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Cross-border access to clinical trials: participation of pediatric patients and language inclusion

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BACKGROUND: Cross-border access to clinical trials in Europe lacks specific regulation. Language diversity in Europe, with 24 official languages, is a key factor that must be considered when including international pediatric patients in multi-country studies. Providing translation enables patients to participate in clinical trials across borders. Specific consideration requires pediatric rare disease clinical trials for conditions with no approved treatment, where only a few countries participate, making cross-border access even more critical.

METHODS: We analyzed retrospective data (2011–2024) of the studies incorporating international patients at SJD Barcelona Children's Hospital. The main objective of this research was to assess the feasibility of cross-border access to pediatric clinical trials and identify lessons learnt that could help prevent the future exclusion of patients due to their limited proficiency in the official language of the country where the trial site is located.

RESULTS: Twenty-one clinical studies have been analyzed. One hundred eighty-one patients from both European and non-European countries ($N = 44$) were screened, 37.02% of the patients were from Europe, versus 62.98% from non-European countries. In 52.38% of the studies, the translation services were provided by the site; in 14.28% by the sponsor. In 33.33% of the studies, no translation was necessary because the site staff could communicate with the families in Spanish or English. 57.14% of the studies included one or more PROMs or QoL scales, requiring, in some cases, the use of validated translations in the mother tongue of the patient.

CONCLUSION: Participation in pediatric cross-border clinical trials is feasible. The decision to include international patients should prioritize potential medical benefits rather than using the patient's mother tongue or home country as eligibility criteria. Language barriers can be addressed by providing the necessary resources to ensure the scientific reliability of data collected, as well as to enhance the patient experience during participation in a trial abroad.

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IMPACT:

- The SJD Barcelona Children's Hospital Clinical Trials Unit operates under a one-stop-shop model, managing clinical studies with a special focus on rare diseases, centralizing all the needs of international patients (translations, accommodation, visas, etc.).
- The inclusion of international patients in pediatric clinical studies is feasible. Pediatric rare diseases require a small sample of patients, highly specialized sites, and flexibility to accommodate the necessary translations for patients.
- The final decision regarding the inclusion of international patients lies with the sponsor. Flexibility in including international patients directly impacts the study plan and execution, preventing time deviations.

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INTRODUCTION

Cross-border access to clinical trials in Europe lacks specific regulation; however, cross-border healthcare has a specific regulation (Directive 2011/24/EU)[1] on the application of patients' rights. The health systems in the European Union are a central component of the Union's high levels of social protection and contribute to social cohesion and social justice as well as to sustainable development. This directive applies not only when the patient receives healthcare in a Member State, but also to the prescription, dispensation, and provision of medicinal products and medical devices when these are supplied as part of a health service.

The principles and patients' rights that this Directive promotes are related to the values of universality, access to good quality care, equity, and solidarity. All the Member States should ensure that these values are respected, and patients are treated equitably across Europe based on their healthcare needs rather than on the basis of their Member State of affiliation. The principle of non-discrimination (Article 4.3)[1] underpinning the free movement of patients across Member States must ensure respect for the patient's nationality, as well as other related principles that uphold the diversity of language, sex, gender, age, and other factors.

The Regulation (EU) No 536/2014[2] of the European Parliament ensures the harmonization of rules for conducting clinical trials across the European Union. This regulation has no reference to the concept of cross-border clinical trials, multi-region or international studies in which patients from different Member States participate in a clinical trial executed in a different Member State where they reside. This Regulation aims to ensure the standardization of processes across European Commission states rather than to specifically cover topics related to patients' rights that are covered by other regulations, such as the Charter on Fundamental Rights of the European Union (2000).[3]

Despite the existence of general legal frameworks in Europe and globally that endorse the principle of non-discrimination based on the language of the patient, several cases have been reported by clinical trial sites (including SJD Barcelona Children's Hospital) and parents where children have been excluded from accessing cross-border pediatric clinical trials due to their mother tongue. Specific publications have also analyzed the issue of language discrimination in accessing clinical trials[4,5] and specifically in pediatric clinical trials.[6] In the European regulatory framework, the average of Member States involved in a clinical trial is 3.1 for commercial studies, and 1.2 for non-commercial studies.[7] Data on pediatric studies have not been published, but considering that a high percentage of these studies refer to rare disease clinical trials targeting a small sample of patients, the average number of Member States involved in conducting pediatric studies is likely to be smaller.

Considering that the European Union is made up of 27 Member States, with 24 official languages, the probability that children can participate in a clinical trial in their own Member State of residence and with no need for a translation service is low. Including the United Kingdom, from 2017 to 2024, the top five Member States of the European Union (UK, France, Germany, Spain, and Italy) concentrated the 51%[8] of the clinical trials addressed to pediatric patients.

Language discrimination is not only an issue for pediatric patients participating in clinical trials outside their country of origin. It can also affect patients living in the country where the study is conducted (such as short-term residents, immigrants, refugees, etc.) due to their limited proficiency in the official language of their country of residence.

