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Cross-border access to paediatric clinical trials in Europe: preventing language exclusion– an EnprEMA initiative

Recommendations for including paediatric patients in cross-border clinical trials in Europe without language discrimination

Comments should be provided using this template.

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Glossary

The following section defines key concepts and explains how these terms are used throughout this document.

Term	Definition (used in this document)
Cross-border clinical trial	Clinical study conducted at a site in one country that includes participants (patients) who travel from other countries to take part in the trial.
Multi-national clinical trial	Clinical study conducted simultaneously at multiple sites located in different countries, all following a single protocol.
Best practices	Activities or actions carried out by a sponsor, Contract Research Organisation (CRO), Clinical Trial Unit (CTU) or other stakeholder involved in trial execution that facilitate the inclusion of international participants in paediatric clinical trials conducted in a European country different from the patient's country of residence, specifically addressing any needs related to the patient's native language.
Case of discrimination	Situation in which international patients who are potential participants in a clinical trial are excluded, in practice or by criteria, on the basis of language and/or country of residence, where such exclusion is not justified by the protocol's scientific objectives, participant safety, or data quality/integrity considerations.
Diversity plan	Prospective, structured strategy designed to ensure that the children and young people enrolled in a clinical trial reflect the full variety of the populations affected by the condition, including demographic, linguistic, cultural, socioeconomic and health-related dimensions.
Patient Reported Outcomes Measures (PROMs)	Validated instruments used to capture patient-reported outcomes (PROs), i.e., reports from patients about their health condition and its impact (e.g., symptoms, functioning, HRQoL) without interpretation by clinicians or others.
Patient Reported Experience Measures (PREMs)	Standardised instruments that capture patients' direct reports on their experience of receiving care (including in the context of the participation in a clinical trial). Unlike PROMs - focused on health status or outcomes - PREMs emphasise process and care delivery elements as perceived by patients.

Executive Summary

This document addresses the challenge of language-based exclusion in cross-border access to paediatric clinical trials in Europe. Although regulatory frameworks at European level and globally (see Table 1, page 7) prohibit discrimination based on language or country of residence, children and families continue to face barriers to trial participation due to linguistic differences and insufficient language accommodation.

Findings from protocol analyses, surveys, and stakeholder input reveal that language requirements, whether explicit or implicit, can unjustifiably restrict access to innovative therapies for children, particularly those affected by rare diseases with no approved treatment who may need to travel internationally for trial participation [1,2,3,4]. Constraints in the availability of validated translations for patient-reported outcome measures (PROMs) and quality of life (QoL) instruments, as well as in some cases the limited access to professional translation and interpretation services, further compounds these barriers.

To address these issues, the EnprEMA working group on cross-border paediatric clinical trials recommends a comprehensive set of actions:

- **Eliminate language as an eligibility criterion** unless a clear scientific justification exists.
- **Facilitate access to fit-for-purpose translation and interpretation resources** for patient-facing materials and trial communications.
- **Incorporate explicit cross-border access and diversity plans** in paediatric trial protocols, with defined strategies for language inclusion.
- **Involve patients, families, and patient organisations** in trial design and protocol review to identify and address linguistic and cultural needs.
- **Harmonise operational procedures** and strengthen collaboration among sponsors, clinical trial units, and regulatory authorities to ensure consistency and quality.
- **Establish mechanisms to monitor and report language-based discrimination**, promoting transparency and continuous improvement to design and deliver inclusive clinical trials across Europe.

The guidance underscores that scientific and ethical excellence in paediatric clinical research requires making language inclusion a core principle. By removing language barriers and promoting best practices, Europe can ensure that all children, regardless of their native language, have equitable access to the benefits of clinical research.

Introduction

Paediatric clinical research in Europe faces unique challenges due to the continent's linguistic diversity and the rarity of many childhood diseases. For children affected by rare or ultra-rare conditions, participation in clinical trials often represents the only opportunity to access innovative therapies, particularly when no approved treatments exist in their home country. However, language barriers—stemming from the 24 official languages of the European Union and additional languages across the continent—can limit access of children and families to research, undermining both scientific progress and patient rights.

Recent studies and surveys revealed that language requirements in trial protocols, lack of validated patient-reported outcome measures (PROMs) in multiple languages, and insufficient translation support are significant obstacles to cross-border trial participation [1,2,3,4]. Analysis of European paediatric trial protocols showed that while most do not explicitly use language as an eligibility criterion, a notable minority do, often without scientific justification. This practice risks discrimination and restricts equitable access to research, particularly for international patients and those not proficient in the host country's language.

Parents and caregivers across Europe have expressed willingness to support participation in clinical trials across national borders when needed, as well as to accept decentralised or digital trial procedures, provided appropriate language support is available [2]. Their experiences highlight the burden of travel, the importance of clear communication, and the need for translated consent forms, questionnaires, and information materials. Clinical Trial Units and sponsors have demonstrated that accommodating language needs, through professional interpreters, written translations, and flexible protocol design, is both feasible and essential for equitable inclusion.

