Pharmaceutical Medicine (2026) 40:209–223
https://doi.org/10.1007/s40290-026-00607-z

ORIGINAL RESEARCH ARTICLE

Paediatric Phase I/II Clinical Trial Assessments Under the New EU Clinical Trial Regulation: A Descriptive Analysis

Laura Fankhauser[1,2,3,4] · Franca Ligas[5] · Giovanni Lesa[5] · Anette Solli Karlsen[6] · Marianne Lunzer[7] · Monique Al[8] · Sabine Scherer[9] · Sylvie Benchetrit[10] · Claudia Riedel[9] · Annette Kopp-Schneider[11] · Ruth Witt[1,2,3,4] · Olaf Witt[1,2,3,4] · Dominik Karres[5] · Cornelis M. van Tilburg[1,2,3,4]

Accepted: 24 March 2026 / Published online: 4 May 2026

Abstract

Background Children remain underrepresented in clinical research, despite regulatory frameworks like the EU Paediatric Regulation and Paediatric Investigation Plans (PIPs). The 2024 Declaration of Helsinki revision now recognises excluding vulnerable populations from research as a potential ethical concern. The Clinical Trial Regulation (EU) No 536/2014 aims to harmonise clinical trial application assessment procedures through a coordinated process involving a Reporting Member State (RMS) and Member States Concerned (MSCs).

Aims To determine if harmonisation is occurring, we conducted the first systematic analysis of Phase I/II paediatric trial application assessments across Member States (MS) in the European Union (EU) focusing on assessment variability, evidence requirements, PIP integration, and adolescent inclusion practices in adult trials.

Methods In the context of the European Medicines Agency collaborating expert program, non-public data of 160 paediatric Clinical Trial Applications (CTAs) submitted through the Clinical Trial Information System (January 2022–July 2024) were screened, with inclusion of 55 Phase I/II trials in the main analysis (selected for their focus on innovative treatments and complex risk-benefit assessments). For each CTA, requests for information (consisting of considerations stated by the RMS and MSCs), assessment reports, sponsor responses, and PIP documentation were reviewed. The number of considerations in the requests for information per MS was analysed with median values calculated. Also, considerations were systemically categorised and assessment patterns between RMS and MSC roles were compared. It was examined how PIPs were integrated into assessments and approaches to adolescent inclusion in adult trials was analysed through systematic review of MS considerations.

Results Of the 160 paediatric CTAs screened, 145 received authorisation, 10 were not authorised, and 5 were withdrawn. Among the 145 authorised CTAs, 61 were Phase I/II trials, 55 of which were included in the main analysis. Analysis of these applications revealed significant heterogeneity in both the number and type of considerations raised across MS, with the median number of considerations per CTA ranging from 5.5 to 26 across MSs ($p = 0.025$), with particularly marked variation when MSs acted as MSCs compared to RMSs—where additional considerations ranged from zero to 25 per CTA on top of those raised by the RMS. In 36% (20/55), MSs raised concerns about insufficient (pre-)clinical evidence pointing to divergent interpretations of evidence requirements. The degree to which PIPs were integrated into CTA assessments varied considerably—ranging from strict adherence to PIP elements to minimal consideration. In 92% (11/12), MSs showed reluctance to include adolescents in adult Phase I/II trials.

Conclusions Despite the CTR's harmonisation goals, substantial variations persist in assessment practices across MSs, particularly regarding evidence requirements, PIP integration, and adolescent inclusion in adult trials. These variations

Previous Presentations: Oral presentation at ACCELERATE conference, held on 7th February, 2026 in Brussels. An abstract of this project was selected for oral presentation at the 2025 SIOP Annual Meeting and was awarded with the young investigator award (https://siop-online.org/young-investigator-award/).

Extended author information available on the last page of the article

directly impact equitable access to clinical trials for children across the EU. Urgent regulatory guidance is needed to align interpretation of evidence standards, clarify the role of PIPs in CTA evaluation, and support evidence-based approaches to adolescent inclusion in adult trials.

Key Points

Despite new EU regulations intended to standardise how clinical trials are reviewed, our analysis of 160 applications revealed significant differences in how various countries assess paediatric Clinical Trial Applications, potentially limiting some children's access to potentially life-saving treatments.

Most European regulators showed reluctance to allow adolescents to participate in adult studies, which may delay access to new treatments for this age group and slow the development of medicines for the paediatric population.

