REPORT

EU-X-CT PUBLIC STAKEHOLDERS' FORUM

MAKING CROSS-BORDER ACCESS TO CLINICAL TRIALS A REALITY

WEBSITE

EU-X-CT C/O EFGCP
https://eu-x-ct.eu/

eu-x-ct

INTRODUCTION

The pan-European public-private EU-X-CT initiative aims to facilitate cross-border access to clinical trials. As a first step, we are collecting information on the regulatory, ethical, social security, liability insurance and organisational conditions for the involved stakeholders, as well as experiences and best practices in all European countries.

At the **Public Stakeholders' Forum** held in **Brussels on April 12, 2024**, the national conditions for patients, clinical investigators, academia/public funders, and industry sponsors needing cross-border participation of patients in clinical trials were reviewed. The EU-X-CT leadership presented the initial results of the EU-X-CT gap analysis.

This report summarises key insights from the meeting.

CONTENT TABLE

Table of Content

ACKNOWLEDGEMENTS

THE EU-X-CT THANKS ITS CONTRIBUTORS FOR THEIR CONTINUED SUPPORT

INITIATIVE LEADERSHIP

EFCCP

efpia

WITH THE SUPPORT OF

GOLD

Roche

SILVER

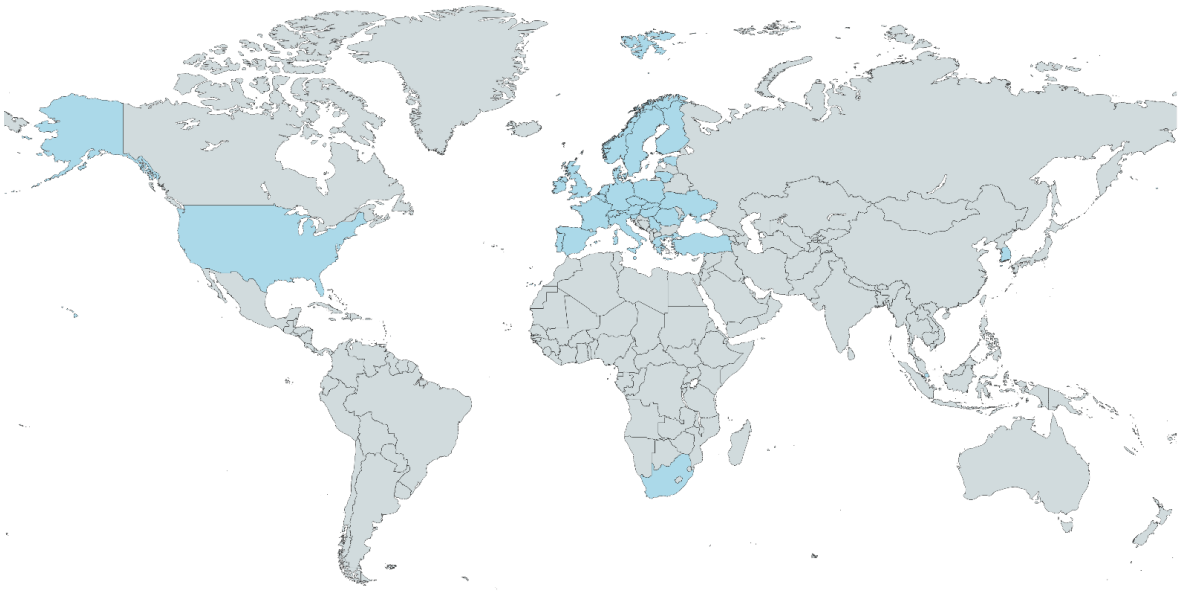
Johnson&Johnson

BRONZE

Pfizer

ATTENDEES

Participants joined from many different countries



In-person meeting attendees

Country	#
Austria	1
Belgium	15
Czech Republic	4
Denmark	1
Estonia	1
France	4
Germany	5
Greece	1
Hungary	1
Italy	1
Netherlands	8
Poland	1
Spain	3
Suomi	1
Sweden	4
Switzerland	2
United Kingdom	2
Total	**55**

Virtual attendees

Country	#
Belgium	9
Czech Republic	6
Denmark	1
Estonia	6
Finland	4
France	1
Germany	7
Great Britain	6
Greece	13
Hungary	14
Ireland	2
Italy	1
South Korea	7
Luxembourg	7
Malta	1
Netherlands	4
Norway	1
Poland	5
Portugal	4
Romania	2
Serbia	11
Singapore	4
Slovakia	1
Slovenia	11
South Africa	1
Spain	8
Sweden	2
Switzerland	1
Turkey	1
Ukraine	7
USA	1
Total	**149**

12 APRIL, 2024
SCHEDULE

09:00 **Registrations & Welcome Networking Coffee**

SESSION 1: WHERE ARE WE TODAY?