This manuscript focuses on the analysis of the cross-border clinical trials conducted at SJD Barcelona Children's Hospital Clinical Trials Unit from 2011 to 2024. This is one of the top three pediatric hospitals in Europe, with a huge expertise in conducting clinical trials covering all pediatric medical specialties. The main objective of this research was to analyze the most relevant data about these studies and to identify lessons learned that could help prevent the future exclusion of patients due to their limited proficiency in the official language of the country where a clinical trial site is located.

This research is part of a European initiative, conducted by a Working Group at the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA).[9] This initiative was addressed to analyze the state of the art about multi-region and cross-border access in pediatric clinical trials in Europe and the impact of language discrimination. The overarching project, which defined the data to be collected from pediatric clinical trial units across Europe (including data from SJD Barcelona Children's Hospital), was approved by the Ethics Committee of Institut de Recerca Sant Joan de Déu on March 9, 2023 (code PIC-40-23).

International Patients Department at SJD Barcelona Children's Hospital

The Clinical Trials Unit collaborates closely with the International Patients Department, which supports families coming from abroad for medical care or participation in clinical trials. In 2023, a standard operating procedure was implemented to streamline the assessment and inclusion of international patients in clinical studies.

Patients may be referred by physicians from European countries under the Cross-border Healthcare Directive (2011), following approval of the S2 form. Referrals can also come from non-European countries. Families often contact the hospital directly, typically via the Clinical Trials Unit's online form published on the hospital's website or email.

Regardless of how contact is made, the International Patients Department provides tailored support. Since cross-border clinical trials are not regulated in Europe, the final decision to include international patients lies with the study sponsor.

A Case Manager from the International Patients Department assists families before and during the trial, unless the sponsor provides this service. Translation support is available in 15 languages through in-house staff, including Spanish, Catalan, English, French, Italian, Arabic (Mashriqi and Maghrebi), Chinese (Mandarin and Cantonese), Russian, Polish, Romanian, German, Ukrainian, Slovak, Czech, Portuguese, and Japanese (non-native speaker).

For languages not covered internally, external vendors are contracted. Additionally, a device-based translation system is available for up to 60 patients, especially useful during emergencies or off-hours. If a patient speaks a foreign language, a translator or Case Manager will always be available.

To begin the assessment process, the Case Manager collects the medical information required by the principal investigator. For complex studies (e.g., CAR-T or gene therapy), telemedicine visits may be arranged with the patient's doctors and the family. Interpreters are provided when needed. Once the assessment is complete and the sponsor approves, the family is informed about eligibility, study details, and any associated costs (e.g., travel, accommodation). Translation support begins upon the family's arrival and continues throughout the hospital stay.

Patient-facing documents—including the Patient Information Sheet, Informed Consent Form (ICF), and, for patients over 12, the Informed Assent Form (IAF)—are translated into the family's native language by accredited vendors. If the sponsor does not provide translations, SJD Barcelona Children's Hospital uses one of seven approved vendors. All translations are reviewed and approved by the hospital's Ethics Committee.

After the participation of the patient in the trial has finished, a final medical report is translated into English to ensure continuity of care when the patient returns to their home country. These reports are validated by a physician at SJD Barcelona Children's Hospital.

METHODS

The general aim of this study was to describe how international patients were included in pediatric clinical trials at SJD Barcelona Children's Hospital and, when translations were needed, how these were accommodated. Confidential information was not considered in the analysis (e.g., EUDRA-CT number, ClinicalTrials.gov identifier, clinical trial title, sponsor name, or patients' personal data).

The data analyzed for each study included: study phase, therapeutic area, formulation of the investigational medicinal product, patient age, overall study duration (in months), total number of visits (from first to last), existence of patient or parent-reported outcome scales (and their availability and validation in the patient's native language), use of language as an inclusion or exclusion criterion, total patient sample, and other relevant data on patients screened and enrolled at SJD Barcelona Children's Hospital (including number, country of origin, age, and sex).

The Clinical Trials Unit at SJD Barcelona Children's Hospital operates under a one-stop-shop model, managing clinical studies across all pediatric specialties, with a particular focus on rare diseases (68%).[10] In this research, we analyzed data from 2011 to 2024, encompassing 21 clinical studies in which 181 patients from both European (26 countries) and non-European countries (18) participated in the recruitment process. During this period, several patients were excluded from participating in a clinical trial by the sponsor due to language barriers, even though their native language could have been accommodated through translation services and the use of validated language versions of Patient-Reported Outcome Measures (PROMs) tools and Quality of Life (QoL) questionnaires.

The data were collected from clinical trial protocols, principal investigators, research nurses, and data management teams, as well as from the EudraCT and ClinicalTrials.gov online databases. Specific research was conducted to determine the language availability of validated PROM tools and QoL questionnaires at the time the studies were carried out. The data collection process also included updated information from ongoing studies up to July 31, 2024.

All data were entered into a database for analysis. Access to EudraCT and ClinicalTrials.gov records for the various studies was used to retrieve specific information not included in the clinical study protocols, such as the number of countries involved, the total number of patients planned for inclusion, the actual number of patients enrolled, and the status of the clinical trial as 1st of August 2024. To obtain this information, we reviewed both the publicly available study summaries on each database and any accessible clinical trial reports or attached documents. Descriptive statistical analysis was performed to examine key parameters from all the studies. The analysis focused on the main characteristics of each study (e.g., phase, drug formulation, therapeutic area) and on language-related aspects, including patients' country of origin, mother tongue, translation services required, informed consent process, and the language used in PROMs and QoL scales.

