in certain countries, however study participants did not provide concrete examples.
- In the case of **rare diseases**, the **population size** has to be taken into consideration. For instance, given the overall population size of countries such as France or Germany, the absolute numbers of patients with a certain rare disease are higher than in smaller EU Member States.
- The **phase of the trial** matters as well: as stated by the representative of an academic sponsor of clinical trials: *“if you speak about phase 1, early phase 2 [clinical trials], even for quality and monitoring purposes, you shouldn’t have too many centres.*
- The **experience of medical staff** and the **quality of equipment** available in local hospitals. Naturally, these would differ between Member States and the preference would be towards countries where there is overall more experienced medical staff and better equipped centres.
- According to a policy expert, **“clinical trials happen where the markets are”**. More specifically, according to this study participant, companies prefer to set up clinical trials in the countries where they know that the medicine will receive market access and be reimbursed.

TOPIC 15: STUDY PARTICIPANTS' VIEW ON FUTURE ACTIONS

This research project did not only aim at creating a better understanding of the relevance and hurdles for cross-border access to clinical trials but also wanted to collect ideas for improvement of the situation from all involved stakeholder groups. The proposals partly already mentioned above are summarised below.

INTERVIEWS

The topic was investigated with

QUESTION 20: IN YOUR OPINION WHICH ACTIONS WOULD FACILITATE/SUPPORT CROSS-BORDER PARTICIPATION IN CLINICAL TRIALS?

19 solutions were proposed. They are presented below in two groups. First, study participants' suggestions that directly address cross-border access to clinical trials. Second, suggestions that address other related issues (e.g., the need to have more clinical trials opened closer to where patients live) and which indirectly could alleviate the need for cross-border access.

ACTIONS THAT COULD FACILITATE CROSS-BORDER PARTICIPATION IN CLINICAL TRIALS

1. Multi-stakeholder guidelines with pragmatic solutions.

According to study participants, such guidelines should ideally have the status of official guidelines issued or at least endorsed by an EU body, such as the EU Commission or the European Medicines Agency (EMA). “*European Commission Guidelines*” or at least a “*Recommendation from the European Commission*”. Moreover, the guidelines development and support should be a combined effort by all stakeholders. Interviewees proposed patient organisations as the preferred lead of such a project. With contributions from whom?

2. Clarifying note on the Cross-border Healthcare Directive, issued by the European Commission. According to some study participants, this could be a potential way to include clinical research in the scope of the Directive.

3. Mixed model: issuing of multi-stakeholder guidelines with pragmatic solutions coupled with a change in the legislation applicable to clinical trials. However, the Interviewees did not provide any concrete examples as to how exactly the legislation should be changed.

4. Setting up discussions between key stakeholders, which could also be a first step towards the creation of the multi-stakeholder guidelines with pragmatic solutions described above. Three types of discussions were proposed:

a/ discussions that would help clarify the role and allocation of responsibilities of the different stakeholders involved in cross-border participation in clinical trials;

b/ discussions between sponsors and sites to actively foresee the feasibility for recruiting foreign patients;

c/ discussions exclusively related to a future political uptake of the issue.

5. **Optimisation of the ways relevant information is disseminated.**
 - a/ establishing more optimal and user-friendly ways for patients to be informed about currently running clinical trials;
 - b/ national authorities should provide more and better structured information about clinical trials;
 - c/ establishing conditions for higher awareness for treating physicians with respect to enrolling clinical trials;
 - d/ more optimal use of digital services on EU and national level.
6. Creating a **pan-European multidisciplinary tumour board** or at least **national tumour boards/expert panels**, following the example currently operating rather successfully in Denmark and Norway.
7. Establishing a **stronger role for the European Reference Networks**: either acting as the boards described above, or as part of the infrastructure that provides logistics support (including referral) for cross-border access to clinical trials.
8. Negotiating **bi-lateral agreements between neighbouring countries** defining the conditions for cross-border participation in clinical trials.
9. Utilising the existing system of **National Contact Points** for the provision of logistical and informational support for cross-border participation in clinical trials.
10. Establishing a **European fund** that would support cross-border participation in clinical trials.
11. Establishing a **European organisation** with the objective to provide support on EU level for cross-border participation in clinical trials. More specifically, several study participants spoke of *“an ‘EORTC’ for cross-border access”*.
12. **Encouraging local treating physicians to refer** patients to clinical trials. No concrete suggestions were provided on how this should be conducted in practice.
13. **Establishing and regulating a stronger role for patient organisations**, regarding:
 - a/ provision of information
 - b/ provision of logistical support
 - c/ political uptake of the issue.
14. Encouraging Member States to follow the example of Denmark and allow the use of **the S2 form also for clinical trials**.
15. Accepting and making available the **opportunity for local pre-screening of patients for inclusion in a trial**.
16. **Negotiation of insurance terms** (nationally, bi-laterally, or at EU level) in a way that the health insurance of patients participating in a clinical trial abroad would reimburse the expenses which the sponsor does not cover.