10:00 **Welcome and Introduction to EU-X-CT**

Welcome from EFGCP and EFPIA
Ingrid Klingmann, *Pharmaplex, EFGCP*
Susan Bhatti, *Merck BV, Chair CREG (EFPIA)*

Welcome from the academia members
Jacques Demotes Mainard, *ECRIN*

Welcome from the patient members
Lisbeth Snede, *Patients Unite*

10:20 **Round table: Current experience with cross-border trial participation**

Moderator:
Lisbeth Oxholm Snede, *Patients Unite*

Panelists*:*
Michel Zwaan, *Prinses Máxima Centrum voor kinderoncologie BV*
Violeta Astratinei, *Melanoma Patient Network Europe*

10:50 **Keynote: Overcoming borders will make Europe a more attractive place for clinical trials**

Elmar Nimmesgern, *European Commission DG R&I*

Q&A

11:20 **The issues of cross-border access to clinical trials in Europe: The EU-X-CT gap analysis**

Moderation and Introduction:
Susan Bhatti, *Merck BV*

Presentations by Task Force leads:
Maren Koban, *Merck Healthcare KGaA*
Lisbeth Snede, *Patient Unite*
Maja Pizevska, *Berlin Institute of Health at Charité (BIH)*

Q&A

12:20 **Panel and Open Forum Discussion:**
- Is this picture accurate and comprehensive?
- Where are the assessment gaps?
- What other EU initiatives would benefit from improved cross-border access to clinical trials?

Moderator:
Solange Corriol-Rohou, *AstraZeneca*

Panelists*:*
Elmar Nimmesgern, *European Commission DG R&I*
Emilie Prazakova, *Roche*
Janek Kapper, *Estonian Inflammatory Bowel Disease*
Marianne Lunzer, *AGES, CTCG co-chair*
Michel Zwaan, *Prinses Máxima Centrum voor kinderoncologie BV*
Monique Al, *CCMO, CTCG co-chair, MedEthicsEU co-chair*

13:00 **Lunch**

SCHEDULE

SESSION 2: WHERE DO WE WANT TO GO?

14:00 **Enabling cross-border access to Clinical Trial**

Moderator:
Sabine Kläger, *ECRIN*

PCM4EU and PRIME-ROSE - cross-border access to pragmatic precision medicine trials
Bettina Ryll, *Stockholm School of Economics Institute for Research and Melanoma Patient Network Europe*

Industry experience with Cross-Border Enrolment in Rare Diseases
Joanna Sprague, *ICON*

Q&A

14:30 **The way forward: How do we make progress in cross-border access to Clinical Trials?**

Moderator:
Bettina Ryll, *Stockholm School of Economics Institute for Research and Melanoma Patient Network Europe*

Panelists:
Begonya Nafria Escalera, *Hospital San Juan de Déu, eYPAGnet*
Elmar Nimmesgern, *European Commission DG R&I*
Jacques Demotes Mainard, *ECRIN*
Marianne Lunzer, *AGES, CTCG co-chair*
Monique Al, *CCMO, CTCG co-chair, MedEthicsEU co-chair*
Susan Bhatti, *Merck BV*

15:30 **Break**

15:50 **Open Forum Discussion: How can EU-X-CT achieve the most urgent goals and how to make them sustainable?**

Moderators:
Ingrid Klingmann, *Pharmaplex, EFGCP* and **Susan Bhatti**, *Merck BV*

16:50 **Conclusions and next steps**

Ingrid Klingmann, *Pharmaplex, EFGCP*

17:00 **End of meeting**

WHERE ARE WE TODAY

SUMMARY OF SESSION 1

Introduction to EU-X-CT

EU-X-CT co-chairs Ingrid Klingmann and Susan Bhatti welcomed all participants on behalf of the chairing organisations – EFGCP and EFPIA –to the first public stakeholders' meeting of the EU-X-CT initiative.

Sabine Kläger welcomed the participants on behalf of the academic community, and Lisbeth Snede welcomed the participants on behalf of the patient community.

They emphasised the need to make Europe more attractive for clinical trials by enabling better cross-border access and the concrete action needed in the next couple of months to ensure the initiative's success.

VIOLETA'S EXPERIENCES AS A CAREGIVER AND PATIENT ADVOCATE

Violeta shared her personal experience with cross-border trial participation as a caregiver to a melanoma patient and her professional experience as a patient advocate for melanoma patients.

- She shared her personal experience as a caregiver to her sister in Romania, who died of melanoma at the age of 51. She described seeking care abroad as difficult and "not a walk in the park." The most support came from the Melanoma Patients Network Europe. As a result of her efforts, her sister was able to access a clinical trial in Germany and a compassionate use program in Brussels, Belgium.