This case study, based on a retrospective collection of anonymous data, did not require specific Ethics Committee approval, in accordance with the criteria established by Spanish Biomedical Law.[11]

RESULTS

In the following sections, we will present the analysis of the most relevant features of the 21 cross-border clinical trials conducted at SJD Barcelona Children's Hospital, with a specific focus on the elements that required the accommodation of translation services to facilitate the inclusion of international patients.

Clinical studies involving international patients in the screening process: main features

From January 2011 to the end of July 2024, a total of 21 clinical studies were initiated at SJD Barcelona Children's Hospital involving children living abroad. The *distribution of the studies by research phase* was as follows: Phase I ($n = 3$; 14.29%), Phase 1B ($n = 1$; 4.76%), Phase I/II ($n = 3$; 14.29%), Phase II ($N = 7$; 33.33%), Phase II/III ($n = 1$; 4.76%), Phase III ($n = 5$; 23.81%), and Phase IV ($n = 1$; 4.76%) (Table 1).

Only 4 of these studies were *academic-initiated studies* (19%). Of the 21 studies, 11 (52.38%) were related to oncology, 8 (38.10%) to neurology, 1 (4.76%) to ophthalmology, and 1 (4.76%) to an infectious disease (Table 2).

Table 1. Study phase distribution.

Phase	N	%
Phase I	3	14.29%
Phase 1B	1	4.76%
Phase I/II	3	14.29%
Phase II	7	33.33%
Phase II/III	1	4.76%
Phase III	5	23.81%
Phase IV	1	4.76%

Table 2. Therapeutic area clinical trials distribution.

Therapeutic area	N	%
Oncology	11	52.38%
Neurology	8	38.10%
Ophthalmology	1	4.76%
Infectious disease	1	4.76%

Table 3. Formulation clinical trials distribution.

IMP formulation	N	%
Intravenous infusion	11	52.38%
Cell infusion	2	9.52%
Oral suspension	2	9.52%
Intracerebroventricular	1	4.76%
Intrathecal injection	1	4.76%
Intravitreal	1	4.76%
Ophthalmic nanoemulsion	1	4.76%
Subcutaneous injection	1	4.76%
Tablet	1	4.76%

The most common *formulation* of the investigational medicinal product in the clinical studies was intravenous infusion ($n = 11$, 52.38%), followed by cell infusion ($n = 2$, 9.52%) and oral suspension ($n = 2$, 9.52%). The remaining six studies used the following formulations: intracerebroventricular ($n = 1$, 4.76%), intrathecal injection ($n = 1$, 4.76%), intravitreal injection ($n = 1$, 4.76%), ophthalmic nanoemulsion ($n = 1$, 4.76%), subcutaneous injection ($n = 1$, 4.76%), and oral tablet ($n = 1$, 4.76%) (Table 3).

The distribution of studies according to the *age of the patients* included the range of ages from 0 months to 18 years old. The mean age of the patients who participated in the screening process of these studies was 6.41 years, and the median age was 5.5 years. In terms of *sex*, 64% ($n = 115$) of the patients were males and 36% females ($n = 66$).

18 out of the 21 clinical studies (85.71%) have a standard duration for all the patients, meaning that the number of weeks from the first visit until the last visit was the same for all the patients. 3 out of the 21 studies (14.29%), oncology clinical trials, have varying durations depending on the patient's medical evolution and prognosis. Considering the studies with the same duration for all the patients, the *mean duration in weeks* (including the follow-up period) was 105.83 (2 years, 1 week, and 6 days). The standard deviation was 102.57 weeks (1 year, 1 month, 3 weeks, and 3 days). The study that had the longest duration (including the follow-up period) lasted 384 weeks (6 years 4 months), and the shortest one lasted 6 weeks. In terms of the *overall number of medical visits* related to the 18 clinical studies with the same time duration for all the patients, the mean number of visits until the end of the study was 19.44, and the standard deviation was 11.08.

Informed consent process

2 out of the 21 (9.52%) clinical trial protocols included *references in the inclusion criteria* about the consent process, while 19 protocols (90.48%) didn't include any reference. Regarding the eligibility criteria, in none of the studies was language a criterion to be considered in the recruitment process. Table 4 summarizes the text sequence of the inclusion and exclusion criteria stated in the protocol that refers to the consent process.

International patients screened

A total of 314 patients were screened in the 21 clinical studies analyzed in this research. Of these, 133 patients (42.35%) resided in Spain, while 181 (57.64%) came from abroad. Among the 181 international patients screened, 131 participated or are currently participating in a clinical trial at SJD Barcelona Children's Hospital. Specifically, 5 patients were excluded due to their mother tongue. Table 5 summarizes the status of these 181 patients as of July 31, 2024, the date on which the data collection was completed.