The substantial variations we found in how countries evaluate required evidence and consider existing paediatric development plans highlight the need for harmonised guidance to create a more equitable system for children seeking access to clinical trials across Europe.

1 Introduction

Historically, children have been underrepresented in clinical research, leading to significant gaps in access to new treatments and innovations and reliance on off-label use of medicines [1–4]. For example, over a five-year period, far fewer paediatric clinical trials were conducted compared to adult trials: adult clinical trials were registered in ClinicalTrials.gov at more than ten times the rate of paediatric trials [5]. While this disparity is partly expected due to the larger adult population and their less-vulnerable status, recent data from the Clinical Trial Information (CTIS) analysed in the present study showed an even greater imbalance. During a 1.5-year period of mandatory CTIS use in the European Union (EU), the number of adult Phase I/II Clinical Trial Applications (CTAs) authorised exceeded the number of paediatric CTAs authorised by more than 15-fold (CTIS submissions from January 2023 to July 2024).

The EU Clinical Trial Regulation No 536/2014 (CTR) states under Article 32 the requirements for a paediatric clinical trial: "a paediatric clinical trial may only be conducted if it is intended to investigate treatments for a medical condition that only occurs in minors (in the EU, typically individuals aged < 18 years) or is essential to validate data obtained in adult clinical trials or by other research methods" [6]. While protecting vulnerable populations like minors remains crucial, the 2024 revision of the Declaration of Helsinki acknowledges that excluding such groups from research may itself pose ethical concerns by limiting and delaying access to innovative evidence-based treatment options [7].

Additionally, the EU Paediatric Regulation requires development for new medicinal products by means of a Paediatric Investigation Plan (PIP) [8]. Paediatric Investigation Plans are development plans that pharmaceutical companies must submit to the European Medicines Agency (EMA), for discussion at EMA's Paediatric Committee (PDCO) outlining how they will develop their medicine for use in children. Thus, many paediatric clinical trials stem from agreed PIPs; however, not all trials are conducted as part of PIP aimed at obtaining market approval. For example, investigator-initiated trials, or trials conducted in therapeutic areas with PIP waivers may proceed independently of the PIP framework.

Although the EU Clinical Trial Regulation No 536/2014 (CTR) [6] (implemented on January 31, 2022) was introduced to harmonise procedures for the conduct of clinical trials across the EU, there is concern that for paediatric trials, harmonisation is hampered by different interpretations of CTR requirements by individual Member States (MSs) during the assessment process. Key areas of interpretational variability include the evidence standards required under Article 32, the acceptability of risk-benefit profiles, the role of PIPs in trial design, and ethical considerations specific to vulnerable populations. Under this regulation, the responsibility of trial approval lies with the EU MSs. Clinical trial applications are assessed through a coordinated assessment process in the CTIS where one MS, as involved by the sponsor, acts as the Reporting Member State (RMS), coordinating the evaluation, while others participate as Member States Concerned (MSCs). The assessment is divided into two parts: Part I covers the scientific and ethical assessment of the study protocol and is conducted through a coordinated review process (led by the RMS), resulting in a harmonised decision. Part II addresses country-specific national requirements (such as local ethics committee requirements, data protection, and site-specific considerations) and is evaluated independently by each MS. While this coordinated system applies to all clinical trials, paediatric studies are particularly

susceptible to assessment variability due to their additional regulatory requirements under Article 32, integration with PIP obligations, and more stringent ethical considerations for vulnerable populations. Furthermore, the lower volume of paediatric CTAs provides fewer opportunities for assessors to develop consistent interpretation patterns compared to high-volume adult trials.

There is growing concern that lack of harmonisation across EU/European Economic Area (EEA) MSs in interpreting CTR requirements may lead to conservative assessment approaches for paediatric clinical trials. This was recently confirmed at a multi-stakeholder methodology workshop (EMA/105992/2024) [9] from the Accelerating Clinical Trials in the European Union initiative (ACT EU), which specifically highlighted inconsistent interpretations of Article 32. Stakeholders suggest this could delay access to innovative treatments, discourage pharmaceutical companies from initiating paediatric trials in the EU/EEA, and perpetuate off-label use. Although these concerns appear to be shared by many stakeholders, they have yet to be systematically analysed.

This descriptive analysis aims to provide a baseline understanding of current paediatric Phase I/II CTA assessment practices across MSs by exploring variability patterns and examining the influence of PIPs on the evaluation process. Additionally, we analysed how the inclusion of adolescents in adult CTAs was assessed. Phase I/II CTAs were selected because they typically involve innovative new treatments and represent first-in-children approaches with complex risk-benefit assessments. The findings are intended to inform subsequent initiatives to harmonise and optimise paediatric CTA assessments across the EU, such as further supporting assessors workshops on paediatric clinical trials by providing additional direction to address the challenges identified [10].

