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ORIGINAL RESEARCH ARTICLE

Language as an Eligibility Criterion in Pediatric Study Protocols Conducted in Europe (2007–2024) Reported in the ClinicalTrials.gov Database

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Abstract

Background One of the challenges in accessing cross-border clinical trials involving international participants in Europe is language diversity, with 32 official languages in the European continent. Some patients have reported being excluded from trials owing to their native language, and in certain studies, language has been used as an eligibility criterion for participation. Considering that pediatric studies in Europe are not conducted in all countries, cross-border access to clinical trials may represent the only therapeutic opportunity for children living with rare diseases for which no approved treatment exists.

Objective This study aimed to assess the use of language as an eligibility criterion in pediatric clinical trial protocols conducted in Europe (2007–2024) and published in the Clinicaltrials.gov database. It evaluated the frequency and context of language requirements and whether these were scientifically justified. The overall objective was to identify potential sources of language-based discrimination that may prevent cross-border access to pediatric clinical trials.

Methods The 32 official languages of the European continent were used as keywords to search the eligibility criteria of 1,754 pediatric clinical trial protocols for studies conducted in Europe between 2007 and 2024 and registered in the largest clinical trial registry, ClinicalTrials.gov, via an Application Programming Interface. Acceptable scientific justifications to use language as an eligibility criterion were defined as being (1) related to specific therapeutic areas that required language or cognitive assessments in communication with the health professionals, who do not speak the patient's language or (2) related to the use of patient- or caregiver-reported outcome measures that had only been validated in specific languages.

Results The majority of the study protocols (95.2%) did not include any reference to European official languages in the eligibility criteria. Of the 85 study protocols that did include language requirements, only 23 (27.1%) had a scientific justification for the use of this criterion. The most frequent European languages required as eligibility criteria were English (20%) and French (16.5%).

Conclusions A minority of European paediatric studies (4.8%) included language in eligibility criteria in the study protocols, but of those that did, most offered no reasonable explanation for the restriction. To prevent language-based discrimination within the European regulatory framework, we recommend that ethics committees should require justification for any language-based eligibility criteria. Additionally, including dedicated sections on cross-border access in clinical trial protocols will help ensure the provision of appropriate resources such as translations, interpreters, travel, and accommodation when recruiting international participants.

Plain Language Summary

Pediatric clinical trials are needed to find safe and effective treatments for children. However, language requirements that are not scientifically necessary may prevent some children from taking part. In Europe, some families have reported that their child could not join a clinical trial because they did not speak a required language. This study examined 1,754 pediatric clinical trial studies conducted in Europe between 2007 and 2024, using data from a large database termed ClinicalTrials.gov. The researchers looked for any mention of language in the study entry rules (the criteria used to decide who can participate).

Extended author information available on the last page of the article

They found that only a small number of trials (4.8%) mentioned language. However, when a language requirement was included, it was often not clearly justified. In only 27% of studies it was a scientific reason, for example, when tests required a specific language or relied on speech or understanding. English and French were the most commonly required languages. The study also identified other requirements that could limit participation, such as needing access to a mobile phone, Internet, or enrollment in a specific national health system. These factors may make it harder for international families or those with fewer resources to participate. The authors recommend that ethics committees carefully review language requirements and require a clear scientific reason before approving them. They also suggest that study plans include a section explaining how children from different language backgrounds and countries can be included.

Key Points

The study analyzed 1,754 pediatric clinical trial protocols conducted in Europe and found that 4.8% included language-related eligibility criteria.

Among the 85 trials that did mention language, only 27% provided a scientific justification.

English and French were the most frequently required languages, often without necessity based on validated patient-reported outcome measures or cognitive assessments.

The findings emphasize that research ethics committees should require explicit justification for language-based criteria and encourage protocol designs that prevent linguistic and cross-border discrimination in pediatric research.

1 Introduction

On 26 January, 2007, the Paediatric Regulation (EC No 1901/2006) [1] came into force in the European Union (EU). Grounded on the principle that children should be subjected only to clinical trials that are necessary, the regulation facilitates the development and authorization of medicines for children. The Paediatric Regulation established the Paediatric Committee as the scientific entity responsible for evaluating and coordinating the European Medicines Agency's (EMA's) activities related to medicines intended for pediatric use in collaboration with the EMA.

The Paediatric Regulation and the Clinical Trials Regulation (EU) No 536/2014 [2], both integral components of the regulatory framework governing clinical trials in the EU, do not address the concept of cross-border clinical trials, that is, multi-regional or international studies in which patients from one Member State participate in a clinical trial conducted in another Member State. A significant challenge associated with such trials is the linguistic diversity across Europe: the EU recognizes 24 official languages, whereas continental Europe encompasses 32. In accordance with the Charter on Fundamental Rights of the European Union (2000) [3] and the United Nations Convention on the Rights of the Child [4], the rights of the patient, particularly regarding their nationality and the related principles of diversity in language, gender, age, and culture must be respected in all clinical research activities.

The ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) E17 Harmonized Guideline of General Principles for Planning and Design of Multiregional Clinical Trials (2017) [5] highlights the lack of harmonization in the conduct of multi-regional clinical trials and the significant potential burden on sponsors. Within the context of the ICH E17 Guideline, the term "region" refers to a geographical region, country, or regulatory region. Multi-regional clinical trials facilitate the assessment of an investigational product's efficacy and safety across diverse populations under a single protocol. The guideline also addresses various clinical trial and protocol-related issues, including the requirement to use validated scales and/or scores in languages appropriate to the patient population. In addition, when trial-related documents (e.g., case report forms) are translated into local languages, it is important to maintain consistency across languages. This may involve the use of back translation to ensure accuracy and equivalence of the translated materials.

Cases of language-based discrimination against children participating in clinical trials conducted in countries outside their country of residence have been reported across Europe and in other regulatory jurisdictions [6, 7]. Language discrimination to access to clinical trials in this research refers to the exclusion or unequal treatment of potential participants based on their language proficiency, native language, or literacy. Language choice and/or proficiency should not serve as an eligibility criterion when adequate translation and interpreter services can be provided and there is no scientific justification for its consideration as an eligibility criterion. The inability

to understand the official language of the host country should not constitute a barrier to participation in clinical research, particularly when effective communication can be accommodated.

The Convention of the Rights of the Child (1989) affirms that all minors have the right to protection from discrimination "*no matter who they are, where they live, what language they speak, what their religion is, (…). No child should be treated unfairly for any reason*". (Art. 2). At the same time, the Convention states that "*Children have the right to use their own language, culture and religion - even if these are not shared by most people in the country where they live*" (Art. 30) and "*Children have the right to the best health care possible*" (Art. 24).

The Belmont Report [8] (1979), which outlines the Ethical Principles and Guidelines for the Protection of Human Subjects of Research, states that it is unjust to "*offer potentially beneficial research only to some patients who are in their favor*" [9]. Similarly, the Charter of Fundamental Rights of the European Union (2000) [4] prohibits any discrimination on the basis of language and other attributes (Art. 21).

In 2024, the World Health Organization published its Guidance for Best Practices for Clinical Trials [10], which also addresses the issue of language barriers in the context of international research. Section A2.2.7 emphasized that "*[i]nternational organizations, sponsors and funders should make efforts to reduce the language barrier in capacity-building by providing documents and organizing events in languages other than English*". Although this Guidance does not mandate the provision of translation or interpreter services for patients not proficient in the official language of the host country, Section 2.2.1 affirms that "*information should be provided in a clear manner and in suitable languages and formats for the intended audiences*".

See Table 1 for a summary of the regulations, frameworks, and instruments that should be considered when designing, planning, and conducting clinical trials and pediatric studies in Europe, including specific considerations related to cross-border access, language accommodation, and children's rights.

This article presents an analysis of language-based eligibility criteria in pediatric clinical trials conducted in Europe between 2007 and 2024, as registered in the ClinicalTrials.gov database. This registry, the largest of its type, provides public access to trial data and was therefore selected as a representative source for conducting such an analysis. The primary objective of this study is to examine the use of language as an inclusion or exclusion criterion in pediatric clinical trial protocols and to assess whether these criteria were supported by an adequate scientific rationale.

In addition, this study includes an exploratory analysis of other eligibility criteria that may infringe on the rights of children, and their families, including discriminatory practices such as requiring access to mobile phones or Internet connectivity, or requirements related to the travel distance to the clinical trial site. Although not explicitly language related, this analysis intends to evaluate eligibility criteria that, directly or indirectly, may limit equitable access and participation.

This research was conducted as part of a broader European initiative led by a working group within the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) [11]. The mission of this working group was to evaluate the current landscape of multi-regional and cross-border pediatric clinical trials in Europe

Table 1 Regulations and frameworks related to the design and conduct of pediatric clinical trials in Europe

Regulations/framework	Scope	Relevance to cross-border pediatric trials	Language/non-discrimination provisions
Declaration of Helsinki (2024)	International	Ethics in medical research	Understandable information, informed consent
WHO guidance (2024)	International	Best practices in clinical trials	Reduces language barriers
ICH E17/E6 (R3) (2017)	International	Multi-regional trial design, GCP	Validated translations, clear communication
Clinical Trials Regulation (EU) 536/2014	EU	Harmonizes trial conduct, but does not regulate cross-border access	Non-specific
Directive 2011/24/EU	EU	Establishes right to cross-border healthcare	Non-discrimination, including language
Paediatric Regulation (EC) 1901/2006	EU	Requires PIP for pediatric medicines	Non-specific
Charter of Fundamental Rights of the EU (2000)	EU	Fundamental rights, including healthcare	Article 21: no discrimination by language
UN Convention on the Rights of the Child (1989)	Global	Child rights, including healthcare	Articles 2, 24, and 30: no discrimination, right to language

EC European Commission, *EU* European Union, *GCP* Good Clinical Practices, *ICH* International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, *PIP* Pediatric Investigational Plan, *UN* United Nations, *WHO* World Health Organization

with a particular focus on language-related barriers and potential discrimination. The project was approved by the Ethics Committee of the Institut de Recerca Sant Joan de Déu on 9 March, 2023 (code PIC-40-23).

2 Methods

2.1 Trial Selection and Study Sample

Data from a total of 2,285 pediatric clinical trials were retrieved from the ClinicalTrials.gov database. A total of 1,754 trials were retained in the final analysis after data curation by the principal investigator of this research, which involved: (1) eliminating data from 154 duplicated trials; (2) excluding three trials that were only focused on adults; and (3) removing 374 trials initiated before 26 January, 2007. The European Paediatric Regulation (EC No 1901/2006) came into force in January 2007 and this timepoint was therefore selected as the starting point for data inclusion. Data collection was completed on 29 October, 2024. Therefore, the data analyzed in this research included all the pediatric clinical trials published in the ClinicalTrials.gov database of interventional studies (phase I to phaseIII).