The mean of countries involved globally in the clinical trials analyzed according to information reported in the Clinicaltrials.gov or EudraCT databases was 5.75 (standard deviation 4.99). Specifically, the patients involved in the recruitment process from abroad and who participated in clinical trials at SJD Barcelona Children's Hospital came from 44 different countries of origin (26 non-European countries and 18 European countries) (Table 6). The average of countries involved in the recruitment process of 21 clinical studies, including international patients at SJD Barcelona Children's Hospital, was 4.10 (standard deviation 3.97). The country where the highest percentage of patients came from was China (24.86%), and the second one was Argentina (11.60%).

The distribution per continent of the patients that participated in the recruitment process ($N = 181$) was: 37.02% Europe, 29.28% Asia, 26.52% South America, 3.31% North America, 2.21% Africa, and 1.66% Oceania (Table 7).

International patients incorporated

The 131 patients incorporated in the 21 cross-border studies analyzed came from 32 different countries. The top five countries where the patients came from were: China (31.30%), Argentina (9.92%), Poland (7.63%), Russia (6.87%), and Mexico (6.11%) (see Table 8).

The distribution per continent of the patients that participated in the clinical studies ($N = 131$) was: 35.11% Europe, 33.59% Asia, 26.72% South America, 1.53% North America, 1.53% Africa, and 1.53% Oceania (Table 9).

Mother tongue of the international patients incorporated

The 131 international patients who participated or are currently participating in a clinical trial at SJD Barcelona Children's Hospital speak 12 different mother tongues. Two of these languages are not official in Europe (Chinese and Russian), accounting for 55 out of the 131 international patients (41.98%). All these patients who speak a non-European official language came to SJD Barcelona Children's Hospital for an oncology clinical trial (Table 10).

PROMs and QoL scales reported by the patients and/or parents

Nine out of the 21 (42.86%) clinical trials did not include any specific *Patient Reported Outcomes Measures* (PROMs) or *Quality of Life Scales* (QoL) to be completed by the patients or the parents. From these studies, 6 are addressed to oncology conditions (66.66%), 1 addressed to a neurology disease (11.11%), one to an ophthalmology condition (11.11%), and one to an infectious disease (11.11%).

Twelve out of the 21 clinical studies (57.14%) included one or more PROMs or QoL scales. Only one study included tools to be reported by the patients, and this clinical trial addressed a neurological condition. According to the therapeutic area, 5 out of the 11 (45.45%) clinical trials targeted for oncology conditions included PROMs or QoL addressed to the patients or the parents. Seven out of the 8 (87.5%) clinical studies targeted for neurological conditions included PROMs or QoL addressed to the patients or the parents.

Translation support provided

In 5 out of the 21 studies (23.80%), the sponsor directly provided the translation service. In three of these studies (14.28%), the translation specifically covered the ICF and PROMs, while in the other two studies (9.52%), it included all translations required during the various medical appointments throughout the patient's participation in the clinical trial.

In 5 studies (23.80%), translation services were not required because the patient and the family were competent in Spanish.

The translation services of the International Patients Department at SJD Barcelona Children's Hospital were provided in 11 out of the 21 studies (52.38%). These translations covered official European languages, as well as Chinese and Russian.

Table 11 describes the different PROMs and QoL scales in the 12 studies that required reporting this information by parents or patients. The mother tongue of the participants is detailed, the language of the ICF, the language in which the tools were reported, and the use of the translation services. Despite the fact that in some studies the PROs and QoL scales were not available in the mother tongue of the patients/parents, the information could be translated by the professional translations provided by the site or the sponsor, and make feasible to collect the data from the participants of the study or their caregivers.

DISCUSSION

Most clinical trials targeting the pediatric population focus on rare diseases. This implies a small population living with a specific rare condition, whether within a single country, across a continent, or globally. All (100%) of the cross-border studies conducted at SJD Barcelona Children's Hospital, part of this research, addressed rare conditions. A total of 131 patients from SJD Barcelona Children's Hospital participated or are currently participating in these studies, representing 10.48% of the planned global sample size ($N = 1250$ patients). The 21 studies involved 120 countries worldwide, with an average of 5.71 countries per trial and a standard deviation of 4.99 (Max: 15; Min: 1). Considering these figures, the likelihood of a patient in Europe or globally being able to participate in a clinical trial in their country of residence is quite low. Facilitating cross-border access in clinical trials in the field of pediatric rare diseases can, in some cases, be the only therapeutic opportunity available for patients with a rare disease condition that lacks approved treatment options. 95% of rare diseases don't have a targeted approved treatment.[12]

Cross-border access to pediatric clinical studies may also help to facilitate that clinical studies are conducted without deviations from the planned overall duration as per protocol. Incorporating international patients can help to reduce the potential risk of recruitment issues and delays, which is one common reason for clinical trials deviations,[13,14] if only patients living in the countries where the sites are located can be eligible. While including international patients may involve higher costs (e.g., travel, accommodation, time compensation, and translation services), the delays in recruitment, protocol amendments, and other deviations from the clinical study plan are likely to result in even higher expenses.[15,16] Further research in this sense will be needed to analyze the economic impact of including or not including international patients in clinical trials, but the data already published about the frequency of substantial amendments show that 57% of the protocols have at least one substantial amendment with an associated average cost of 141,000 US $ for a phase II study or 535,000 US$ for a phase III protocol study.[17] Smith et al.[18] showed that the estimated direct daily cost to conduct a clinical trial is approximately $40,000 per day for phase II and III clinical trials, demonstrating that delays in the conduction

Table 4. Mentions about the informed consent process in the inclusion and exclusion criteria section of the clinical trial protocol.