ACTIONS TO ADDRESS OTHER ISSUES RELATED TO CLINICAL TRIALS IN THE EU AND THUS INDIRECTLY ALLEVIATE THE NEED FOR CROSS-BORDER ACCESS TO CLINICAL TRIALS

17. Regulating and supporting the performance of **remote/decentralised clinical trials**. An example of how interviewees would understand the term remote/decentralised trials could be found in the words of a policy expert: *“imagine that you have one site (...) in Berlin. And then, there are patients, that are suitable for the clinical trial in Munich, but you don’t have a site there, but you just make sure, that the doctors, who are handling the patients, are also equipped, so they become investigators for the study”*.
18. **Harmonisation of the EU framework for clinical trials**, which would allow the opening of more pan-EU clinical trials. In addition, an academic sponsor representative suggested that a new requirement for the sponsor could be added in the current legislation, namely an obligation to justify why the clinical trial is planned to open only in certain Member States.
19. Creation of a **common ethical approval framework** in the EU (the last proposal was also cited as a way to facilitate cross-border access to clinical trials).

SURVEY

QUESTION 25: IN YOUR VIEW, WHICH ACTIONS WOULD FACILITATE CROSS-BORDER ACCESS TO CLINICAL TRIALS?

The question had eight pre-defined answers (including “I do not know” and the option “Other”). Study respondents could select multiple answers.

77% (n=304) of all survey respondents answered this question. In Figure 32 below the answers are shown in a descending order of preference based on the number of responses each of them received. Highest ranked was “Reliable and easily accessible information for patients, physicians and patient organisations about the legal and administrative framework for patients crossing borders for clinical trials” (68%, n=207), followed by “A change in relevant EU legislation is needed in order to harmonise the conditions for cross-border access to clinical trials within the EU (67%, n=204).

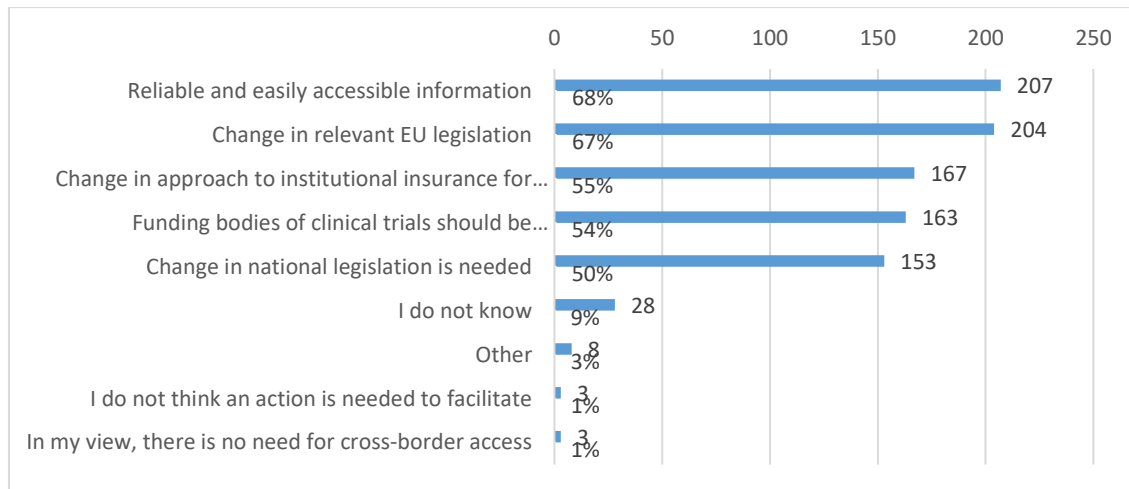
The lowest number of responses received the two answers that described no need for action, namely “I do not think an action is needed to facilitate cross-border access to clinical trials” (1%, n=3) and “In my view, there is no need for cross-border access to clinical trials” (1%, n=3).

3% (n=8) of respondents answered the “Other” option. Responses that could enhance the discussion in some way included:

- Focus on ways to address the obstacles presented by Ethics Committees: e.g., *“Ethics Committees need better training and harmonisation - is ethics approval in the country you recruit from or just in site country required?”, “Informed consent forms in the respective languages or at least an additional English consent form by default”*

- Call for a multi-stakeholder approach: *“It certainly seems as if a multi-stakeholder approach would best facilitate the promotion of cross-border trials”*
- Insight into the challenges for cross-border access: *“While healthcare is a national rather than EU discretion, I think that will over-ride any proposals here”*
- Echoing the need for more reliable information: *“More transparency for paediatric centres and patients on the availability of clinical studies”*
- Admitting that the issue requires a complex approach: *“Most of the above [actions]. Highly complex and not worth the investment”*

Figure 32. Opinion on actions which would facilitate cross-border access to clinical trials



The correlation between the answers to Question 25 and the results of Question 2 (stakeholder groups of the study respondents) was investigated (see Annex IV) and showed that there was not much divergence between the overall preference ranking of answers and the ranking per stakeholder group.