Ethical and regulatory frameworks, including the Charter of Fundamental Rights of the European Union[5] and the United Nations Convention on the Rights of the Child[6], prohibit discrimination based on language and affirm the right of every child to the best possible healthcare. Facilitating cross-border access to paediatric clinical trials, supported by robust language accommodation, is therefore not only a scientific necessity but also an ethical obligation. It ensures that research populations reflect the diversity of affected children, improves the generalisability of trial results, and upholds the rights and dignity of all participants.

These recommendations are informed by evidence collected through surveys of clinical trial sites and parents, as well as regulatory analysis, to propose practical measures to mitigate language-related barriers to participation. Harmonising practices, promoting routine translation of participant-facing materials, and involving patients and families in protocol design, may support more inclusive participation in paediatric clinical research across Europe.

This guidance has been designed by a working group within the European Network of Paediatric Research at the European Medicines Agency (EnprEMA). The group's mandate was to evaluate the current landscape of cross-border paediatric clinical

trials in Europe with a particular focus on language-related barriers and risks of discrimination.

Background

Regulatory frameworks and references on cross-border access to paediatric clinical trials

Facilitating cross-border access to paediatric clinical trials in Europe requires navigating a complex landscape of regulations, ethical guidelines, and operational practices. While the scientific and ethical imperative for inclusion is clear, the regulatory environment presents both opportunities and gaps that must be addressed to prevent language-based exclusion and ensure equitable participation.

European Union

- Clinical Trials Regulation (EU) No 536/2014[7]. This regulation harmonises the conduct of clinical trials on medicinal products for human use across EU Member States and EEA EFTA Member States, aiming to improve transparency and safety. It does not specifically regulate cross-border patient access or address language barriers for international participants. The inclusion of children from other countries in a trial remains at the discretion of sponsors and sites, with language accommodation often handled ad hoc.

- Paediatric Regulation (EC) No 1901/2006 [8]. This regulation mandates a Paediatric Investigation Plan (PIP) for new medicines intended for children, or new indications, new pharmaceutical forms or routes of administration for medicines under patent, ensuring that paediatric studies are scientifically and ethically robust. It does not provide guidance on cross-border participation or language inclusion.

- Directive 2011/24/EU on Patients' Rights in Cross-Border Healthcare [9]. This directive establishes the right of EU citizens to seek healthcare in other Member States. It highlights principles of universality, equity, and non-discrimination, including language, and requires Member States to ensure that patients are treated equitably based on healthcare needs rather than nationality or language. Participation in clinical trials falls outside the scope of this Directive.

- Charter of Fundamental Rights of the European Union (2000) [1]. Article 21 prohibits discrimination on grounds such as language, national origin, or other status. Article 24 affirms the rights of the child, including protection, care, and consideration of their best interests. Together, these provisions provide an ethical foundation for inclusive research practices.

International and ethical guidelines

- United Nations Convention on the Rights of the Child (1989) [2]. This global treaty protects children from discrimination, including on the basis of language (Article 2), and affirms their right to the best possible healthcare (Article 24) and to use their own language (Article 30).

- ICH E17 Guideline (2017) [10]. The International Council for Harmonisation's E17 guideline recommends harmonisation in the planning and design of multi-regional clinical trials. Where trial related documents are translated to local languages,

consistency across language versions should be ensured (e.g. through reverse translation), emphasising the importance of validated translations of patient-facing materials and outcome measures.

- ICH Good Clinical Practice E6(R3) [11]. This guideline requires clear communication of study information to patients and caregivers in a language they understand, and the use of valid, reliable, and culturally adapted measurement instruments. This guideline emphasises that informed consent and study-related communications must be clear and comprehensible; translation of patient-facing documents (like ICFs and diaries) is considered essential for patient comprehension.
- Declaration of Helsinki (2024) [12]. The Declaration sets ethical principles for medical research involving human subjects, stressing the need for informed consent and understandable information for participants. It explicitly mandates that all essential information be communicated in clear and understandable language, ensuring participants can fully comprehend the details necessary to give truly informed consent.
- WHO Guidance for Best Practices for Clinical Trials (2024) [13]. The World Health Organization recommends efforts to reduce language barriers and provide information in suitable languages and formats for intended audiences.

Table 1. Regulations and frameworks that need to be considered when designing and planning cross-border paediatric clinical trials.