Study number	Therapeutic area	Inclusion criteria	Exclusion criteria
1	Oncology	*Written informed consent from legal guardian(s) and/or child must be obtained in accordance with local regulations. Pediatric patients must provide assent as required by local regulations.*	N/A
2		*Written informed consent from legal guardian(s) and/or patient in accordance with local regulations. Children must provide assent as required by local regulations*	N/A
3		*Signed written informed consent and assent forms, if applicable, must be obtained prior to any study procedures*	N/A
4		*Obtaining informed consent in writing and signed by the patient's legal representative and, if applicable, by the minor (in patients over 12 years of age).*	N/A
5		*The Investigator, or a person designated by the Investigator, will obtain written informed consent from each study participant or the participant's legally acceptable representative, parent(s), or legal guardian and the participant's assent, when applicable, before any study specific activity is performed. The Investigator will retain the original copy of each participant's signed consent/assent document.*	N/A
6		N/A	N/A
7		*Written informed consent from legal guardian(s) and/or patient in accordance with local regulations. Children must provide assent as required by local regulations (≥12 years old).*	N/A
8		N/A	N/A
9		*Signed informed consent form.*	N/A
10	Neurology	*Signed informed consent.*	N/A
11		*Written informed consent by parent/legal guardian, or authorized legal representative to participate in the study.*	*Inability or unwillingness of parent/legal guardian or subject to comply with the study procedures.*
12		*Evidence of signed and dated informed consent/assent document(s) indicating that the subject (and/or his parent/legal guardian) has been informed of all pertinent aspects of the trial. Note: If the study candidate is considered a child under local regulation, a parent or legal guardian must provide written consent prior to initiation of study screening procedures and the study candidate may be required to provide written assent.*	N/A
13		*Able to give written informed assent and/or consent signed by the subject and/or parent(s)/legal representative (in accordance with local regulations),*	N/A
14		*Signed informed consent of parent or guardian. Ability of the participant's legally authorized representative (e.g., parent or legal guardian), as appropriate and applicable, to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations.*	N/A
15		*Signed Informed Consent Form + Signed Assent Form when appropriate, as determined by patient's age and individual site and country standards*	N/A
16		*Participants/legally acceptable representatives who are capable of giving assent/signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the assent/informed consent document and in this protocol.*	N/A
17		*Has (a) parent(s) or legal guardian(s) who is (are) able to understand and comply with the study visit schedule and all other protocol requirements. // Is willing to provide informed assent (if applicable) and has (a) parent(s) or legal guardian(s) who is (are) willing to provide informed consent for the subject to participate in the study.*	N/A
18	Ophthalmology	*Signed informed consent from (ICF) parents or patient's legally authorized representative(s).*	N/A

Table 4. continued

Study number	Therapeutic area	Inclusion criteria	Exclusion criteria
19	Infectious disease	*Parent/both parents or legally authorized representative (LAR) must provide signature of informed consent and there must be documentation of assent by the participant, as age appropriate, before completing any study-related procedures.*	N/A
20	Oncology	*Subject (when applicable, parental/legal representative) must understand and voluntarily provide permission to the ICF/IAF prior to conducting any study-related assessments/procedures.*	N/A
21		*Signed informed consent indicating awareness of the investigational nature of this program*	N/A

Table 5. Status of the patients involved in the recruitment process (Data updated on the 31st of July, 2024).

Status	Number of patients
Excluded (screening failure patients)	62
Screening (patients currently involved in the assessment process)	2
Finalized (patients who participated in the last visit of the study)	91
Follow-up (Patients who completed the treatment period but were required to participate in follow-up visits before the clinical study's completion.)	17
Open-label extension (Patients who are receiving the experimental treatment for an extended period of time.)	9
Total	**181**

of a clinical trial have a high economic impact on the overall cost to deliver the study, with deviations according to the study plan. The costs of delays in studies in the respiratory, rheumatology, and dermatology areas have the highest relative daily direct costs.

Diversity is increasingly becoming a key element expected to be integrated into the recruitment plans of clinical studies.[19] Including patients from different countries and continents ensures that the diversity inherent to patient communities living with a specific condition is adequately represented. This approach also helps ensure that any approved treatment will demonstrate consistent levels of safety and efficacy across all population subgroups affected by the condition. Using a patient's mother tongue as an eligibility criterion (inclusion or exclusion) without a valid scientific justification violates human rights and the rights of European citizens, which explicitly state that no one shall be discriminated against based on their mother tongue. When it concerns pediatric patients, it also violates the United Nations Convention on the Rights of the Child.[20] Clear recommendations, guidance, and regulations are necessary to promote a fair, ethical, and scientifically sound approach to the use of language as both an explicit and implicit eligibility criterion in clinical trial protocols.