2 Material and Methods

2.1 Study Sample and Selection

All paediatric CTAs (age category < 18 years) submitted through CTIS from January 31, 2022, to July 31, 2024, were screened. This period encompassed both the one-year transition phase (January 2022–January 2023), when CTIS use was optional, and the first 18 months of mandatory usage (February 2023–July 2024).

Inclusion Criteria:

- Paediatric CTAs (age category <18 years) submitted through CTIS between January 31, 2022, and July 31, 2024.
- Screening: all paediatric CTAs.
- Detailed analysis: Phase I/II paediatric CTAs.
- Analysis of adolescent inclusion practice: adult CTAs including age categories <18 years ("adult-adolescent CTAs").

Exclusion Criteria:

- Withdrawn CTAs (due to incomplete assessment).
- Transitioned CTAs from previous systems (which were only technically transitioned to CTIS, not newly assessed).
- CTAs evaluating paediatric formulations in adults.
- Resubmissions of previously rejected CTAs (only the initial CTA was analysed).
- CTAs exclusively concerning long-term follow-up observational studies without intervention.

Rationale for Phase I/II Selection:

Phase I/II trials were selected for detailed analysis of assessment processes for several reasons: they typically involve innovative new treatments, often represent first-in-children approaches with complex risk-benefit assessments, and frequently utilise novel study designs that may be interpreted differently across MSs. Importantly, these early-phase trials are often where PIP requirements are first implemented in practice. By contrast, Phase III–IV CTAs typically involve treatments already tested or authorised in children and were therefore considered less informative for our analysis.

Adult–Adolescent CTA Selection

For analysis of adolescent inclusion practices, all authorised adult CTAs submitted during the same period were screened, and those including age categories <18 years were selected for review.

2.2 Data Collection

Data access was facilitated through an ACCELERATE Fellowship at the EMA. ACCELERATE is a multi-disciplinary stakeholder platform, which aimed to find solutions for more and better innovative therapies for children and adolescents with cancer [11]. In the context of its educational programme (called “Aladdin”), the fellowship (also called “rotation”) represented a 6-month part-time placement at the EMA involving a research project within the Collaborating Expert programme. The fellowship enabled comprehensive access to both public and non-public datasets within CTIS.

Trial information including sponsor, therapeutic area, market authorisation and phase was extracted from CTIS. For each authorised CTA, request for information (RFI) with considerations of RMS and MSCs before and after consolidation (process of combining considerations of each MSC in the final RFI), Sponsor Response documents, final assessment report of Part I assessment, Part II assessment conclusions, Opinion and Summary report of PIPs and respective modifications, if applicable, were extracted. When necessary to understand specific modifications requested during the assessment process, the corresponding study protocols were also reviewed.

2.3 Data Analysis

2.3.1 Analysis of Authorisation Status

The final authorisation status was analysed for all Phase I–IV paediatric CTAs. For authorised trials, characteristics (therapeutic area, sponsor, phase, RMS) were examined. For non-authorised trials, a detailed review of the assessment reports and final decisions was conducted. For adult-adolescent CTAs, final outcome was analysed considering if and how younger age groups were included in the final study protocol.

2.3.2 Analysis of Assessment Process

The number of considerations in RFIs was analysed for each MS in their roles as both RMS and MSC in authorised paediatric CTAs. Median numbers of considerations per MS were calculated separately for RMS and MSC roles, including only those MSs that had participated in more than two trials in the respective role. For Phase I/II adult-adolescent CTAs, assessment processes were analysed with a focus on the approach of MSs to adolescent inclusion, including their considerations and discussion comments regarding the inclusion of adolescent participants.

2.3.3 Categorisation by Subject

Considerations in RFIs were divided into the following ten categories adapted from Beck et al. [12]: formalities, toxicity and safety, manufacturing and import, inclusion and exclusion criteria, study population and design, risk-burden-benefit analysis, study rationale, drug administration, dosing and required evidence. Median numbers of considerations in the categories per MS were calculated. Again, only those MSs that had participated in more than two trials were included. In addition, each consideration in the RFIs was screened to identify those relating to the required evidence in the context of Article 32.