Instrument/Framework	Scope	Relevance to Cross-Border Paediatric Trials	Language/Non-Discrimination Provisions
Clinical Trials Regulation (EU) 536/2014	EU	Harmonises trial conduct, but does not regulate cross-border access	Nonspecific
Paediatric Regulation (EC) 1901/2006	EU	Requires PIP for paediatric medicines	Nonspecific
Directive 2011/24/EU	EU	Establishes right to cross-border healthcare	Non-discrimination, including language
Charter of Fundamental Rights of the EU	EU	Fundamental rights, including healthcare	Article 21: No discrimination by language
UN Convention on the Rights of the Child	Global	Child rights, including healthcare	Article 2, 24, 30: No discrimination, right to language
ICH E17/E6(R3)	International	Multiregional trial design, GCP	Validated translations, clear communication

Declaration of Helsinki	International	Ethics in medical research	Understandable information, informed consent
WHO Guidance (2024)	International	Best practices in clinical trials	Reduce language barriers

Recent analyses of European paediatric clinical trial protocols reveal that most do not explicitly use language as an eligibility criterion, but a notable minority do, often without scientific justification (e.g. neurodevelopmental assessment in a child requiring the use of language). Additionally, there are documented cases of paediatric patients being excluded from participation in a clinical trial conducted in another European country due to their native language, despite this not being specified as an eligibility criterion in the trial protocol. This can result in exclusion of non-native speakers and restrict equitable access to research.

Surveys of parents and clinical trial units conducted by the EnprEMA working group highlight the feasibility and necessity of language accommodation, including professional interpreters, written translations, and flexible protocol design [2]. These findings underscore the ethical imperative to mitigate against language-based exclusion and the need for harmonised practices across Europe.

While the European regulatory landscape provides a strong foundation for non-discrimination and patient rights, there is a gap in explicit regulation and operational guidance for cross-border access and language inclusion in paediatric clinical trials. Addressing these gaps requires harmonised practices, proactive planning, and a commitment to equity and inclusion at every stage of trial design and conduct. This guidance provides recommendations to facilitate the inclusion of paediatric patients in clinical trials conducted at sites in a European country other than their country of residence, ensuring that there is no language-based discrimination.

Objectives

The implementation of the recommendations included in this guidance aims to achieve the following objectives:

1. Facilitate equitable cross-border access to paediatric clinical trials by ensuring non-discriminatory practices that account for language diversity.

2. Promote best practices for language accommodation when paediatric patients have cross-border access to clinical trials (e.g. translation of patient information sheets and informed consent forms, PROMs and QoL scales, etc.).

3. Ensure that any language-based eligibility criteria are scientifically justified.

4. Involve patients, families, and stakeholders in protocol design when study expects to recruit international patients, and specifically in language requirements of the clinical trial (e.g. translations of the informed consent, validation of PROMs, etc.).

5. Harmonise operational procedures across Europe in regard to the language support when incorporating international patients in paediatric clinical trials

6. Facilitate the reporting and analysis of cases of cross-border and language discrimination.

7. Advance scientific and ethical excellence facilitating the inclusion of paediatric patients in cross-border clinical trials.

Scope

This guidance provides comprehensive recommendations to support the participation of paediatric participants in cross-border clinical trials in Europe without exposure to language-based discrimination. It addresses the operational, ethical, and regulatory challenges that arise when children and families seek access to clinical research opportunities outside their country of residence, particularly in the context of rare and ultra-rare diseases where local trial options are limited.

The recommendations may also be applied to paediatric patients and their families living in a country where they are not proficient in the official European language(s) (e.g. immigrants, refugees), and who therefore require language accommodation to participate in a clinical trial in their country of residence.

Preventing discrimination based on a child's mother tongue, while also ensuring that clinical trials are inclusive and respectful of diversity, brings additional benefits. These include improved patient recruitment, smoother trial conduct in line with planned timelines, and, in the medium to long term, the potential for earlier access to medicines reaching the market.

Methodology

Data collection: state-of-the-art analysis

Three sources of data were used to gather evidence on the current state of paediatric patients' access to cross-border clinical trials and to assess how language accommodation is managed:

1. Analysis of language and country of residence as eligibility criteria in clinical trial protocols. Data from paediatric study protocols published in EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) and ClinicalTrials.gov between 2007 and 2024 were analysed to examine the scientific and ethical rationale for using language and country of residence as exclusion criteria [14].

2. Expertise and experience of Clinical Trial Units (CTUs) across Europe in conducting paediatric clinical trials involving international participants. Three surveys were conducted: the first collected information on general CTUs expertise, the second focused on best practices in trials with international participants, and the third aimed to identify documented cases of discrimination, particularly those related to native language requirements. Data from 17 European countries were analysed using descriptive statistics and thematic analysis [15].

3. Experiences and preferences of parents of children living with rare diseases regarding access to cross-border clinical trials. An anonymous online survey was

designed and translated into 22 official European languages. It comprised five sections: (1) sociodemographic information; (2) experience participating in a clinical trial; (3) experience when the patient was unable to participate in a study abroad; (4) experience participating in a clinical trial abroad; and (5) preferences regarding decentralised trial options [2].

Detailed results from these studies are publicly available. Supplementary stakeholder input from selected advisory boards, patient organisations, and clinical trial experts (e.g., members of Ethics Committees) was also obtained.