2.2 Data Extraction and Classification

We used the ClinicalTrials.gov Application Programming Interface to extract data on all clinical trials registered involving the pediatric population conducted in Europe between 2007 and 2024. The data were retrieved using a Python-based workflow and represented as a pandas DataFrame. This dataset includes trials from 39 countries, encompassing both EU Member States and non-EU countries (i.e., European Economic Area countries and Switzerland). We included phase I to phaseIII clinical trials across all pediatric therapeutic areas, with participants aged from birth to 17 years.

For each trial entry, we also processed additional files when available, specifically the study protocol and the statistical analysis plan. These documents were downloaded in a PDF format and converted to plain text files using the pdf library. The keyword search process was executed entirely in Python, both on the structured trial data and on the extracted text content of the additional documents. The resulting DataFrame was exported to a Microsoft Excel file to facilitate further statistical analysis and review. All compliant available records accessible through the ClinicalTrials.gov online database were screened and included in the final dataset.

2.3 Eligibility Criteria

Three datasets were analyzed in this research from the ClinicalTrials.gov database. The first focused on all pediatric clinical trials registered in the ClinicalTrials.gov database and conducted in Europe between 2007 and 2024. From this sample of 1,754 clinical trials, a second subset ($n = 85$) was created with the trials that included any mention of official European languages or European countries in their eligibility criteria. A third dataset ($n = 79$) was created to assess trials that referenced other eligibility criteria considered potentially restrictive in terms of patients' rights to access clinical trials (e.g., access to the Internet) (Table 2).

2.4 Data Analysis

Descriptive analyses were conducted on the characteristics of the three data subsets: the general dataset containing all identified pediatric clinical trials, and two subsets derived from keyword searches. One subset focused on references

Table 2 Keywords analyzed in the ClinicalTrials.gov dataset

Keywords searched in the ClinicalTrials.gov dataset	
Semantic variables ($n = 32$)	Mother tongue, language, native language, first language. Official languages in EU member states ($n = 25$): Bulgarian, Croatian, Czech, Danish, Dutch, English, Estonian, Finnish, French, German, Greek, Hungarian, Irish, Italian, Latvian, Lithuanian, Luxembourgish, Maltese, Polish, Portuguese, Romanian, Slovak, Slovenian, Spanish, Swedish. Official languages in non-member states ($n = 7$): Albanian, Bosnian, Icelandic, Macedonian, Norwegian, Serbian, Ukrainian.
Country of the study ($n = 39$)	EU member states: Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden. EU non-member states: Albania, Andorra, Bosnia and Herzegovina, Iceland, Kosovo, Liechtenstein, Montenegro, North Macedonia, Norway, Switzerland, Ukraine, UK.
Other keywords ($n = 13$)	Mobile, Wi-Fi, Internet, travel, country, accommodation, hotel, overnight, informed consent, ICF, translation, country of residence, native.

EU European Union, *ICF* informed consent form

to official European languages ($n = 32$) and European countries ($n = 39$), while the other examined keywords related to requirements for accommodating cross-border participants (international patients), such as "country," "accommodation," "travel," "hotel," "internet," "overnight," "fluent," "proficiency," "assent," and "consent form." These terms were selected to assess whether clinical trial protocols included provisions to support participants traveling from another country to the host country, and to identify any language requirements related to the assent and consent process. Specifically, these keywords related to five categories: (1) requirements for phone or mobile access (e.g., availability for phone contact or access to a phone/mobile device); (2) travel to the study site, including proximity to the study site, travel distance, or restrictions such as prohibitions on international traveling; (3) mandatory affiliation with the French healthcare system; (4) access to the Internet; and (5) informed consent and translation (Table 2).

The method used to analyze the subset of data related to European languages and countries involved evaluating the justification for using language as an eligibility criterion. Such criteria were considered acceptable when scientifically justified, for example, when language or cognitive assessments were necessary, when communication with a health professional who did not speak the patient's language was required, or when patient- or caregiver-reported outcome measures were only validated in specific languages. Requirements for English proficiency were not considered cases of country-based discrimination unless limited exclusively to native speakers. Language-based exclusion was also assessed in relation to patient-reported outcome tools or quality-of-life scales that were available in other languages but not accepted under the inclusion criteria. Finally, the use of keywords related to European countries in eligibility criteria was considered discriminatory when a specific country was explicitly named (Fig. 1).

Certain information (e.g., National Clinical Trial number or NCT, title of the clinical trial, and sponsor name) that can identify the clinical trials in each subset of data was not included in this analysis. To confirm the reliability of the research data, all the findings identified from the Comma-Separated Values (CSV) data results were manually re-validated by the principal author against the original ClinicalTrials.gov database public information by cross-checking with published information and documents on the ClinicalTrials.gov website prior to inclusion of the selected data into the final analysis.

Reproducibility of the data is feasible in future studies by using a dataset that includes the full text of the eligibility criteria (inclusion and exclusion) and applying the same Python-based keyword analysis workflow.