2.3.4 Statistical Analysis

Variables analysed included the presence of a paediatric investigation plan (PIP) (dichotomous), the number of considerations per CTA (discrete count variable), MS role (dichotomous: RMS or MSC), and MS identity (categorical). Statistical analyses were performed using R version 4.5.1, the R Foundation for Statistical Computing. Differences in the number of considerations between RMS were assessed using a Kruskal-Wallis test. The Kruskal-Wallis test was selected as the appropriate test for comparing count data across multiple groups, as the primary outcome variable—number of considerations per CTA—consists of count data with relatively low values, for which normality cannot reasonably be assumed, p-values ≤ 0.05 were considered significant. Given the exploratory nature of this evaluation, p-values were not adjusted for multiple comparisons. Statistical testing was not performed on the number of considerations between MSC, as the one-to-many relationship between CTAs and MSCs introduces analytical complexity that would compromise valid statistical inference.

2.3.5 Categorisation by Significance and Feasibility

The considerations put forward by the National Competent Authorities (NCAs) in the assessment Part I were additionally categorised according to their significance and feasibility adapted from Beck et al [12]. The following definitions were applied:

Easy to implement: *Minor Clarifications, questions easy to answer;*

Easy to implement and change of protocol requested: *no substantial protocol changes;*

Difficult to implement: *Clarifications and questions that need to be answered more extensively;*

Difficult to implement and change of protocol requested: *changes that substantially change the study protocol*.

2.3.6 Analysis of CTAs with a PIP

For each CTA, the presence of an associated PIP was verified in CTIS. Where PIPs existed, a comparative analysis examined alignment between the CTA protocol and the PIP, references to the PIP in assessment reports, and consistency between the authorised trial and PIP requirements. Additionally, the time interval between the initial PIP agreement date (determined from the PIP opinion and its corresponding summary report) and the initial CTA submission (derived