These recommendations were developed by an iterative review of the empirical findings and relevant legal and regulatory frameworks. Draft proposals were discussed through structured online meetings of the Working Group. The wording and scope of recommendations were refined through group discussion and consensus. Considering the clinical trial that you are designing or conducting some of these recommendations can be applicable and feasible. We encourage all the different stakeholders involved in paediatric clinical trials to assess the feasibility of these recommendations, and its positive impact in terms of equity, diversity and inclusion.

Recommendations

1. Avoid language as an eligibility criterion unless scientifically justified:

- Limit the use of native language or country of residence as inclusion/exclusion criteria unless there is a clear scientific justification (e.g., neurodevelopmental studies in children that require the assessment of language abilities).
- Ethics Committees should evaluate whether such criteria are appropriately justified and whether translation or interpretation measures could enable participation.

Examples:

- *A neurology trial requires participants to complete cognitive assessments tools only available and validated for use for this purpose in French. The protocol provides a scientific justification for restricting eligibility to participants with sufficient proficiency in French to complete these assessments reliably.*
- *In contrast, an oncology trial does not require any language proficiency due to the nonexistence of patient reported outcomes measures required in the protocol; instead, translation services are provided for all documents and interactions, enabling participation of children speaking any official European language.*

2. Facilitate access to fit-for-purpose translation and interpretation resources:

- Provide professional translation of all relevant documents (patient information sheet, informed consent, PROMs/QoL questionnaires, patient facing materials, etc.) into the patient's/family's native language or a language they are fluent in.

- When previously validated versions of PROMs/QoL tools are not available in the patient's language, consider the use of translations done by professional and certified experts supported by documented quality assurance to minimise the risk of altering measurement properties. Ethics oversight may be appropriate. Where instrument validity is critical to interpretation (in particular for primary or key secondary endpoints), additional evidence is needed to support cross-cultural validity and adequate measurement properties in the target population and context of use.
- Consider the use of technology-assisted or AI-supported translation tools, provided that outputs undergo appropriate review and quality control, and are demonstrated to be accurate and fit for purpose in accordance with applicable regulatory and ethical requirements.

Examples:

- *A trial site contracts certified translators to provide the patient information sheet, informed consent, and questionnaires in the native languages of families who do not speak the site's official language. Ethics Committees are informed about who did the translations and their expertise in the medical field.*
- *A professional cultural mediator supports communication between clinicians and families. This role ensures not only accuracy in the communication, but also sensitivity to cultural context and diversity.*

3. Design protocols with explicit cross-border access and diversity plans:

- Include in the protocol a dedicated section on cross-border access, specifying objective criteria for the inclusion of international participants and strategies to overcome language barriers.
- Incorporate a diversity plan that ensures representation of relevant linguistic and cultural subpopulations for the condition studied.

Examples:

- *The protocol includes a "Cross-Border Access" section outlining steps for enrolling international participants, such as translation of documents, support for travel logistics, and remote follow-up options.*
- *A "Diversity Plan" specifies that recruitment should reflect the linguistic and cultural diversity of the disease population and sets targets for inclusion of underrepresented groups.*

4. Involve patients and families in review of study design:

- Engage paediatric patients and their families in the design of clinical trials, especially in reviewing informational materials and questionnaires, to identify linguistic and cultural needs.

Examples:

- *Before finalising the protocol, the research team holds focus groups with parents and young patients from different countries to review the consent forms and questionnaires and, educational materials, ensuring clarity and cultural relevance.*
- *Feedback from families leads to the simplification of language and the addition of visual aids in patient materials.*

5. Establish support structures for international participants:

- Recognise the benefits of the services of international patient departments that manage not only translation but also logistics (Visas, accommodation, transport, etc.) and cultural support.
- Facilitate access to cultural mediators and native-speaking healthcare professionals to improve the experience of participants and their families during the trial.

Examples:

- *The hospital's International Patient Department assists families with Visa applications, arranges accommodation, and provides a dedicated case manager who speaks the family's language.*
- *Cultural mediators are available to help families navigate local customs and healthcare systems during their stay.*

6. Promote decentralised and digital trial models:

- Encourage the use of digital technologies, telemedicine, and local/satellite visits to reduce travel burden and facilitate participation of families from different countries and languages.
- Ensure that digital platforms and devices used are available in multiple languages.
- Consider the benefits of including AI solutions that can support the communication needs when for example a cultural mediator is not available (e.g. emergency situations).

Examples:

- *The trial allows remote consent via secure video calls, with interpreters present, and enables families to complete questionnaires online in their preferred language.*
- *Local satellite centres are set up in different countries, so families can attend follow-up visits closer to home, reducing travel burden.*

7. Raise awareness and train research teams:

- Train teams in linguistic and cultural diversity (transculturality), and in the use of interpreters and translation tools.
- Promote ethical awareness of children's rights to participate in research without language discrimination, in line with the Convention on the Rights of the Child and the Charter of Fundamental Rights of the EU.