3 Results

3.1 ClinicalTrials.gov Data: Pediatric Clinical Trials Conducted in Europe (2007–24)

From 26 January, 2007, to 29 October, 2024, a total of 1,754 pediatric clinical trials initiated in European countries were registered in ClinicalTrials.gov. The distribution of the trials by research phase was as follows: early phase I ($n = 14$; 0.8%) phase I ($n = 99$; 5.6%), phase I/II ($n = 121$; 6.9%), phase II ($n = 523$; 29.8%), phase II/III ($n = 128$; 7.3%), and phase III ($n = 869$; 49.6%).

The majority of trials included both sexes (93.8%, $n = 1,645$), while 5.1% ($n = 90$) of the trials were restricted to male participants and 1.1% ($n = 19$) to female participants. Of the 1,754 trials, 20 were targeting gender-based conditions such as Duchenne muscular dystrophy, or Mucopolysaccharidosis II (Hunter syndrome). Of the 1,754 trials, 303 (17.3%) targeted both children and adult participants, while 1,451 trials (82.7%) addressed only pediatric participants.

As of the data collection completion date (29 October, 2024), 1,021 clinical trials (58.2%) were completed, and 290 trials (16.5%) were actively recruiting patients. Table 3 summarizes the overall status of all trials included in this research, noting that 94 of the trials (5.4%) were classified under the category of unknown status.

3.2 Use of Language (Mother Tongue) as Eligibility Criteria

In 95.2% ($n = 1,669$) of the clinical trials, there was no explicit reference to any of the official European languages or the patient's mother tongue in the inclusion or exclusion criteria. Eighty-five (4.8%) of the 1,754 clinical trial protocols reported eligibility criteria (inclusion or exclusion criteria) regarding the language of the patient/family. Sixty-three of the 85 trials had an academic sponsor (74.1%) and 22 (25.9%) had a commercial sponsor.

The minimum and maximum number of countries involved in academic-sponsored clinical trials were 1 and 12, while for commercial-sponsored clinical trials these values were 1 and 10. The interquartile range for academic studies trials was 1 and for commercial trials was 3 (Table 4). These data demonstrate that usually academic-sponsored clinical trials are not conducted as multi-country trials.

Regarding the distribution of clinical trials across pediatric subspecialties. The three pediatric subspecialties with the highest number of trials were: psychiatry ($n = 25$; 29.4%), neurology ($n = 17$; 20%), and endocrinology ($n = 10$; 11.8%) (Fig. 2).