However, the Patients group (patient/carer and representative of a patient organisation) deemed “Reliable and easily accessible information” as most important (77% (n=20) and 84% (n=59) respectively), while the groups of investigators/physicians and sponsors gave the highest number of responses to the option “Change in relevant EU legislation” (63% (n=90) and 66% (n=23), respectively). The difference in numbers between the answers ranked first and second for both stakeholder groups was minimal.

The three study participants who selected the opinions “I do not think an action is needed” were a patient representative, an investigator/physician, and a sponsor. The answer “In my view, there is no need for cross-border access” were a patient representative, a sponsor, and a representative of an ethics committee.

- By amending the Cross-border Healthcare Directive or adopting a special Directive on cross-border access to clinical trials

Legislation amendments take too much time for patients in need for finding access to treatment now and in the near future. The adoption of the Cross-border Healthcare Directive, for instance, was marked by a plethora of difficult institutional compromises and a very lengthy legislative process (seven years from inception until transposition into national legislations). Similar or even longer timeframes would have to be envisaged for the development of a Directive on cross-border access to clinical trials. Amending the Cross-border Healthcare Directive with requirements for clinical trial participation abroad would be another option. However, an issue could be the fact that the Directive was intended to codify the CJEU jurisprudence in the field of patient mobility (see Introduction), of which clinical trials have never been a part. Study participants also suggested broadening of the scope of the Directive to clinical trials by a “note” issued by the EU Commission. Indeed, the Directive envisages that the EU Commission is empowered to adopt delegated acts, pursuant to Article 11(5), and Article 12(5). However, the scope of delegation is very limited, namely the Commission can adopt only measures that would exclude specific categories of medicinal products or medical devices from the recognition of prescription, or acts that define the criteria and conditions that ERNs should fulfil.

- By implementation of the S2 form (introduced with Regulation 883/2004) also for cases of cross-border access to clinical trials

It was valuable to discover that the S2 form is used in Denmark also in the cases of cross-border access to clinical trials. This means that patients can benefit from the reimbursement rules established by Regulation 883/2004. As shown in the introduction, Regulation 883/2004 is more beneficial than the Cross-border Healthcare Directive for patients crossing border to receive healthcare. Interviewees commented numerous times that encouraging Member States to allow the use of the S2 form would be a good solution. Regulations require that Member States apply them in their entirety, without deviation (unlike directives which only set certain principles, but it is up to the individual Member States to devise their own laws on how to integrate these principles). Given the fact that one Member State was reported to have broadened the use of the S2 forms, further investigation into the possibilities for interpreting Regulation 883/2004 also to clinical trials should be conducted.

4. DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS FOR FUTURE ACTIONS

REFLECTION ON THE CHOSEN RESEARCH APPROACH

This exploratory study employed a mixed-methods research design. It allowed the research team to acquire a comprehensive understanding of the issues at hand and to collect as much valuable data as possible within the time and budget frame. Moreover, the comparison between the interviews and the survey results proved to be beneficial as the in-depth insights and explanations gathered through the interviews were complemented by the concrete data from the survey. As could be shown, in most cases the results from the qualitative and quantitative parts of the project were in alignment.

A multidisciplinary team of researchers performed the project, thus providing a balance between different expertise and professional experience. This was crucial as the cross-border access to clinical trials is a highly complex process touching upon very divergent frameworks.

LIMITATIONS

The study aimed to explore the relevance, reasons, conditions, challenges and potential solutions for cross-border access to clinical trials and was thus not set-up to provide comprehensive figures and statistical analyses on the different aspects. A much larger survey, more sophisticated interview techniques like Focus Groups or Delphi Groups and an in-depth investigation of the national legal conditions for cross-border access to clinical trials would be required to generate an exact presentation of the frequency of occurrence, size of the different stakeholders' needs and regional differences. For instance, a crucial next step would be to include the views and experience of national healthcare agencies and health insurance providers.

The research project strived for an equal representation of the EU countries and the involved stakeholder groups. However, this was not fully achieved in practice. As shown in the case of NCPs, for example, one of the possible reasons for this result could be a lack of interest to participate and/or lack of experience with the topic. In a follow-up research it would be important to further investigate the reasons for the lower response rate from Eastern European countries. Efforts are required in order to engage the representatives from this region, especially as the study indicated that the need for cross-border access is more acute there. In addition, it would be beneficial to seek a more comprehensive approach for engaging regulators and ethics committees.