- As a patient advocate with Melanoma Patients Network Europe, she had experience with patients from Ukraine who were forced to move to neighboring countries due to the war in Ukraine in 2022. One of the countries they moved to was Romania. However, there were challenges with the language and informed consent forms (ICFs) for the clinical trials in Romania. The speaker also mentioned that the sponsors and clinicians were concerned that the duration of the war would not align with patient participation in trials and that statistics would suffer.

- She concluded that clinical trials abroad are highly needed but come with financial, logistical, and mental burdens for cancer patients and caregivers. Occasionally, proactive, highly educated, and well-connected patients succeed in participating in clinical trials abroad, but this is not a sustainable or equitable solution.

"I was surprised that despite all of this, her last words before she died, was whether there was anything more available for her out there, a clinical trial… something to save her life. My sister had trust and hope that the research would benefit people like her."

— Violeta Astratinei

Challenges to cross-border clinical trial access:

- Only patients/caregivers with the education, language capabilities, and financial means are currently able to access clinical trials abroad.

- Identifying hospitals and investigators involved in the right clinical trial is very challenging.

- Hospitals sometimes cite lack of capacity as a reason for not accommodating patients from other countries. Certain hospitals even ask for a deposit from cross-border patients.

- Insurance companies cite the lack of regulations as a reason not to support cross-border participation.

- Getting medical data across borders is also a challenge, particularly once back in the home country.

"If you have the financial means, then you can go with your money to Germany or Belgium and occasionally to Italy. But lately, some hospitals in Germany have started to ask for a deposit of 10,000 euros for trial participation."

— Violeta Astratinei

A CAREGIVER'S AND AN INVESTIGATOR'S CROSS-BORDER CLINICAL TRIAL EXPERIENCES

Prof. Michel Zwaan, a Paediatric Oncologist at the Prinses Máxima Centrum voor kinderoncologie BV, and Frederik, the father of a paediatric patient, shared their first-hand experience with a cross-border trial.

Frederik's daughter was a paediatric patient who was diagnosed with leukaemia in Belgium and initially treated there. However, she did not respond well and was then referred by her physician to the Prinses Maxima Centrum in the Netherlands, which had a suitable trial open (as the only site in EU). She responded well to the experimental treatment, but unfortunately passed away later following a transplant operation.

Positive experiences:

- Communication was not an issue here, as the two countries' common language was Dutch. A translation of the informed consent form was not necessary
- There were cultural differences between hospital care in the two countries. However, it was a welcome change for the little girl. She was happy at the hospital in the Netherlands, which had a music studio and art facilities
- Also, unlike the hospital in Belgium, her father was taught how to give her the medication, which he appreciated

Negative experiences:

- There were issues with approvals from the Belgian health insurance, which was difficult as time was critical
- Transport from Belgium to the Netherlands was not easy, and the father had to make a bed in his car to move his daughter because an ambulance would have been too expensive
- Once Frederik's daughter started feeling better, the transition from the clinic to recovery outside the clinic was rapid, which led to some feelings of insecurity
- After being sent home to Belgium following a bone marrow puncture, the puncture site bled during the car ride, necessitating a visit to a Belgian hospital for further checks and an additional two-night stay

ROUND TABLE: CURRENT EXPERIENCE WITH CROSS-BORDER TRIAL PARTICIPATION

Lisbeth Snede (Patients Unite) moderated the panel. The panellists included Michel Zwaan (Prinses Máxima Centrum voor kinderoncologie BV), Frederik, the father of a paediatric patient treated at Maxima, and Violeta Astratinei (Melanoma Patient Network Europe).

The discussion revolved around their experiences with cross-border trial participation, focusing on data sharing, finding clinical trials, and the role of patient networks.

Data sharing and continuity of care:

- Violeta shared her experience with data sharing during her time as a caregiver. She faced challenges in communication and transparency, particularly when moving CT scans and other medical data.
- She also highlighted the difficulty of managing toxicity after returning to their home country, as the treating physician was not familiar with the new drug used in the trial.
- Michel stressed the importance of physician involvement in data sharing and patient referrals by treating physicians. At Maxima, they only accept patients in clinical trials with the permission of the treating physicians to make sure that medical dossiers are shared directly between physicians.

Finding suitable clinical trials:

- Frederick, the father of the paediatric patient, relied on the treating physician, while Violeta utilized a patient network (Melanoma Patient Network Europe), online research and her personal network to find the clinical trials.
- Michel stressed the importance of physician involvement in finding the right clinical trials for patients. As an example, he mentioned the establishment of an International Leukemia/Lymphoma Target Board at Maxima. This board allows physicians to present cases and discuss the best next steps with international experts.
- The panellists agreed that patient networks play a significant role in helping patients navigate clinical trials and make informed decisions.

Actionable insights from the discussion:

Systematically consider what can be done to improve the process of finding and matching patients to suitable clinical trials.