Fig. 1 Analysis process

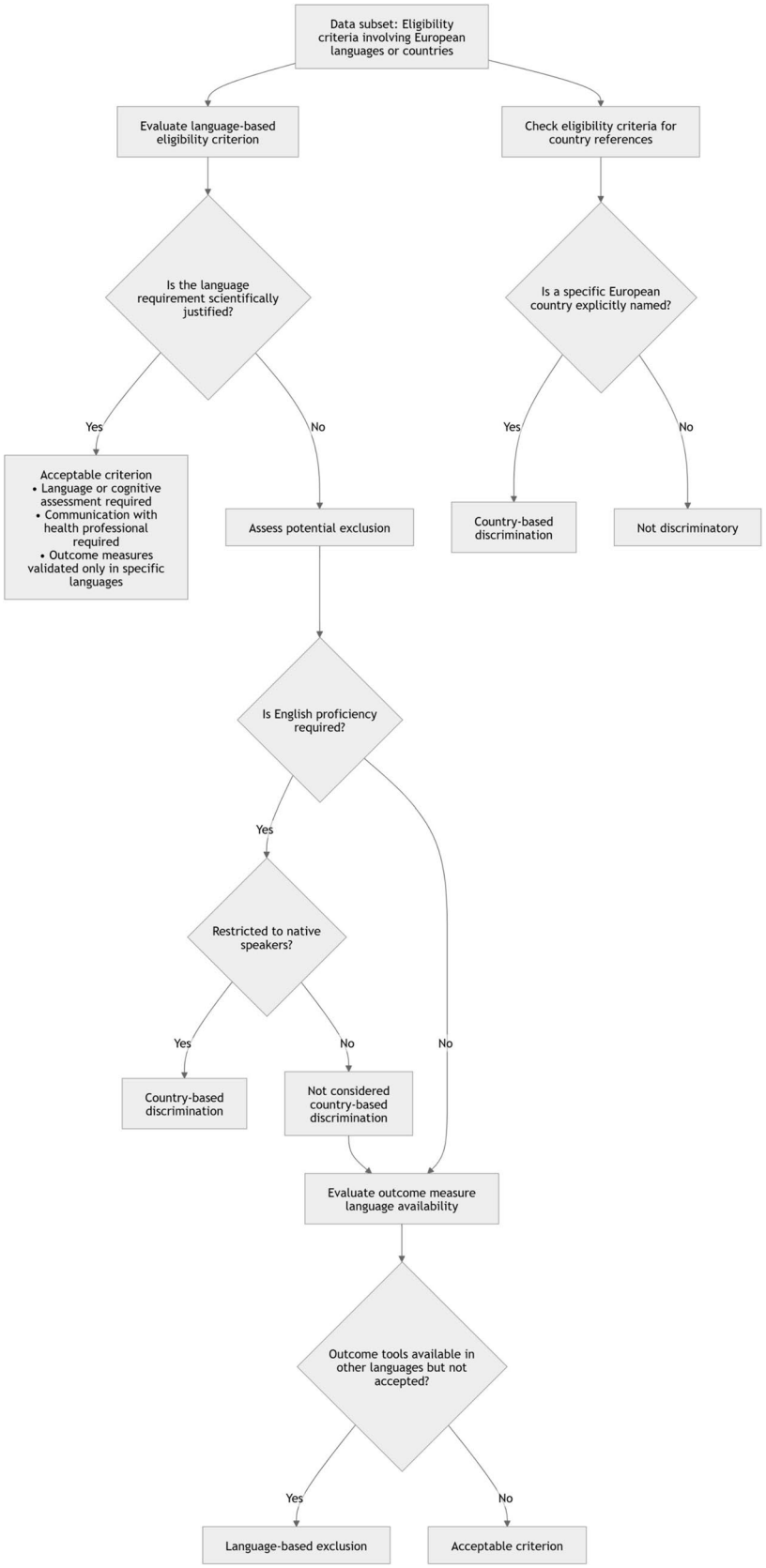

Table 3 Overall status of the clinical trials

Overall status	*n*	%
Active not recruiting	135	7.7
Completed	1021	58.2
Enrolling by invitation	6	0.3
Not yet recruiting	22	1.3
Recruiting	290	16.5
Suspended	6	0.3
Terminated	180	10.3
Unknown status	94	5.4
Total	**1754**	**100**

Table 4 Statistics of European countries involved in the clinical trials

	Academic trials	Commercial trials
Maximum	12	10
Minimum	1	1
Interquartile range	1	3

References to European official languages or the term "*language*" with no specification of which language were found in 48 out of the 85 clinical trials (56.5%) as inclusion criteria, in 29 trials (34.1%) as exclusion criteria, in four trials (4.7%) in both inclusion and exclusion criteria. In these trials, the keyword language referred to "local language," "primary language spoken at home," "language that parents/caregivers clearly understand," "understandable language," and "language barrier". In four clinical trials (4.7%), the reference of a European official language was in the study title (Table 5).

Of the 85 clinical trials that specified a language requirement as an eligibility criterion or in its title, English was the most frequent ($n = 18$, 21.2%) followed by French ($n = 14$, 16.5%). In total, 13 out of the 24 European official languages were included (Table 6).

The Electronic Supplementary Material (ESM) includes a table summarizing the detailed references to one or more European official languages (keywords) across the 85 clinical trials, along with other parameters: therapeutic area, countries participating in the clinical trial, type of sponsor, and the section of the study protocol where the keywords were mentioned. In four of these trials, one of the keywords referred to a European official language in the title (Danish in one and Norwegian in three); in these cases, however, the terms referred to participants' nationality and the country of the study rather than the requirement for these languages during the conduct of the trial.

3.3 Inclusion Criteria: Analysis of Text Referring to Language(s)

Of the 85 clinical trials analyzed, 48 (56.5%) included at least one keyword related to official European languages in the inclusion criteria. Each of these trials was assessed for potential language- and country-based requirements, as well as whether there was a scientific justification for requiring specific language proficiency (Table 7).

In 41 of the 48 clinical trials (85.4%), the requirement of proficiency in at least one European official language was

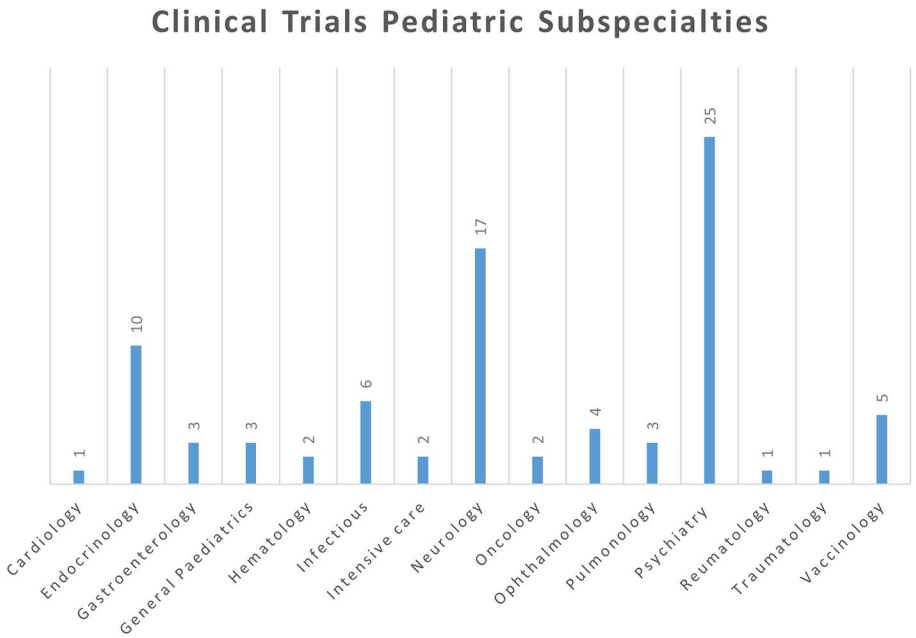

Fig. 2 Number of clinical trials according to the pediatric subspecialties

Table 5 Use of European languages or the word "language" as eligibility criteria in the clinical trial protocol