While the survey suggested that introducing an amendment to EU legislation is favoured by a significant number of stakeholders, the interviews offered more nuanced arguments. In-depth legal research has to be conducted prior to engaging in normative recommendations. More specifically, a detailed look into the EU's competences in the field of cross-border research and reimbursement and the eventual legal limits to a change would be a meaningful next step. Furthermore, legal comparative research on existing bi-lateral agreements for collaboration in the sphere of cross-border clinical trials and economic analysis would be essential.

As the study showed, cost coverage remains the biggest constraint to cross-border participation. Concrete identification of cost coverage options on national and EU levels and their financial implications would need to be developed.

CONCLUSIONS

- The study achieved a high response rate: 396 evaluable survey responses and 38 Interviewees from 7 stakeholder groups. All four European sub-regions were represented. The most responses came from Western Europe, while the least from Eastern Europe.
- Investigators/physicians and patients were the stakeholder groups who participated the most. In particular, the strong patient representation from oncology indications but also rare diseases was very important as it provided a clear indication of the patients' interest and needs, and furthermore involved them in the identification of challenges and the search for solutions from the very first stages of investigation.
- The study showed that cross-border access to clinical trials occurs, however very rarely.
- Cross-border access to clinical trials was identified as needed by the overwhelming majority of study participants from all stakeholder groups. However, imposing some limitations by, e.g., facilitating it specifically in the case of rare diseases or when there is no suitable treatment available in the patient's home country, was seen as an option by all stakeholders but the patients.
- The current system is regarded as sub-optimal and there is a strong need to improve it.
- The strongest motivation for cross-border access to clinical trials was access to treatment not available in the home country of the patient. This was the opinion of representatives from all stakeholder groups included in the study.
- The strongest reason for denying cross-border trial participation was the distance between home and location of the trial site.
- Countries located in Western Europe were shown to be the most attractive for patients seeking to participate in a clinical trial abroad. The main reasons why certain countries were more attractive included geographical proximity, lack of language barrier, countries where sponsors are more likely to open sites, and trust in the excellence of the foreign healthcare system.
- The countries of origin for patients who seek participation in a clinical trial abroad were shown to be primarily Member States in Central and Eastern Europe (CEE) as these countries' healthcare systems were perceived as offering inferior healthcare in comparison to other EU Member States and that less clinical trials are conducted in CEE.
- The biggest challenges for cross-border participation in a clinical trial mentioned were financial, administrative and legal burden and lack of access to reliable and easily accessible information.
- Especially by physicians enabling cross-border access to clinical trials was seen as only part of the required solutions to enabling access to a suitable clinical trial to all patients. Bringing clinical trials closer to the patient through modern technologies and a simplification of the regulatory framework for clinical trials were considered very relevant as well.
- Several divergent solution frameworks were proposed to clarify responsibility for costs coverage and organisation of logistics. Most study participants preferred cost coverage by the sponsor in case of

industry-sponsored clinical trials. In non-commercial/publicly sponsored trials different proposals for sharing responsibilities between host and home country of the patient were also proposed by different stakeholders.

RECOMMENDATIONS

The exploratory character of the study presupposed the need for further, broader research on the topic that would enable a normative judgement about next steps. At the current moment and level of knowledge, and after carefully balancing the needs and possible solutions for future actions proposed by study participants, the consortium decided to make a pragmatic recommendation:

Provision of reliable and easily accessible information on options and best practices for cross-border access to clinical trials was the most preferred solution in the survey and by most Interviewees. In the research team's opinion, this seems to be the most pragmatic approach. This could be elaborated in form of a guideline covering elements such as:

- Encouraging EU Member States to enable neighbouring country healthcare solutions like in the Nordic countries or university-based solutions like in the border region between Germany and The Netherlands,
- Adding this topic to the agenda of European Research Networks established according to the Directive on Cross-border Access to Healthcare
- Defining the needs for clarifying the patient liability insurance conditions if enrolled patients come from another country than the investigator's
- Defining recommendations for the social security and healthcare conditions for long-term follow-up in the patient's home country
- Clarifying the role of the patients' treating physician at home as contributor to data collection for the clinical trial

The guideline should be realized with input from all key stakeholder groups in all EU Member States.

It could be assumed that the establishment of a comprehensive multi-stakeholder, multi-national guideline could make cross-border access to clinical trials more frequent over time. In a second step, change in legislation could be envisaged. However, as showed in the Limitations, more detailed research is required prior to proposing specific legal and regulatory actions.

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