Examples:

- *All staff involved in the trial receive training on cultural competence, working with interpreters, and the ethical importance of non-discrimination.*
- *The trial team regularly reviews cases where language barriers were overcome and shares best practices internally and with other centres.*

8. Facilitate reporting and analysis of language-based discrimination:

- Establish mechanisms to collect and analyse cases of exclusion due to language, both at the design stage and during trial execution.
- Share good practices and lessons learned among European Clinical Trial Units and clinical research networks.

Example:

- *The trial unit keeps a log of any cases where patients were excluded due to language, and reports them to the Ethics Committee and the national competent authority and/or a humans right institution.*
- *Good practices—such as successful inclusion of non-native speakers—are documented and shared at European paediatric research conferences, manuscripts, training of stakeholders, among other initiatives.*

NOTE:

See Table 2 on the next page for a summary of the stakeholders that can be involved in the implementation of each recommendation.

Table 2. Stakeholders that can be involved in the decision-making process and implementation of each recommendation.

Recommendation	Stakeholders
1. Avoid language as an eligibility criterion unless scientifically justified	• Trial sponsors (pharma, academic) • Ethics Committees • Regulatory authorities
2. Facilitate access to fit-for-purpose translation and interpretation resources	• Trial sponsors • Clinical research organisations (CROs) • Site investigators and research coordinators • Healthcare institutions • Research networks
3. Design protocols with explicit cross-border access and diversity plans	• Trial sponsors • Ethics Committees • Patient and parent representatives • Patient involvement experts
4. Involve patients and families in review of study design	• Patient and parent representatives • Patient involvement experts • Sponsors • Clinical investigators • Clinical trials Sites • Research networks
5. Establish support structures for international participants	• Trial sponsors • Clinical trials Sites • Social workers and patient navigators
6. Promote decentralised and digital trial models	• Trial sponsors • Digital health and IT providers • CROs • Regulators • Ethics Committees
7. Raise awareness and train research teams	• Sponsors • Clinical trials Sites • Professional societies • Research networks
8. Facilitate the reporting and analysis of cases of language discrimination	• Trial sponsors • Ethics Committees • Regulatory authorities • Clinical investigators • Patient advocacy organisations • Research networks

Conclusion

Language-based exclusion in cross-border paediatric clinical trials in Europe remains a significant ethical, scientific, and operational challenge. The analysis conducted by the EnprEMA working group demonstrates that, although most trial protocols do not explicitly use language as an eligibility criterion, there are still cases where a child's

native language or country of residence unjustifiably limits their participation as an international patient.

Language barriers, the lack of validated translations for patient-reported outcome measures (PROMs) and quality of life (QoL) instruments, and insufficient access to professional translation and interpretation services are major obstacles to equity in paediatric research. Such practices not only contravene European and international regulatory and ethical frameworks—such as the Charter of Fundamental Rights of the European Union and the United Nations Convention on the Rights of the Child—but also undermine the representativeness and scientific validity of clinical trial results.

The evidence gathered through protocol analysis and stakeholder surveys highlights both the feasibility and necessity of implementing language inclusion measures. These include professional translation of all patient-facing materials, the presence of interpreters, flexible protocol design, and the active involvement of patients and families in reviewing study documents and procedures. These actions are not only possible but essential to ensure the participation of children from diverse linguistic and cultural backgrounds.

Therefore, the following conclusions are drawn:

- **Language should not be used as an exclusion criterion unless supported by a clear and robust scientific justification**. This principle should gradually become standard practice in European paediatric clinical research.
- **Access to professional translation and interpretation resources should be facilitated throughout all stages of the trial**, from informed consent to data collection and communication of results. The right funding should be allocated to ensure it.
- **Protocols should include dedicated sections on cross-border access and diversity**, with clear strategies for including international participants and overcoming language barriers.
- **Patients, families, and patient organisations should be actively involved** in the design and review of clinical trials to identify needs and improve the quality and relevance of research.
- **Harmonisation of operational procedures and collaboration among sponsors, trial units, and regulatory authorities is essential** to ensure consistency and quality across countries and sites.
- **Mechanisms should be established to report and analyse language-based discrimination**, promoting transparency and continuous improvement of practices.
- **Scientific and ethical excellence can only be achieved if language inclusion becomes a cross-cutting principle**, ensuring representativeness, validity, and respect for the rights of all child participants.

In summary, achieving truly inclusive and equitable paediatric clinical research in Europe requires a strong commitment to linguistic diversity, the removal of barriers, and the active promotion of good practices. Only by doing so can we ensure that no child is excluded from the benefits of research due to language.