Reference of European languages in the study protocol sections	*n*	%
Inclusion criteria	48	56.5
Exclusion criteria	29	34.1
Inclusion criteria/exclusion criteria	4	4.7
Title	4	4.7
Total	**85**	**100**

Table 6 Search results of the keywords related to European official languages or related to language in the eligibility criteria and title

Language	*n*	%
Danish	5	5.9
Dutch	4	4.7
English	18	21.2
English/German	1	1.2
English, Spanish, US Spanish, French, German, or Polish	1	1.2
English/Dutch	1	1.2
English/Spanish	2	2.4
Finnish	2	2.4
French	14	16.5
German	7	8.3
Italian	3	3.5
Language	15	17.6
Non-English	1	1.2
Norwegian	7	8.2
Spanish	1	1.2
Swedish	3	3.5
Total	**85**	**100**

The table summarizes the findings for the keywords identified in each study protocol. In cases where more than one language was required within the same clinical trial's eligibility criteria (e.g., English/Dutch), the trial was categorized only once, as all languages correspond to the same study protocol

Table 7 Search results of the keywords related to European official languages or related to language in the inclusion criteria for 48 clinical trials

Type of patient discrimination identified	*n*	%
Language discrimination	41	85.4
Country discrimination	35	72.9
Scientific justification about language requirement	13	27.1
Language discrimination + country discrimination	32	66.7
Language discrimination + scientific justification about language requirement	11	22.9
Country discrimination + scientific justification about language requirement	9	18.8

Table 8 Search results of the keywords related to European official languages or related to language in the exclusion criteria from 29 pediatric clinical trials

Type of patient discrimination identified	*n*	%
Language discrimination	26	89.7
Country discrimination	21	72.4
Scientific justification about language requirement	10	34.5
Language discrimination + country discrimination	20	69.0
Language discrimination + scientific justification about language requirement	8	27.6
Country discrimination + scientific justification about language requirement	6	20.7

found with no justification. This determination was based on the protocol design, specifically when the patient-reported outcomes, tools, or quality-of-life scales were accessible in a language(s) other than the one required in the inclusion criteria. The authors also considered that the language requirement was not necessary to ensure the achievement of the study's scientific outcomes based on the analysis of the specifics of the clinical trial protocol review (condition, patient-reported outcomes).

In 35 of the 48 clinical trials (72.9%), the language requirement was also considered a case of country-based discrimination, as it required proficiency in a European official language other than English. In five cases, the inclusion criteria required affiliation with the French Social Security System, explicitly country-based discrimination, as it limited eligibility to residents of France.

Thirteen (27.1%) of the 48 trials included an acceptable scientific justification for the language requirement, related either to the therapeutic area that involved language or cognitive assessments or to patient- or parent-reported outcome measures that were only validated in certain languages. See the ESM for detailed information on the data findings.

3.4 Exclusion Criteria: Analysis of Text Referring to Language(s)

Of the 85 clinical trials analyzed, 29 (34.1%) included at least one keyword related to official European languages in the exclusion criteria. Language and country-based discrimination and whether there was a scientific justification for the language requirement were evaluated (Table 8). The analysis followed the inclusion criteria analysis.

In 26 of the 29 clinical trials (89.7%), the requirement of competence in at least one European official language was considered language-based discrimination, given that the protocol required a patient-reported outcomes tool or quality-of-life scale to be available and validated in a language other than the one required in the inclusion criterion. In 21 of the 29 clinical trials (72.4%), the language requirement

was considered a case of language-based discrimination, as it required proficiency in an official language of only one European country and different from English.

In 10 of the 29 clinical trials (34.5%), the language requirement was scientifically justified, either because of the therapeutic area involving language or cognitive assessments, or because the patient/parent-reported outcome tools were only validated in certain languages. The authors considered reasonable the language requirement to ensure the achievement of the study's scientific outcomes. See the ESM for detailed information about the data findings (keyword identified, type of study, type of discrimination, scientific justification, for or against, the use of language as an eligibility criterion, and the literal mention of the relevant keywords in the clinical trial protocol.

3.5 Inclusion and Exclusion Criteria: Analysis of Text Referring to Language(s)

Four (4.7%) of the 85 clinical trials included a reference to a European official language in both inclusion and exclusion criteria (Table 9). In two trials that required English as an eligibility criterion, caregivers of patients could participate if they had the appropriate language skills; further, the criteria did not specifically require residence in the UK, where the trials were conducted. One study conducted in France required proficiency in French and affiliation with the French healthcare system; given that, there was no option for inclusion of international patients, this study represents a case of country-based discrimination. The fourth study, conducted in Italy, required fluency in Italian. This requirement poses a significant barrier, as Italian is official only in one European country and not widely spoken as a second language across European countries.

3.6 Other Cases of Patient Discrimination Based on Eligibility Criteria

In addition to language-related criteria, other eligibility keywords were examined across the 1,754 European pediatric clinical trials. In 79 of 1,754 clinical trials (4.5%), the different keywords were included as an inclusion criterion (77.2%; $n = 61$), exclusion criteria (21.5%; $n = 17$), or both (1.3%; $n = 1$) (Table 10).