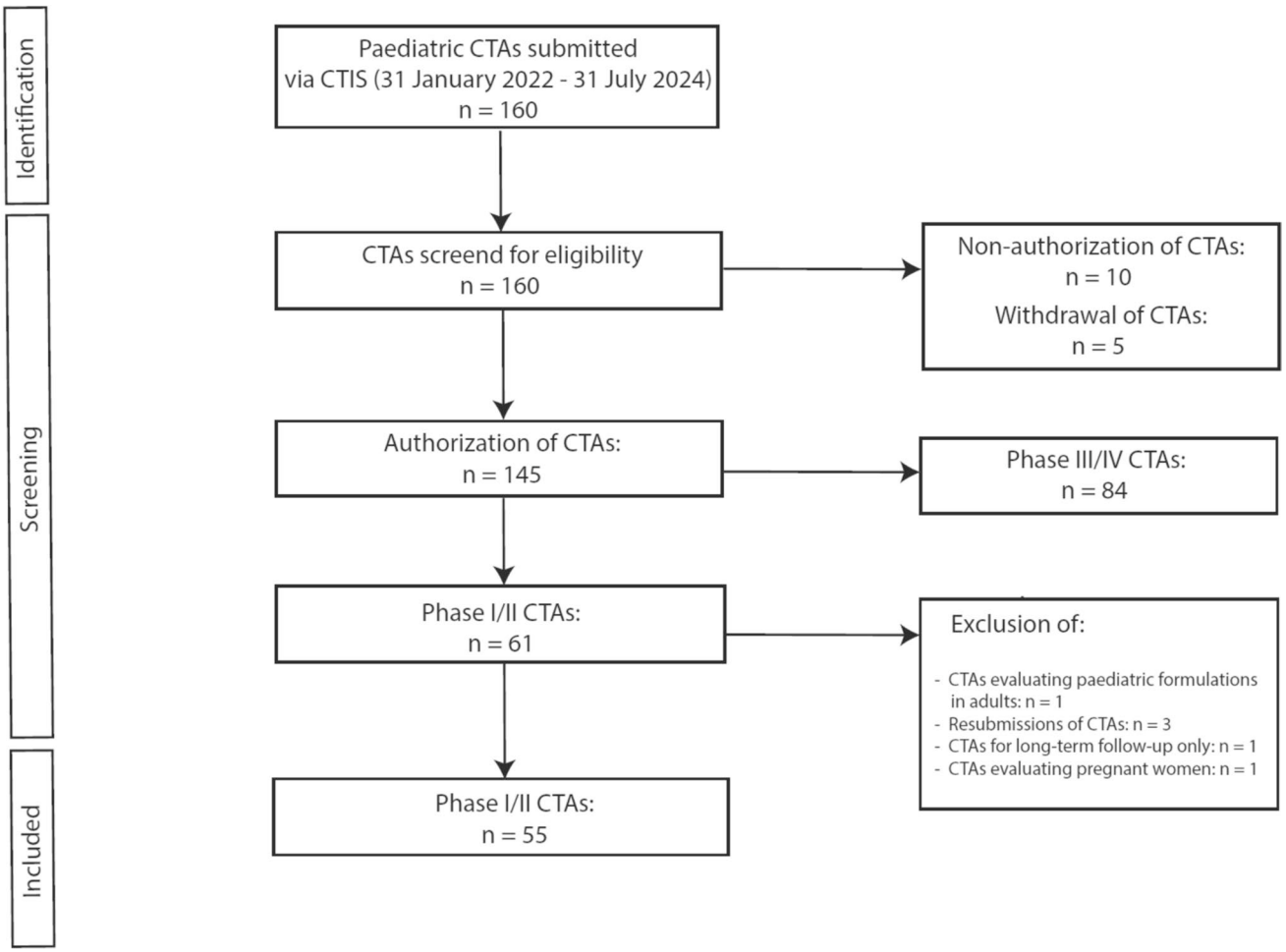


Fig. 1 Selection flowchart of Phase I/II Paediatric Clinical Trial Applications from the Clinical Trial Information System for final analysis. *CTA* Clinical Trial Application

from CTIS) was calculated. The time interval was calculated as the difference in days between the initial PIP agreement date (obtained from the PIP opinion and its corresponding summary report) and the CTA submission date (obtained from CTIS). This interval was expressed in years for descriptive purposes.

2.3.7 Role of the Funding Source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

2.3.8 Ethics Approval

Ethics approval was not required as this study involved retrospective analysis of anonymised regulatory assessment data without access to individual patient information. The analysis was conducted within the framework of an official EMA fellowship with appropriate data access permissions.

3 Results

3.1 Study Sample Characteristics

Of the 160 paediatric CTAs identified, 145 received authorisation, 10 were not authorised, and 5 were withdrawn (Fig. 1). Among the 145 authorised CTAs, 61 were Phase I/II trials, 55 of which were included in the main analysis of the considerations raised by MSs in their requests for information (RFIs).

Table 1 Characteristics of authorised paediatric Phase I/II CTAs

Therapeutic area	Sponsor-type		Phase				Reporting member state			Total *n* (%)
	Academia *n* (%)	Industry *n* (%)	I *n* (%)	II *n* (%)	I/II *n* (%)	II/III *n* (%)	Very large *n* (%)	Large *n* (%)	Small *n* (%)	
Neurology and developmental disorders	5 (25)	15 (75)	2 (10)	13 (65)	2 (10)	3 (15)	14 (70)	2 (10)	4 (20)	20 (36.7)
Oncology	6 (54.5)	5 (45.5)	2 (18.2)	5 (45.5)	3 (27.3)	1 (0.9)	8 (72.7)	2 (18.2)	1 (0.9)	11 (20)
Respiratory	1 (50)	1 (50)	0 (0)	2 100)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	2 (3.6)
Infectious diseases	1 (25)	3 (75)	0 (0)	3 (75)	1 (25)	0 (0)	3 (75)	0 (0)	1 (25)	4 (7.2)
Endocrinology	2 (50)	2 (50)	0 (0)	4 (100)	0 (0)	0 (0)	2 (50)	1 (25)	1 (25)	4 (7.2)
Haematology	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	1 (1.8)
Cardiology	2 (50)	2 (50)	0 (0)	2 (50)	1 (25)	1 (25)	2 (50)	1 (25)	1 (25)	4 (7.2)
GI	1 (25)	3 (75)	0 (0)	3 (75)	0 (0)	1 (25)	3 (75)	1 (25)	0 (0)	4 (7.2)
Anaesthesia	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (1.8)
Allergy	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (1.8)
Rheumatology	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (1.8)
Other	0 (0)	2 (100)	0 (0)	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	2 (3.6)

Non-authorised and withdrawn CTAs are not included here

Very large refers to a population of 20 million or more inhabitants, large = population of ten million or more inhabitants, small = population of less than ten million inhabitants

CTAs Clinical Trial Applications, *GI* Gastrointestinal disorders

Analysis of therapeutic areas, sponsor type, phase and RMS of authorised Phase I/II CTAs revealed that neurology and developmental disorders represented the largest proportion of both overall paediatric CTAs (29%) and Phase I/II CTAs (36%) followed by oncology, accounting for 10% of all paediatric CTAs and 20% of Phase I/II trials (Table 1, Supplementary Table 1). Industry-sponsored trials accounted for most of paediatric CTAs. Clinical Trial Information data on geographic site distribution of authorised Phase I/II CTAs showed similar patterns for adult and paediatric trials, with both RMS and MSC roles predominantly concentrated in countries with larger populations (>10M inhabitants) (Supplementary Fig. 1) [13].