Although language discrimination was not the primary focus of this novel research, we would like to highlight that language is often used as an eligibility criterion in protocol design without valid scientific justification. Additionally, patients are sometimes excluded based on their language or country of residence, even when these criteria are not explicitly stated in the clinical study protocols. The findings of this novel research can be used in the future to facilitate the inclusion of international patients in pediatric clinical trials based on the SJD Barcelona Children's Hospital management model and expertise. Further research on this critical patient rights issue is needed to ensure that no patient is excluded from the opportunity to participate in a clinical trial due to their mother tongue or European country of residence.

The results of the research conducted with the 21 clinical studies involving international patients conducted at SJD Barcelona Children's Hospital allowed us to demonstrate that pediatric clinical trials, including facilitating cross-border access from both European and non-European countries, are feasible (only 37.02% of the patients screened were from European countries versus 62.98% from non-European countries). The close collaboration between the International Patient Department and the Clinical Trials Unit is essential to cover all the needs, beyond language translations that require international patients (travel, visa, accommodation, etc.). The one-stop-shop model of the CTU facilitates a single point of contact for the sponsors to coordinate all the different processes that will require the approval of the inclusion of an international patient in a clinical study.

The in-house translation service was the most used option (52.38%), demonstrating that it has a value, reducing the time that it will require to incorporate external translation services, covered by the hospital or the sponsor. The fact that 41.98% of the families that participated in the studies were competent in English (29.01%) or Spanish (12.97%), this had a positive impact because the staff of the clinical trials unit speaks English, not requiring the need for any translation service in these cases.

PROMs or QoL tools to be reported by the patients or the parents were not included in 42.86% of the studies. In these 9 studies, the limitation that can entail the nonexistence or requirement for patients to complete a validated version of these tools in the mother tongue of the patients was a benefit in terms of incorporating international patients. In cases where a PROM or QoL tools has not been validated in the patient's mother tongue, specific research and guidance would be necessary. This would help determine when verbal translation or other translation services can be accommodated to ensure accurate data collection without excluding patients from participating in clinical studies due to their mother tongue.

The ICH Good Clinical Practice E6(R3)[21] guideline sets international standards for the design, conduct, documentation, and reporting of clinical trials, requiring clear communication of study information to patients and caregivers and the use of valid, reliable measurement instruments. The Declaration of Helsinki (2024)[22] states that research is ethically acceptable only when participants understand relevant information, emphasizing plain language and health literacy. For international patients, this includes providing documents in their native language and translation support during participation. The guidelines on patient-reported outcomes from the U.S. Food and Drug Administration and the European Medicines Agency (EMA)[23,24] require linguistically validated questionnaires to ensure data quality and comparability. Similarly, ISPOR guidelines[25]

Table 6. Patients screened distribution per country.

Country	Patients	%
China	45	24.86%
Argentina	21	11.60%
Poland	11	6.08%
Russia	11	6.08%
Mexico	9	4.97%
Byelorussia	8	4.42%
United Kingdom	8	4.42%
Germany	5	2.76%
Peru	5	2.76%
Portugal	5	2.76%
USA	5	2.76%
India	4	2.21%
Chile	3	1.66%
Australia	2	1.10%
Brazil	2	1.10%
Colombia	2	1.10%
Czech Republic	2	1.10%
Slovenia	2	1.10%
Estonia	2	1.10%
Italy	2	1.10%
Morocco	2	1.10%
The Netherlands	2	1.10%
Venezuela	2	1.10%
Andorra	1	0.55%
Canada	1	0.55%
Cameroon	1	0.55%
Ecuador	1	0.55%
France	1	0.55%
Honduras	1	0.55%
Hungary	1	0.55%
Ireland	1	0.55%
Kazakhstan	1	0.55%
Kirgizstan	1	0.55%
Kuwait	1	0.55%
Malta	1	0.55%
New Zeeland	1	0.55%
Panama	1	0.55%
Romania	1	0.55%
Rwanda	1	0.55%
Sweden	1	0.55%
Switzerland	1	0.55%
Ukraine	1	0.55%
Arab Emirates	1	0.55%
Uruguay	1	0.55%
Total	**181**	**100.00%**

Table 7. Patients screened distribution per continent.

Continent	*N*	%
Africa	4	2.21%
Asia	53	29.28%
Europe	67	37.02%
North America	6	3.31%
Oceania	3	1.66%
South America	48	26.52%
Total	**181**	**100.00%**

Table 8. Patients screened distribution per country.

	N	%
China	41	31.30%
Argentina	13	9.92%
Poland	10	7.63%
Russia	9	6.87%
Mexico	8	6.11%
Portugal	5	3.82%
United Kingdom	5	3.82%
Byelorussia	4	3.05%
Peru	4	3.05%
Germany	2	1.53%
Colombia	2	1.53%
Slovenia	2	1.53%
The Netherlands	2	1.53%
Italy	2	1.53%
Morocco	2	1.53%
USA	2	1.53%
Venezuela	2	1.53%
Chile	2	1.53%
Andorra	1	0.76%
Australia	1	0.76%
Brazil	1	0.76%
Estonia	1	0.76%
Honduras	1	0.76%
Hungary	1	0.76%
Kazakhstan	1	0.76%
Kirguizistan	1	0.76%
New Zeland	1	0.76%
Panamá	1	0.76%
Czech Republic	1	0.76%
Switzerland	1	0.76%
United Arab Emirates	1	0.76%
Uruguay	1	0.76%
Total	**131**	**100,00%**

outline a structured process for translating and culturally adapting PROMs to achieve conceptual and semantic equivalence across languages, rather than literal translation.