Specifically regarding the keyword "travel," which appeared in 16 out of the 79 study protocols (20.3%), it was

Table 9 Language requirements in the inclusion and exclusion criteria

N	Therapeutic area	Language keywords	Countries	Type of sponsor	Protocol section	Mention
1	Neurology	French	France	Academic	IC/EC	IC: affiliated with the French universal healthcare system EC: French language not spoken by parents
2	Neurology	Language/English	UK	Commercial	IC/EC	IC: the subject's caregiver/LAR is English speaking and has sufficient language skills to complete the caregiver assessments and has the ability to keep accurate seizure diaries EC: parents who are deemed to lack adequate English language to understand the written psycho-educational tool, telephone call, and questionnaires will be excluded Our aim in the future, if the intervention is shown to be successful, is to translate the intervention tools into the most frequently encountered foreign languages
3	Psychiatry	Italian	Italy	Academic	IC/EC	IC: Italian fluency for the adolescent and parent EC: intelligence quotient Total score below 70 or Verbal Comprehension Index scores below 80 on the Italian version of the WISC-IV scale []
4	Psychiatry	English	UK	Academic	IC/EC	IC: at least one parent in each family must be literate fluent English speakers to participate because the self-administered intervention will primarily consist of written instructions and information in English EC: non-English speakers or those who are unable to read cannot be included because reading English is required to complete the self-administered intervention

EC exclusion criteria, *IC* inclusion criteria, *LAR* legally authorized representative, *WISC-IV* Wechsler Intelligence Scale for Children - Fourth Edition

Table 10 Keywords distribution in study protocols in eligibility criteria for pediatric clinical trials in Europe

Keyword	*n*	IC	EC	IC/EC	%
Phone	43	39	4	-	54.4
Travel	16	6	10	–	20.3
Mobile	8	8	–	–	10.1
French healthcare system	8	6	1	1	10.1
Internet	2	1	1	–	2.5
Computer	1	1	–	–	1.3
Family	1	–	1	–	1.3
Total	**79**	**61**	**17**	**1**	**100**

EC exclusion criteria, *IC* inclusion criteria

referenced in various contexts, including: "travel time and distance," "willingness to travel to the site," "plans to travel outside the country," "ground-travel distance," "ability/inability to travel," and "safety to travel to the study site." Of these clinical trials, 72.1% were commercially sponsored, while 27.8% were academically sponsored. With regard to pediatric subspecialties, the majority (50.6%) were in the field of infectious diseases followed by neurology (21.5%) (Table 11).

4 Discussion

The initial hypothesis of this research was prompted by reports from caregivers of children living with chronic and rare diseases who had been excluded from participating in pediatric clinical trials because of their native language. Importantly, our review of protocols of clinical trials conducted in Europe from 2007 to 2024 and published in the ClinicalTrials.gov registry revealed specific eligibility criteria related to language only in 85 cases (4.8%).

Table 11 Distribution of clinical trials according to pediatric subspecialties

	n	%
Infectious	40	50.6
Neurology	17	21.5
Pulmonology	7	8.9
Endocrinology	5	6.3
Psychiatry	5	6.3
Gastroenterology	1	1.3
Hepatology	1	1.3
Oncology	1	1.3
Otorhinolaryngology	1	1.3
Ophthalmology	1	1.3
Total	**79**	**100**

This issue was previously analyzed in other regulatory jurisdictions [12–17], such as the USA. In that country, where prior to 2025 there was no official national language, English proficiency was required in 23.4% (n = 1,164) of clinical trials initiated between 1 January, 2019 and 1 December, 2022 (N = 4,982) [14]. Among trials that were academically sponsored, 28.8% required participants to understand English as an eligibility criterion. Of the trials requiring English, only 14.4% provided a justification for the requirement. In our study, a scientific justification for language requirements was identified in 27.1% of the trials (n = 13) when language was used as an inclusion criterion, and in 34.5% of the trials (n = 10) when it was applied as an exclusion criterion.

The absence of explicit language-based eligibility criteria in the ClinicalTrials.gov registry record has been assumed to mean no such restriction exists. This assumption would require further testing in direct analysis of the practice of specific clinical trials. Future research should also examine other forms of discrimination such as protocols having country-specific amendments that are not uploaded to the registry, or sponsor requirements for particular centers, or exclusion by the actions of researchers ("physician discretion"). As such, our estimate of language discrimination is likely an underestimate. This is the case in the majority (95.2%) of European clinical trials published and is consistent with the Convention on the Rights of the Child [8] (1989), which affirms that no child should face discrimination *based on language*. This practice also aligns with the Charter on Fundamental Rights of the EU (2000) [3], which explicitly prohibits discrimination based on language and other protected attributes (Art. 21).

Following a detailed analysis, the majority (76.5%) of clinical trials registered conducted in Europe between 2007 and 2024 that did include language as an eligibility criterion, were sponsored by academic institutions. In such cases, the imposition of language-based eligibility criteria may relate to economic and budgetary constraints that limit translation or interpreter services and/or cross-border support. Nevertheless, the practice results in geographic and linguistic discrimination, which runs counter to the principle of equitable access within the EU.

Among the trials analyzed that included language as an eligibility criterion, scientific justification was identified in 23 cases (27.1%). These justifications predominantly related to therapeutic areas that required language or cognitive assessments or the use of patient- or caregiver-reported outcome measures that had only been validated in specific languages. The findings presented in this article underscore the exclusion of certain patient populations based on language-related criteria that should be explicitly detailed

in the protocols reviewed and approved by research ethics committees. These oversight committees should require adequate scientific justification of such criteria, thereby limiting potential instances of language-based discrimination. This is particularly relevant in the EU, which includes 24 official languages.