Websites such as https://clinicaltrials.gov/ and the European www.clinicaltrialsregister.eu/ and could help but are difficult for patients to use.

KEYNOTE: OVERCOMING BORDERS WILL MAKE EUROPE A MORE ATTRACTIVE PLACE FOR CLINICAL TRIALS

Elmar Nimmesgern (European Commission DG R&I) delivered the keynote address, which covered the regulatory framework for clinical trials in Europe, investments and partnerships in clinical research, and the relevance of cross-border access to clinical trials in Europe.

Regulatory framework for clinical trials in Europe:

- The Clinical Trials Directive was approved by the European Commission to harmonize the conduct of clinical trials; however, there was divergence in how each Member State implemented it. To overcome this challenge, the Clinical Trials Regulation and the Clinical Trials Information System (CTIS) were introduced and became applicable in 2022.
- Elmar emphasised the complexity of harmonizing legislation among diverse EU member states. He believes the current framework benefits regulators and the industry by providing necessary guidance and encouraging the sharing of expertise.
- The ACT-EU partnership aims to improve the clinical trials environment in the European Union through harmonisation, innovation, and collaboration with stakeholders.

European funding and partnerships in clinical research:

- The European Commission has invested almost 3 billion Euros in clinical research through the Horizon and European Research and Innovation framework programs, with nearly a billion Euros dedicated to clinical research.
- The ERA4Health program, in partnership with EU member states, launches calls for clinical trials and supports investigations. The program supports platform trials, a type of clinical trial design in which multiple treatments are evaluated simultaneously to accelerate clinical research.

Cross-border clinical research in Europe:

- Elmar mentioned that the relevance of multi-country trials depends on the research question. Trials for more prevalent diseases, such as heart disease, can be done in a single country e.g. Germany
- An area where cross-border collaboration makes sense is rare diseases, which also include paediatric oncology. Paediatric oncology has demonstrated the importance of collaboration in clinical trials.
- The content of the European Health Data Space Legislation was recently agreed by the legislators. After formal approval and entry into application in the coming years, this legislation is expected to facilitate the portability of health data, making it easier for doctors across countries to access medical records. This could potentially aid in running cross-border registry trials.

THE EU-X-CT GAP ANALYSIS

EU-X-CT co-chair Susan Bhatti, along with task force leaders Maren Koban, Lisbeth Snede, and Maja Pizevska, presented initial results from the EU-X-CT surveys. Results from three surveys aimed at collecting information on legal, regulatory, and ethical aspects (survey 1), financial aspects, including patient liability coverage (survey 2), and aspects important to sponsors/CROs, investigators, and patients (survey 3) were presented.

Survey methodology

The EU-X-CT surveys are aimed to collect information on the following topics:

1. **Legal, regulatory, and ethics:** National laws, regulations, Ethics Committee (EC) requirements
2. **Financial:** Health insurance and patient liability coverage (healthcare systems/ insurers/payers)
3. **People and operational:** Patient organisations, investigators, academia, and industry sponsors/ CROs

EU-X-CT approached a broad range of stakeholders, including regulatory affairs and clinical research experts in the pharma industry and contract research organisations as well as ethics committee members, insurance and healthcare system experts, investigators, academic institutions, patient organisations, and patients to collect data.

Patient surveys were translated into all EU languages.

Summary of results from the survey on legal, regulatory and ethical aspects (n=110)

Legal and regulatory

- Cross-border clinical trial participation is generally not prohibited, and case-by-case participation seems to be feasible.
- Formal national legal/regulatory/ethical frameworks do not seem to exist for cross-border access to trials.
- Several countries (and the heads of medicines agencies) have issued national guidelines for cross-border clinical trial access for patients from Ukraine in the EU.
- There is a general lack of awareness; contradictory responses were obtained from certain countries.

Ethics

- Country-level requirements are mainly determined by ECs and are often based on individual cases.
- EC approval may be required for cross-border clinical trial participation.
- Patient-facing material is generally required to be in the patient's own language; translations/ translators at sites might be required.
- ECs may have ethical concerns regarding travel burden, site follow-up of patients, differences in care between countries, and other practical aspects in a foreign setting.
- Patients may have to take up temporary (or even permanent) residence in the country of the trial.

Summary of results from the survey on legal, regulatory and ethical aspects (n=110)

Financial

Insurance issues and cost coverage are key concerns (across surveys) as they are mostly not clearly defined:

- Costs of travel and/or baseline diagnostics and therapies at the country hosting the trial when not included in the trial site fees covered by industry or academic sponsors
- Coverage of additionally occurring costs such as adverse-event-related medical care or long-term baseline medication needed in the trial in the patient's home country between their study visits
- Coverage of healthcare costs incurred in the patient's home country after participating in a trial conducted in a different country.
- Liability insurance coverage for damages occurring to cross-border patients back home is typically not included in the trial site's insurance.
- Participating in a clinical trial in the US presents fewer administrative hurdles (in addition to more trial options) compared to Europe.