Current recommendations in these various guidelines emphasize the need to translate information into a language that patients and caregivers can easily understand and to use validated translations of tools for collecting patient-reported data. However, these guidelines do not address situations where such validated tools are unavailable. In Europe, Ethics Committees have, in cases where these tools are used to collect data not intended for primary endpoints, approved the use of professional ad hoc translations into the patient's native language. At present, there is no standardized methodological process or ethical principle to guide Ethics Committees in making consistent decisions when validated patient-reported tools do not exist in the language in which patients are proficient.

An important fact of the data analyzed in this research is that all the conditions addressed in the studies were life-threatening and degenerative, scenarios in which families are more likely to consider any therapeutic option, including experimental treatments researched abroad. For some families, participation in a clinical study represented the last opportunity to extend life expectancy. This context underscores the significant burden cross-border clinical trials impose on families. In some instances, families opted to change the country of residence during the trial duration to reduce the distance to the study site (e.g., when patients traveled from other continents or long distances) or to accommodate the frequency of study visits. Analyzing the impact of cross-border clinical trial participation on both patients and their families would be an important avenue for further research.

Innovative and advanced treatments, such as gene and cell therapies, will soon require highly specialized clinical trial sites with expertise in managing these studies.[26,27] This scientific trend also points to a reduction in the number of sites conducting such trials, emphasizing the need for the inclusion of international patients. Additionally, these studies often require long-term follow-up, sometimes up to 15 years. Establishing regulations or guidelines for cross-border access to these complex and long-term experimental treatments would be essential to ensure equal opportunities for all patients across Europe.

CONCLUSION

The number of countries and sites involved in conducting pediatric rare disease clinical studies in Europe is limited. Facilitating the inclusion of international patients can provide significant benefits to the study, enabling execution according to the planned timeline and reducing deviations related to patient recruitment. For patients with diseases lacking approved treatments, cross-border access to advanced phases of clinical trials offers the potential to benefit from the latest research advancements.

The one-stop-shop model of the Clinical Trials Unit at SJD Barcelona Children's Hospital facilitates direct communication between the site and the sponsor. The International Patient Department further streamlines the process of meeting international patients' needs, supported by in-house translation services.

In pediatric clinical trials that do not include PROMs or QoL tools, accommodating translations for patients and families is more straightforward. However, when these tools do not have a validated version in the patient's mother tongue, further research is needed to determine how access can be ensured, at least when they are included as secondary outcomes in clinical trials. In situations where waiting for the publication of a validated language version is not feasible, professional translation services with quality reviews could ensure these tools are accessible to patients and their families. Assessing the ethical considerations of excluding patients from a clinical study due to the absence of PROMs and QoL tools validated in the mother tongue of the patients in life-threatening diseases is strongly recommended, especially in the lack of access to an approved treatment.

In general, patients' rights and children's rights should be carefully considered in cases where patients are excluded due to their mother tongue. Although language was not explicitly detailed as an eligibility criterion in the clinical trial protocols analyzed in this research, it is recognized as a potential limitation—not only for international patients but also for those residing in the host country who lack proficiency in the official language(s) (e.g., short-term residents, immigrants, or refugees). Addressing language barriers requires providing adequate resources to ensure the scientific reliability of the data collected from both patients and caregivers.

Participating in a clinical trial typically imposes additional burdens on patients and their families. In the context of cross-border access to clinical trials, it is essential to assess specific language needs that extend beyond the clinical trial site, such as daily life requirements if families decide to relocate. Language barriers impact not only the patients' participation in the study but also their overall experience, as language is deeply intertwined with culture. Professionals in International Patient Departments play a pivotal role in addressing these diverse needs and

Table 9. Patients screened distribution per continent.

Continent	*N*	%
Africa	2	1.53%
Asia	44	33.59%
Europe	46	35.11%
North America	2	1.53%
Oceania	2	1.53%
South America	35	26.72%
Total	**131**	**100.00%**

Table 10. Patients participating in a clinical study at SJD Children's Hospital distribution per mother tongue and therapeutic area.

Oncology clinical trials			Neurology clinical trials		Ophthalmology clinical trial		Infectology clinical trial			
Language	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	**Total**	**%**
Chinese	44	51.76%							44	33.58
English	11	12.94%	27	61.36%					38	29.01
French	1	1.18%							1	0.76
German/English	1	1.18%							1	0.76
Italian	1	1.18%							1	0.76
Polish	7	8.24%							7	5.34
Portuguese	1	1.18%	5	11.36%					6	4.58
Portuguese/Spanish	1	1.18%							1	0.76
Romanian	1	1.18%							1	0.76
Russian	11	12.94%							11	8.40
Spanish			12	27.27%	1	100.00%	1	100.00%	14	10.69
Ukraine	4	4.71%							4	3.05
Ukraine/Spanish	2	2.35%							2	1.52
Totals	85		44		1		1		131	100%

Table 11. Patient Reported Outcome Scales and Quality of Life Scales reported by parents or patients.