It is essential to raise awareness among all stakeholders involved in the design and execution of pediatric clinical trials about the feasibility and importance of including international patients and those not fluent in the official language of the host country. Incorporating a representative patient population not only upholds the rights of children but also advances the scientific generalizability of the trial results, thereby reducing risks to subpopulations in multi-national regulatory jurisdictions.

In summary, our study has several strengths. First, it provides the first research conducted to analyze the use of language in the eligibility criteria of pediatric clinical trials published in the largest database of clinical trials. This registry allowed us to retrieve data using the ClinicalTrials.gov Application Programming Interface with more granularity and access and to analyze the additional files when available, specifically the study protocol and the statistical analysis plan. The EudraCT (European Union Drug Regulating Authorities Clinical Trials) and CTIS (Clinical Trial Information System) registries do not allow eligibility criteria data to be retrieved via an Application Programming Interface, nor does it permit downloading of study protocol files. Second, the evidence generated by this study will be useful in raising awareness within the scientific community about case studies in which the use of language as an eligibility criterion lacked a scientific rationale, and in helping to prevent the unfair use of language requirements in future clinical trials conducted in Europe. Third, the results of this research will be incorporated into a recommendations document linked to the activities of the Cross-Border Clinical Trials Working Group established within Enpr-EMA, with the aim of facilitating more inclusive pediatric studies.

Nevertheless, some limitations should be acknowledged. First, as our study was based on objective data published in the ClinicalTrials.gov registry, we were unable to analyze cases in which patients may have been excluded owing to their native language based on sponsor or physician discretion, even when this criterion was not specified in the clinical trial protocol. Second, further research related to the goals of this project is necessary, as only 1,754 clinical trials could be analyzed in this initial analysis. This number refers to trials registered in ClinicalTrials.gov, a registry that is not mandatory for trials conducted in Europe.

This analysis highlights that some clinical trial protocols explicitly include language requirements as part of the eligibility criteria without a clear scientific rationale. While this information does not confirm that these clinical trials constitute actual cases of discrimination or that they prevent cross-border participation, such criteria may limit the inclusion of patients from other European countries or those not proficient in the required languages. To accurately identify potential cases of language-based discrimination in cross-border access to pediatric clinical trials, data should be collected from principal investigators, clinical trial site staff across Europe, as well as from parents of children living with health conditions. At the time this article was written, this data collection had already been conducted and will be published in a complementary scientific article.

This study also identified other potentially exclusionary eligibility requirements. These included prerequisites such as access to a mobile phone and/or to the Internet, proximity to the trial site or travel restrictions during the study period, and affiliation with a specific national healthcare system. Socioeconomic barriers associated with technology access raise significant ethical concerns, as they could be mitigated by the provision of technology and digital access. Travel-related restrictions may be defensible based on concerns of infection control or exposure, but these situations are limited. Alternative measures should be considered to mitigate participant burden, including the provision of satellite trial sites, a reduction in required site visits, home nursing services, and/or the use of telemedicine. In the context of rare and ultra-rare diseases where clinical trial sites are often limited in number, the exclusion of participants based solely on geographical constraints is ethically indefensible when feasible alternatives exist.

5 Conclusions

The findings of this study provide evidence on recurring patterns related to the design and conduct of pediatric clinical trials, particularly in relation to eligibility criteria, language requirements, and cross-border participation. These observed patterns suggest that greater attention to the perspectives of pediatric patients and their caregivers may help anticipate and mitigate potential barriers to participation, especially in studies involving rare diseases and those conducted within the framework of pediatric investigation plans.

From these observations, it can be inferred that evaluating study protocols solely on scientific and methodological grounds may be insufficient to fully capture their impact on children and families. Consideration of children's rights, alongside the patient and family experience, emerges as an important implication of the data. In this context, the involvement of young patients and caregivers during protocol development may support the early identification of practices that could inadvertently lead to exclusion or disproportionate burden, including forms of discrimination related to language or other contextual factors.

The results also point to language-related barriers as a potential contributor to unequal access to clinical trials, regardless of whether language is explicitly defined as an eligibility criterion. This suggests a role for patient organizations, investigators, research teams, and sponsors in reviewing protocols prior to finalization and in reflecting on feasibility assessments that account for language accommodation and broader diversity considerations. Such actions, while not directly tested in this study, are consistent with the patterns observed and may inform strategies aimed at reducing unjustified exclusion.

Finally, the analysis underscores the relevance of facilitating access to cross-border clinical trials as one approach for ensuring that the included participant population adequately represents the heterogeneity of the disease. Instances of product withdrawal after marketing authorization, secondary to adverse effects in under-represented subpopulations, demonstrate the importance of an inclusive study design. In this regard, we recommend the incorporation of two specific sections within the study protocol: (1) a separate cross-border access section that defines objective criteria and accommodations for the participation of international patients in clinical trials outside their country of residence and (2) an inclusive recruitment plan that specifies the minimum requirements for patient subpopulations that must be included as participants in the clinical trial [18]. Both potential sections in the study protocol should include strategies for managing language barriers and for addressing the inclusion of international patients.

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Declarations

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