Very limited feedback indicates the lack of information on healthcare costs and insurance/liability beyond a few individual experiences (information on financial aspects were voluntarily offered in response to the other surveys e.g., legal/ethical, investigator, and patient surveys.)

Summary of results from the survey on people and operational aspects (n= >350)

Feedback from patients and patient organisations

- **Difficulty in accessing trials due to financial constraints:** Instances where patients are required to cover substantial out-of-pocket expenses, even when general health insurance coverage is available.
- **Logistics and administrative challenges:** Obtaining the necessary forms for health cost coverage and registration for medical attention in public hospitals can be cumbersome and time-consuming.
- **Uncertainties in legal and insurance aspects:** Processes not clear for cross-border participants.
- **Difficulty in obtaining answers to any open questions**: Leading to a cautious approach to cross-border participation.

Summary of the interim analysis of the surveys

- **490 responses were received:** 110 for survey 1, 27 for survey 2, and >350 for survey 3.
- **Cross-border trials are not explicitly forbidden in any country.** However, the lack of clarity and specific legal and regulatory guidance leads to a very cautious approach to cross-border participation for major stakeholders (sponsors, investigators, patients).
- **Cross-border access is currently managed on a case-by-case basis** and is associated with a high logistical and administrative burden (if not entirely covered by industry trial sponsors).
- **'Who pays for what' is the most critical issue.** Access to insurance coverage is needed, also for background treatment and trial-related injuries. Travel and accommodation costs can mean potentially high upfront out-of-pocket expenses for patients.

- **Language barriers might impact a patient's ability to understand risks.** Patients must be able to make an informed decision about joining the trial. There are also concerns about cultural differences in healthcare practices, the burden of frequent relocation for patients, and the potential impact on a patient's decision regarding risk.
- **Decentralised trial elements** across border may not be feasible in certain countries, although they might be the best option for patients.

PANEL AND OPEN FORUM DISCUSSION I

Solange Corriol-Rohou (AstraZeneca) moderated the panel discussion. The panellists included Elmar Nimmesgern (European Commission DG R&I), Emilie Prazaková (Roche), Janek Kapper (Estonian Inflammatory Bowel Disease), Marianne Lunzer (CTCG co-chair, AGES), Michel Zwaan (Prinses Máxima Centrum voor kinderoncologie BV) and Monique Al (CTCG co-chair, CCMO, and MedEthicsEU co-chair).

Role of ethics committees in cross-border trials and the possibility of a central ethics committee review:

- The panellists discussed the role of ethics committees in cross-border trials, and the topic of creating a European central ethics review body for clinical trials. Monique mentioned that such a possibility is currently explored as part of ACT-EU by the MedEthicsEU group that she co-chairs and that they are looking into the pros and cons and trying to determine the hurdles.
- Michel offered a nuanced perspective, acknowledging the potential benefits of a central ethics committee approval for streamlining processes, but also raising concerns about potential language and cultural barriers. He suggested that a template, adaptable to local contexts, could be a useful solution.
- Marianne mentioned that differences in national treatment standards might be more easily overcome in rare or ultra-rare diseases because, most of the time, the standard of care might not simply exist across Europe.

Role of regulators in cross-border trials:

- The regulators in the panel emphasised the need for a pragmatic approach to single vs. multi-country trials. There is a need for clear planning and a clear concept for cross-border approaches. If there is a clear motivation, it should be reflected in the protocol upfront and planned upfront so as not to surprise regulators with ad hoc needs for quick intervention.
- Monique suggested that we don't need more regulations and laws but need a pragmatic approach with more guidance and clarity.
- Marianne commented that the default expectation should be that patients receive care where they live. However, if there is only a centre of excellence abroad, this is a good reason for cross-border participation.

Pros and cons of single vs multi-country trials:

- Several panellists criticized one-centre trials, arguing that access to trials should not be limited to well-resourced, well-equipped Western European centres.
- Michel highlighted the enormous administrative burden on larger centres and investigators in single-country trials receiving patients from across Europe. He suggested that there should be an obligation to open more centres in Europe for rare diseases, and in the case of single-centre trials, the sponsors should pay for patients' cross-border travel and other costs.

Finding clinical trials:

- The panellists emphasised the importance of clear and accessible information about potential trials of interest.
- They suggested regulators could play a role in ensuring that information about clinical trials is clear, available in the patients' language, suitable for a layperson, and correctly entered into databases. Information needs to be reliable and robust.
- This would help patients find clinical trials that are relevant to them and make informed decisions about their participation.