Working group members

The working group brought together a diverse and highly experienced team of professionals from across Europe, representing clinical research, paediatric medicine, regulatory science, and patient and public involvement. Its members include clinicians, researchers, patient involvement leaders, clinical trial unit specialists, and representatives of major European and international paediatric research networks.

- **Begonya Nafria** (Spain). Head of Patient Engagement in Research at SJD Barcelona Children's Hospital. Founder and Steering Committee member of eYPAGnet (European Young Patients Advisory Group Network). Co-chair of the Children's Medicines Working Party at EFPGCP. Member of the Technical Advisory Group (TAG) on Clinical Research Ecosystem Strengthening at the World Health Organization (WHO). Chair of the working group of cross-border access to clinical trials at EmprEMA.
- **Dr. Gilles Vassal** (France). Paediatric Oncologist. PhD in Pharmacology. He is Professor of Oncology at University Paris-Sud and Head of Clinical Research at Gustave Roussy (France). President of the EU Academic Consortium for Innovative Therapies for Children with Cancer (ITCC). Chair of ACCELERATE multi-stakeholder platform (www.accelerate-platform.eu) to speed up innovation in paediatric oncology.
- **Dr. Ricardo Fernandes** (Portugal). MD, PhD, Consultant Paediatrician. Chair of EnprEMA. Associate Professor in Clinical Pharmacology at the Faculty of Medicine, Universidade de Lisboa. Project lead at STAND4KIDS - Supporting Trials Portugal; Chief Medical Officer, conect4children-Stichting.
- **Dr. Pamela Dicks** (Scotland). Network Manager at Scottish Children's Research Network. Young Person's Advisory Group leader and member of Generation R (United Kingdom). eYPAGnet (European Young Person's Advisory Group Network) founder and Steering Committee Member.
- **Segolene Gaillard** (France). Clinical Trial Unit Project Manager at Hospices Civils de Lyon. Young Person's Advisory Group leader and member of Generation R (United Kingdom). eYPAGnet (European Young Person's Advisory Group Network) founder and Steering Committee Member.
- **Dr. Martine Dehlinger-Kremer** (Germany). Doctorate in Sciences. *Sn Development Strategy Lead Pediatrics, at UCB Biosciences.* She brings +30 years of experience in the research industry, with a distinguished focus on global regulatory affairs, medical affairs, maternal-fetal medicine, and paediatric leadership. Co-chair of the Children's Medicines Working Party at EFPGCP.

Annex 1: Examples of clinical trial protocol sections dedicated to accommodating language diversity for cross-border access

This section provides examples of clinical trial protocol sections that can be incorporated into clinical trial documents to address the diverse needs of international participants, particularly regarding language accommodation during screening and enrolment in trials conducted in a host country different from the family's country of residence.

The use of these sections will help ensure that each clinical trial can be adapted to the specific language requirements of the patient population. When developing the content of these sections it is important to consider the reference to local and European regulations (e.g., EU Regulation 536/2014, Charter of Fundamental Rights, Convention on the Rights of the Child) and to consult with patient representatives and Ethics Committees to ensure appropriateness.

1. Section Title: Cross-border patient inclusion and support.

Objective: To facilitate the inclusion of paediatric participants residing outside the host country, ensuring equitable access to the trial regardless of nationality or language.

Procedures (examples):

- *The trial site will accept referrals from international patients, including those from other EU Member States and non-EU countries.*
- *The International Patient Department (or designated team) will coordinate logistics for travel, accommodation, and Visa support.*
- *All patient-facing documents (information sheets, consent/assent forms, diaries, questionnaires, etc.) will be made available in the patient's preferred language, using professional translation and/or validated versions.*
- *Remote screening and telemedicine visits will be offered where feasible to reduce travel burden.*
- *A case manager or cultural mediator will be assigned to each international family to provide ongoing support.*

2. Section Title: Language inclusion and translation procedures.

Objective: To ensure that language is not a barrier to participation and that all communications are clear, culturally appropriate, and accessible.

Procedures (examples):

- *Language will not be used as an eligibility criterion unless scientifically justified (e.g., language-based cognitive assessments).*
- *Professional translation services will be used for all study documents and patient-reported outcome measures (PROMs/QoL).*

- *Where validated translations of PROMs/QoL tools are unavailable, ad hoc translations will be provided by accredited professional experts and should be informed to the Ethics Committee.*
- *Interpreters (in-person or remote) will be available for all study visits and communications as needed.*
- *All digital platforms (eConsent, diaries, questionnaires) will support multiple languages.*

3. Section Title: Diversity and inclusion plan.

Objective: To promote the inclusion of diverse patient populations, reflecting the epidemiology and cultural backgrounds relevant to the disease under study.