Study code	Therapeutic area	PROMs or QoL scales	Who reports the tools?	Country of the patients	Language of the ICF	Mother tongue of the patients	Language of the PROMs and QoL scales	Tool validated in the mother tongue of the patient	Interpreter services
3	Oncology	EQ-5D	Parents	Ukraine	Russian	Russian	Russian	Yes	Yes
		PedsQL			Russian				
4	Oncology	Lansky scale	Clinician based on information provided by the parents	United Kingdom	English	English	English	Answers reported by the clinicians	No
6	Oncology	Lansky scale	Clinician based on information provided by the parents	Argentina	Spanish	Spanish	Spanish	Answers reported by the clinicians	No
				Morocco	French	French	French		Yes
				Perú	Spanish	Spanish	Spanish		No
				Rwanda	French	French	French		Yes
				Venezuela	Spanish	Spanish	Spanish		No
10	Neurology	Sanfilippo Behavior Scale	Parents	Bielorussia, Czech Republic, Estonia, the Netherlands, Germany, Russia, and the United States	English	Russian	Russian	Translated	Yes
						Czech	Czech	Translated	Yes
						Estonian	English	Yes	No
						Dutch	English	Yes	No
		PedsQL scale	Parents			German	German	Translated	Yes
						Russian	Russian	Translated	Yes
						English	English	Yes	No
11	Neurology	EQ-5D-5L	Parents	Chile, Argentina, and Mexico	Spanish	Spanish	Spanish	Yes	No
					Spanish	Spanish	Spanish	Yes	No
					Spanish	Spanish	Spanish	Yes	No
12	Neurology	Pediatric Outcomes Data Collection Instrument (PODCI)	Parents	Portugal	Portuguese	Portugal	Portuguese	Brazilian Portuguese	Yes
		Disease status/activities of daily living survey	Parents		Portuguese		Portuguese	Brazilian Portuguese	Yes
14	Neurology	Assessment of Caregiver Experience with Neuromuscular Disease (ACEND)	Parents	UK	English	English	English	Yes	No
		Parent Assessment of Swallowing Ability weekly survey	Parents				English	Yes	No
		PedsQL	Parents				English	Yes	No
15	Neurology	EQ-5D-5L	Parents	Argentina	Spanish	Spanish	Spanish	Yes	No
									No

Table 11. continued

Study code	Therapeutic area	PROMs or QoL scales	Who reports the tools?	Country of the patients	Language of the ICF	Mother tongue of the patients	Language of the PROMs and QoL scales	Tool validated in the mother tongue of the patient	Interpreter services
16	Neurology	Pediatric Outcomes Data Collection Instrument (PODCI)	Parents	China and Slovenia	English	Chinese	English	No	Yes
		Pediatric Parent/ EuroQol 5 Dimensions	Parents				English	No	Yes
		Youth Health Questionnaire Proxy Version (EQ-5D-Y Proxy)	Parents			Slovenian	English	No	Yes
		Patient Global Impression of Severity – Ambulatory Activities of Daily Living	Parents/ **Patients**				English	No	Yes
		EQ-5D-5L	Parents				English	No	Yes
17	Neurology	PROMIS	Parents	Hungary and Slovenia	English	Hungarian and Slovenian	English	No	Yes
		CaGI-S -C	Parents				English	No	Yes
		EQ-5D	Parents				English	No	Yes
20	Oncology	PedsQL Generic Core module	**Patients**	Brazil	Portuguese and Spanish	Portuguese and Spanish	Spanish	Yes	No
		PedsQL Cancer module	**Patients**				Spanish	Yes	No
		PedsQL multidimensional Fatigue Scale	**Patients**				Spanish	Yes	No
		Parent Report PedsQL Generic Core module	Parents				Spanish	Yes	No
		Parent Report PedsQL Cancer module	Parents				Spanish	Yes	No
		Parent Report PedsQL multidimensional Fatigue Scale	Parents				Spanish	Yes	No
		Parent Report PedsQL Family Impact Module	Parents				Spanish	Yes	No
21	Oncology	Lansky scale	Clinician based on information provided by the parents	Poland	Polish	Polish	Answers reported by the clinicians	No	Yes

providing essential support to international patients participating in cross-border clinical trials. To further enhance the trial experience and adapt it to the cultural context of patients and their families, the involvement of cultural mediators and/or native healthcare professionals can be invaluable. These roles can provide critical support not only to the patients and families but also to the clinical trial site staff.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Begonya Nafria (BN) was responsible for the conception and design of the paper. All authors were involved in the acquisition, analysis, and/or interpretation of the data captured in the case study. Begonya Nafria drafted the paper and subsequent re-drafts. All authors reviewed the manuscript and approved the final version. Conceptualization: Begonya Nafria. Data collection: all authors. Data curation: Begonya Nafria. Formal analysis: Begonya Nafria. Investigation: Begonya Nafria. Methodology: Begonya Nafria. Writing—original draft: Begonya Nafria. Writing—review and editing: all authors.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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