"If your intervention is so complicated that no one else will be able to do it, then this would be a clear motivation for a single site and for a cross-border approach… And if there is a clear motivation reflected in the protocol upfront, plan it upfront, don't surprise us with ad hoc needs for quick intervention…time is critical most of the time in many diseases, so clear planning and a clear concept would be beneficial for the patients."

— Marianne Lunzer

"If you have a rare disease, such as in paediatric oncology there should be an obligation to open more countries in Europe, because you have to find these patients. And if you decide not to do that, maybe there is an obligation to pay for the cost."

— Michel Zwaan

Safety of patients between study visits and continuity of care in the home country:

- A participant raised concern about ensuring proper care for patients participating in clinical studies outside their home country. It is crucial to consider the safety of patients participating in clinical trials, especially at home between study visits.
- Once the patient returns to the home country, local doctors may lack the necessary information to handle adverse events or toxicities.
- Michel shared this concern and acknowledged the difficulty of maintaining open communication with the patient's local physician and monitoring their condition between visits. He mentioned the efforts to provide the local physician with information about potential side effects and 24/7 contact for emergencies. However, he admitted that this is a challenging process that takes time. He emphasised the importance of having these measures in place before sending a patient home, considering the potential need for the patient to stay for extended periods in a foreign country for the study.

Insurance issues:

- Michel pointed out that the insurance and healthcare coverage issues in the patients' home country are difficult to solve and require a lot of time spent by investigators.
- Emilie mentioned that access across Europe to clinical trials needs to be available for all EU citizens and not just those with money, connections and the ability to understand English.
- Patients need support to navigate administrative hurdles as well as people to support them overcome the cultural and practical challenges in the country where the trial site is located.

The role of clinical trial ambassadors and patient organisations:

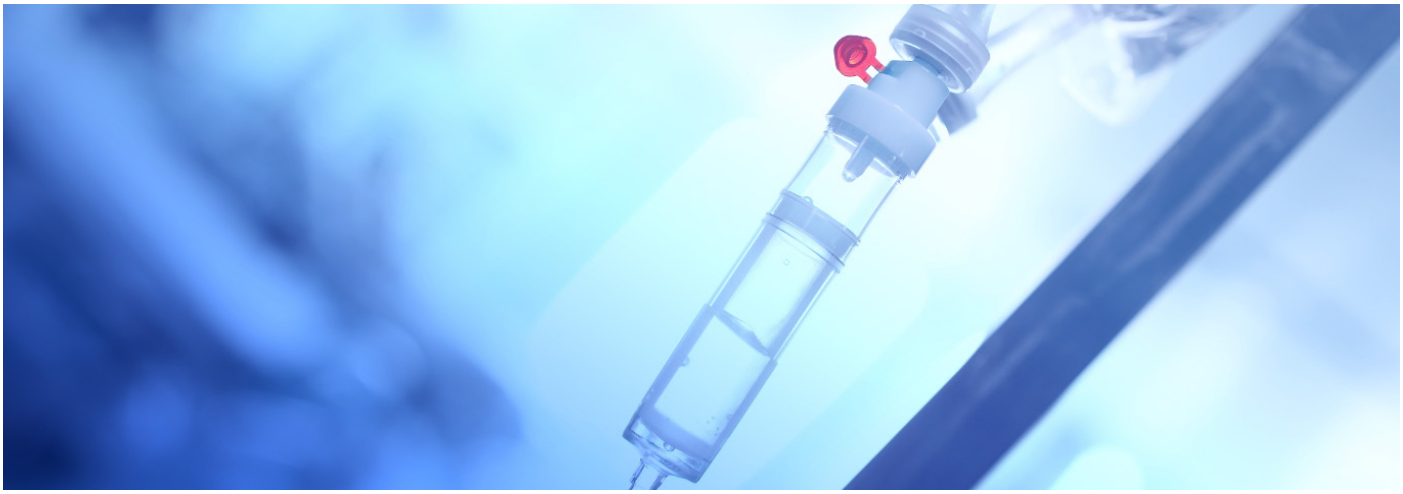
- A participant introduced a clinical trial ambassadors programme in Europe consisting currently of 52 clinical trial ambassadors and their numbers are increasing.
- Patient organisations are encouraged to have a clinical trial ambassador trained to provide patients with information about clinical trials and help them find suitable ones.
- The panellists also discussed the importance of translating information about clinical trials into local languages and sending it to specific disease associations.

WHERE ARE WE TODAY

SUMMARY OF SESSION 2

PCM4EU & PRIME-ROSE: CROSS-BORDER ACCESS TO PRAGMATIC PRECISION MEDICINE TRIALS

Bettina Ryll, from the Stockholm School of Economics Institute for Research and the Melanoma Patient Network Europe, introduced two Horizon Europe Mission on Cancer-funded projects: PCM4EU and PRIME-ROSE, and the challenges and motivations for cross-border clinical trial participation in Europe.