Procedures (examples):

- *Recruitment strategies will target underrepresented linguistic and cultural groups. This study aims to include at least 20% of participants from non-local language backgrounds.*
- *The protocol will set targets for inclusion of participants from different countries, ethnicities, and language backgrounds.*
- *Patient and family representatives will be involved in reviewing study materials for cultural and linguistic appropriateness.*
- *Data on participant demographics (including language, country of origin, ethnicity) will be collected and monitored throughout the study.*
- *Barriers to inclusion (e.g., language, travel, digital access) will be identified and addressed proactively.*

4. Section Title: Eligibility Criteria: language.

Objective: require language as an eligibility criterion when there is a scientific justification.

Procedures (examples):

- *Language proficiency will not be used as an eligibility criterion unless justified by the scientific objectives of the study (e.g., language-based cognitive assessments).*
- *If validated translations of PROMs/QoL tools are unavailable, ad hoc translations will be prepared by qualified certified translators and approved by the Ethics Committee. Professional interpreters (in-person or remote) will be available for all study visits and communications as needed. All digital platforms used for eConsent, diaries, and questionnaires will support multiple languages (specifically the languages of the participants recruited).*

Annex 2: Sponsor and CTU checklist

Actions to accommodate language diversity in paediatric clinical trials

This section lists actions that can be implemented at the sponsor or Clinical Trial Unit level to support the inclusion of international participants in paediatric clinical trials conducted in a country different from the patient's country of residence.

Sponsor checklist:

- ☐ Translate informed consent forms (including back-translation).
- ☐ Translate and culturally adapt patient education materials.
- ☐ Provide validated translations for PROMs questionnaires.
- ☐ If not, available PROMs validated provide ad hoc translations by certified professionals.
- ☐ Translate emergency instructions and safety reporting guidelines.
- ☐ Include language accommodation in trial budget and contracts.
- ☐ Offer multilingual hotline or support contact.
- ☐ Regulatory compliance: Ensuring translations meet local authority requirements.
- ☐ Technology adaptation: Multilingual ePRO systems and patient portals.
- ☐ Audit documentation: Proof of translation and back-translation processes.

CTU checklist

- ☐ Arrange interpreter services for all patient visits (on-site or remote).
- ☐ Provide verbal explanation of consent with a certified interpreter or cultural mediator present.
- ☐ Train staff on working with interpreters and multilingual tools.
- ☐ Distribute translated patient education materials.
- ☐ Support patient in completing multilingual PRO tools.
- ☐ Send appointment reminders in patient's language.
- ☐ Offer multilingual hotline or support contact.
- ☐ Document interpreter uses and communication in source notes.
- ☐ Providing and arranging interpreter services: On-site or remote during visits.

Annex 3: Ethics Committees responsibilities

When an international paediatric patient is enrolled in a clinical trial abroad, the Ethics Committee (EC) has specific, enhanced responsibilities to protect the rights, safety, and welfare of the child participant. These responsibilities include:

- **Prevent language-based exclusion:** Trials must avoid using native language as an exclusion criterion when there is no scientific justification. Ethics Committees are responsible for requiring trial sponsors to include multilingual strategies in protocol design to enable equitable access.
- **Mandate translations for participant-facing materials:** Informed consent documents, assent forms, recruitment brochures, and any explanatory materials must be translated into the language(s) understood by each participant's family.
- **Require professional translation standards:** Translations should be done by qualified or certified translators with medical-scientific expertise, and include documented quality checks, version tracking, and translator credentials.
- **Promote ongoing language comprehension efforts:** Ethics Committees should verify that the consent process is a continuous dialogue in the participant's language, not merely a one-off translated document, ensuring genuine understanding.
- **Evaluate whether non-EU participants will have equal protection**, ensure studies comply with EU ethical and Good Clinical Practice (GCP) standards, regardless of locale[16].
- **Address vulnerabilities of underrepresented international participants**, such as potential coercion or differential access.

How Ethics Committees embed language accommodation:

- **Protocol Stage Review:** Examine the protocol's language support measures, including which materials require translation, timing of translations, and processes for oral interpretation or literacy support.
- **Continuous oversight:** require the expertise of the language translation services necessary to accommodate international patients.
- **Cultural & linguistic sensitivity:** Probe whether consent tools are culturally appropriate and adapted to the child's developmental level, and how assent is obtained in the child's primary language and format appropriate to their age group.

Annex 4: Patient Experience Data (PED)

Patient Experience Data (PED) refers to data that directly reflect the experience of a patient or caregiver, without input or interpretation by a healthcare professional, third party, or an artificial intelligence (AI)-based device. Patient experience can include, but is not limited to, health and functional status, disease symptoms, disease progression, treatment preferences, quality of life (QoL), factors influencing treatment adherence, treatment outcomes, and side effects.

Tools used to collect patient experience data are not always part of the primary endpoints of a clinical trial, and in most of the cases are part of the secondary endpoints. In such cases, it is recommended that participants or their caregivers complete language- and culturally validated versions of these tools. Specific considerations should apply to clinical trials for conditions without an approved treatment, when the PED are part of the secondary endpoints, ensuring that patient participation is not limited simply because these tools are unavailable in the patient's native language. In this case it is recommended to use a professional interpreter to assist the process to complete these tools and have the approval of the Ethics Committee.