DRUP-like clinical trials run under the PCM4EU and PRIME-ROSE projects:

- PCM4EU and PRIME-ROSE aim to provide Europe-wide access to precision medicine for cancer patients. While PCM4EU focuses more on the diagnostic side, PRIME-ROSE focuses on setting up joint cohorts for clinical trials.
- The clinical trials run under the projects called DRUP-like clinical trials are independently organized academic trials that were inspired by the original Dutch Drug Rediscovery Protocol (DRUP) protocol used for research on repurposing of authorised medicines for new indications.
- One goal of such a trial methodology is equitable access to clinical trials in cancer precision medicine across Europe.
- Cross-border trial participation was considered a solution to the issue of access to these trials. However, currently, they are focussing on a different, more pragmatic approach that combines harmonisation at the European level with local independence.
- The goal is to have one master agreement at the European level for everyone connected, which will then be ratified at the national level independently. Currently, most active trials are in Western Europe but are slowly expanding to Eastern Europe.
- The speaker highlighted Norway as a good example of how equitable access can be made practical. Norway has connected all its clinical centres to a National Molecular Tumour Board, where any patient in the country, regardless of where they are, has access to the same quality and service. This is an example of a truly inspiring structure in which other countries are following suit. The setting up of a European National Tumour Board is under discussion.

Cross-border trials in various European regions – where are they happening:

- Successful cross-border clinical trial participation was mainly in paediatrics or when pharmaceutical companies set it up.
- Success was also found where there was established contact between two or more institutions, and in border regions. The speaker gave the example of an initiative between two institutions, one in Portugal and the other in Spain, where clinicians work together and coordinate the movement of patients back and forth.
- Motivation is particularly high in border regions, where potential trial patients may live on the other side of the border. Bettina gave the example of an initiative in Ireland working across the border with the UK.

> "At the moment, it relies too much on single individuals... individuals who can make it work. We need everyone... and the trial to the patient is a better solution than the patient to the trial..., and borders should no longer be barriers."
>
> **— Bettina Ryll**

INDUSTRY EXPERIENCE WITH CROSS-BORDER ENROLMENT IN RARE DISEASES

Joanna Sprague (ICON) shared experiences with cross-border enrolment for a rare disease clinical trial from a CRO perspective.

Cross-border trial setup for a rare disease clinical study:

- Pre-screening and recruitment: The case study involved recruiting of around 50 babies for a rare disease study. Due to the nature of the disease and the lack of treatment options in home countries, the parents/carers were very motivated to join the study. Pre-screening for the study was done by collecting and reviewing various details such as diagnosis, language skills, passport status, visa requirements, and willingness to travel while ensuring patient confidentiality and then matching patients to a site based on their requirements, preferences, and location. Nearly all the study participants were recruited across borders, both within and outside the EU.
- Ethics committees: The study team created and submitted a proposal document to different ethics committees, which included details on the justification for recruitment, pre-screening and consent, maintenance of confidentiality, insurance coverage, logistics, patient support, patient documentation, and post-study support. Ethics committee requirements and involvement varied.
- Logistics and language: The sponsor paid for travel and lodging for the patient and their parent/caregiver, and a third-party vendor was contracted to arrange the logistics. This vendor served as a confidentiality buffer between the sponsor and the patients, handling logistics without disclosing personal identifiers. It also proved beneficial in addressing language and cultural issues. The sponsor also paid for a patient liaison to support the patient with language and cultural issues.
- Informed consent: The patient's parents and investigator were required to sign the Informed Consent Form (ICF) in their language, with an interpreter also signing as an impartial witness. Additionally, caregivers were asked to bring copies of source data, which were then verified by a Clinical Research Associate fluent in that language.
- Insurance: International travel insurance was arranged for patients traveling between countries, and they were advised to carry their European Health Insurance Card (EHIC) if they were within the EU.
- IP shipment: The shipment of investigational products was found to be easier within the EU but posed logistical challenges outside of it.

The key learnings from the case study and suggestions for cross-border trial conduct:

- The study team should anticipate the possibility of cross-border recruitment, prepare accordingly, and educate the entire team about its potential and impact.
- Discuss the potential for cross-border recruitment with sites early on during pre-study site selection visits, assessing their willingness and ability to receive patients from other countries. Considerations include staff availability, technology, infrastructure, and the ability to manage the transfer of medical records and accommodate non-native language speakers.
- Engage with ethics committees early in the process, addressing the possibility of cross-border recruitment during initial applications in a proposal document to be shared prior to the actual application. For instance, through a phone call, if possible, before submitting the documents. Some ethics committees may require approval while others only want notification.
- Use pre-screening to identify suitable patients and ensure confidentiality is kept until consent is obtained.
- Recommend using a vendor to sort out insurance, travel, and lodgings for patients.
- Explore the use of decentralised clinical trials to facilitate cross-border recruitment. This approach, which involves remote patient monitoring and treatment, is showing promise within countries and could potentially be applied across borders.
- Consider the steps needed to ship investigational products across borders on an ongoing basis, particularly for patients with chronic illnesses. This aspect was not covered in the case study but is an important consideration.

THE WAY FORWARD: HOW TO MAKE PROGRESS IN CROSS-BORDER ACCESS TO CLINICAL TRIALS?

The panel discussion was moderated by Bettina Ryll (Melanoma Patient Network Europe) and panellists were: Begonya Nafria Escalera (Hospital San Juan de Déu and eYPAGnet); Elmar Nimmesgern (European Commission DG R&I); Jacques Demotes Mainard (ECRIN); Marianne Lunzer (AGES, CTCG co-chair); Monique Al (CCMO, CTCG co-chair, MedEthicsEU co-chair) and Susan Bhatti (Merck BV). All shared views on how to tackle the issue of cross-border clinical trial access.

A pragmatic approach to cross-border access to clinical trials:

- Cross-border trials are feasible, and various elements are already in place to facilitate them. The challenge is to know about options, to connect the available dots, leveraging the existing resources and initiatives.
- Providing guidance to Member States by showcasing a few examples, would be a pragmatic first step towards a solution.
- Reducing uncertainty would help reduce the administrative burden.

"When a commercial sponsor is actually setting the trial up, there is money available….we want to have involvement in our trials….the key thing is the preparation and making sure that you have reached out to the sites, to the patients, to patient organisations, to ethics committees, and basically told them upfront that there might be a necessity to do this so that people are not surprised and suddenly put under pressure to approve something"

— Susan Bhatti

A need for better preparation:

- Several panellists mentioned the importance of preparing for cross-border access to clinical trials, including reaching out to sites, patients, patient organisations, and ethics committees in advance

The potential of decentralised clinical trials (DCTs):

- The panellists suggested that using decentralised trial elements, such as remote monitoring, digital consent, and home delivery of treatments, could facilitate cross-border access and reduce the burden on patients.
- They also emphasised the need to raise awareness among patients and patient organisations about the possibilities and benefits of decentralised trials, as well as the existing guidance and tools for finding and participating in them.
- A successful DCT involving COVID patients in the UK was mentioned.

"I'm questioning.. Do member states even have a guidance of their own with respect to cross border research? Somebody says no. What is the basis of their response? …I think a first step would be to make an inventory if there is guidance. And if you have a guidance, what does it mean? Where can we harmonize things? I think harmonisation is the keyword, but it's also challenging."

— Bettina Ryll

The need for better harmonisation and standardisation:

- The panellists discussed the importance of agreeing on standards, processes, and infrastructure to facilitate cross-border access to clinical trials.

The challenges of language and cultural differences:

- Some panellists mentioned the challenges posed by language and cultural differences and the need to ensure that language is not used as an exclusion criterion.
- They also discussed the need to translate and validate informed consent forms, questionnaires, and other materials.

The importance of a risk-appropriate approach:

- Several panellists emphasised the importance of a risk-appropriate approach to cross-border access to clinical trials, where risks are identified, managed, mitigated, or simply accepted.

HOW CAN EU-X-CT ACHIEVE THE MOST URGENT GOALS AND HOW TO MAKE THEM SUSTAINABLE?

EU-X-CT co-chairs, Ingrid Klingmann and Susan Bhatti, presented a 6-point action plan based on the results of the EU-X-CT gap analysis and the multi-stakeholder discussions at the Public Forum

1. To work out the minimal ethics committee requirements for cross-border participation in clinical trials in collaboration with MedEthicsEU.
2. To develop a set of recommendations for industry and academic sponsors as well as CROs, on how to approach cross-border trials in their protocols, when to inform the relevant ethics committees about the planned conditions, and how to prepare and support sites for hosting patients from abroad.
3. To develop a set of recommendations for investigators and sites on aspects they need to clarify when wanting to host patients from abroad.
4. To reach out to payers and health insurance companies to get clarity on the cost coverage of cross-border trial participation.
5. To clarify with liability insurance companies how damages occurring to the patient in his/her home country could best be covered.
6. To raise awareness among patients and treating physicians about the option of cross-border participation in clinical trials. Establishing national contact points for patients was also suggested.

THANK YOU

All speakers and participants of the EU-X-CT Public Forum 2024

All EU-X-CT members and collaborators

EFGCP and EFPIA

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Report written by Dr. Roshini Beenukumar (Medical Writer) based on notes taken during the meeting and recordings of the talks. Summaries reviewed by Dr. Susan Bhatti and Dr. Ingrid Klingmann.

EU-X-CT PUBLIC STAKEHOLDERS' FORUM

MAKING CROSS-BORDER ACCESS TO CLINICAL TRIALS A REALITY

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