Recommendations regarding the need to accommodate translations of PED are outlined below:

Early planning in protocol development:

- Identify all PED to be used and confirm availability of validated translations for target languages before trial initiation.
- If necessary, include language adaptation requirements in the protocol and budget.

Validate the engagement qualified translators and linguistic experts:

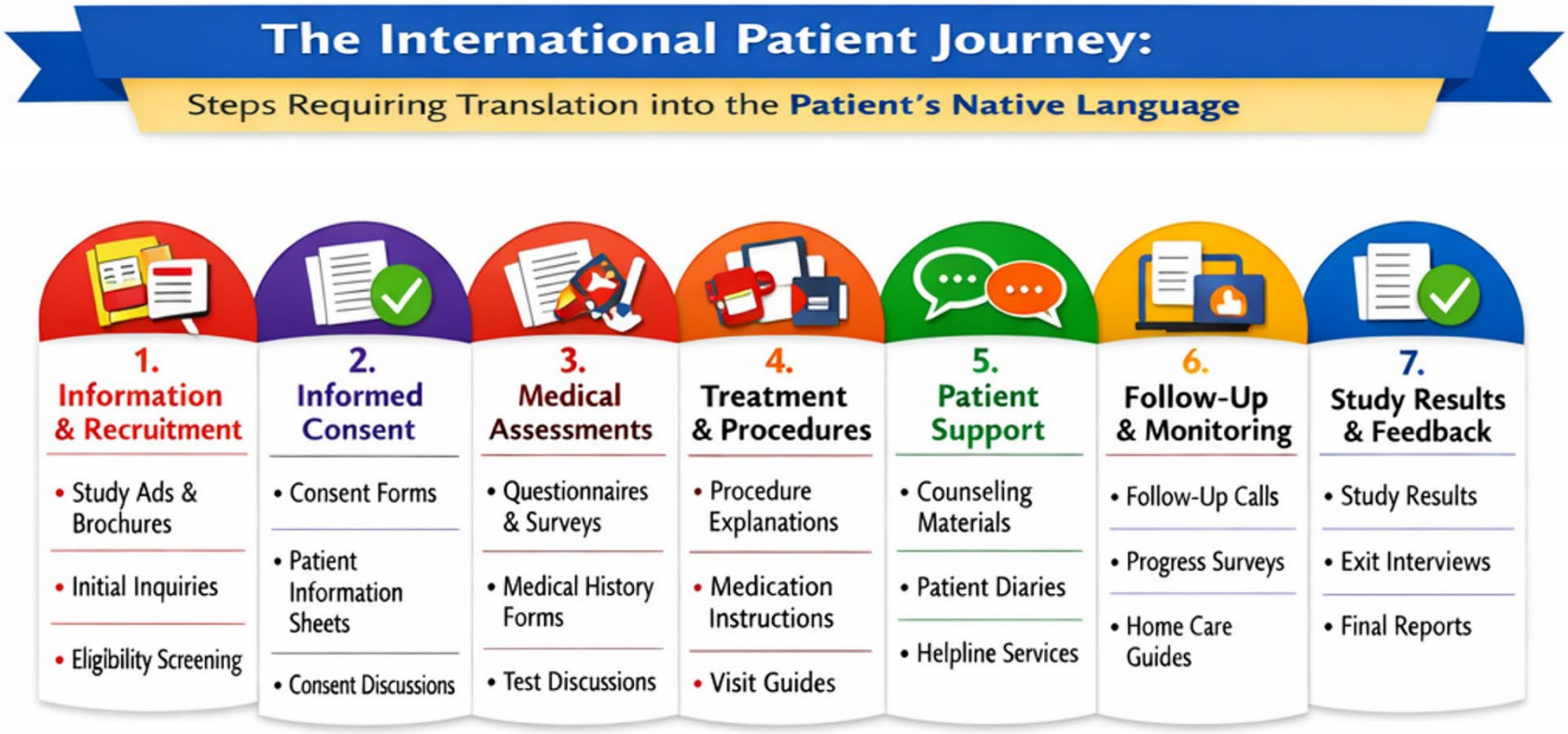
- Use translators certified and experienced in medical terminology and PED adaptation.
- Apply standardised methods (forward/backward translation, cognitive debriefing). Recommended source: ISPOR Guidance on Translation and Cultural Adaptation[17].

Cultural adaptation:

- Ensure translations are not only linguistically accurate but culturally appropriate for the patient population.
- Conduct pilot testing with native speakers from the target population.
- Suggest collaborating with cultural mediators to facilitate the completion of PED tools (validated or not) in the patient's or family's native language, if this is beneficial for ensuring the accuracy of data collection.

They can both translate the items of the PED tools and assist in the process of reporting the data.

Annex 5: International Patients Journey



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