3.2 Non-authorised Clinical Trial Applications

Of the ten non-authorised paediatric CTAs, oncology represented the largest proportion (4/10) (Table 2), despite representing only 10% authorised CTAs (Table 1). Three CTAs had an approved PIP yet failed to receive trial authorisation. Assessment outcomes revealed that while all CTAs

Table 2 Characteristics of non-authorised CTAs ($n = 10$)

Study	A	B	C	D	E	F	G	H	I	J
Therapeutic area	Oncol.	Oncol.	Oncol.	Oncol.	ID	ID	Ophthal.	Dermat.	NDD	NDD
Sponsor	Academia	Industry	Academia	Industry	Industry	Industry	Industry	Industry	Academia	Industry
Paediatric investigation plan	No	Yes	No	No	No	Yes	No	Yes	No	No
Reporting member state	MS1	MS3	MS1	MS2	MS5	MS1	MS4	MS2	MS6	MS1
Phase	I	I/II	I/II	III	I	II	III	III	III	I/II
Assessment Part II	Acceptable	Acceptable with conditions	Acceptable	Acceptable with conditions	Acceptable	Acceptable	Acceptable	Not acceptable	Acceptable	Acceptable

Each MS is consistently represented by the same number

CTAs Clinical Trial Applications, *Dermat.* Dermatology, *ID* Infectious Diseases, *MS* Member State *Oncol.* Oncology, *Ophtal.* Opthalmology, *NDD* Neurology and Developmental Disorders

were deemed "not acceptable" in Part I of the evaluation, nine were considered "acceptable" or "acceptable with conditions" in Part II (Table 2), suggesting that scientific and methodological concerns were the primary drivers of non-authorisation. Key deficiencies identified included insufficiency of required evidence, particularly lack of adult or non-clinical data and toxicity concerns (Supplementary Table 2). Study design issues were also prominent, with problems in sample size, randomisation, and cohort selection.

3.3 Assessment Patterns Across Member States

Analysis of the assessment process of Phase I/II CTAs revealed heterogeneity in the number of considerations raised by different RMS (Fig. 2a, Supplementary Fig. 2a, Supplementary Table 3A).

The median number of considerations per Phase I/II CTA ranged from 5.5 (interquartile range [IQR]: 3.5–12.5) to 26 (IQR: 16–28) across different MSs, demonstrating a statistically significant variation across the dataset ($p = 0.025$). Examination of specific assessment categories (Fig. 2b, Supplementary Table 3B) showed that study population and design issues generated the most considerations across all MSs. Statistically significant differences were observed between MSs acting as RMS in the median number of considerations raised for study population and design ($p = 0.005$) and inclusion and exclusion criteria ($p = 0.036$). When comparing CTAs for products with prior marketing authorisation versus CTAs for products without prior marketing authorisation (Supplementary Fig. 2b), trials with unauthorised products did generate slightly more considerations (median 20, IQR: 7–23 vs 24, IQR: 16–33). Review of study protocols identified 15 CTAs with a two-part design. Subsequent analysis of RFIs and assessment reports revealed that substantial modifications (SMs) were requested between the Phase I and Phase II parts in seven cases, while no SM was required in the remaining eight.

When analysing the assessment process from the MSC perspective, more pronounced differences emerged (Fig. 3, Supplementary Fig. 3, Supplementary Table 3C). The median number of considerations raised per MS when acting as MSC showed substantial variation, with the absolute range spanning from zero to 25 considerations per CTA on top of considerations raised by RMS (Fig. 3).

Analysis of the feasibility and significance (Tables 3 and 4) showed that most considerations were classified as "easy to implement". However, the proportion of more challenging considerations varied notably among MSs, ranging from 15% to 36% when acting as RMS. These differences were even more pronounced when acting as MSC, with patterns ranging from one MS raising only considerations classified as "easy to implement" to another where 40% of considerations were categorised as difficult to implement.

3.4 Analysis of Required (Non-) Clinical Evidence

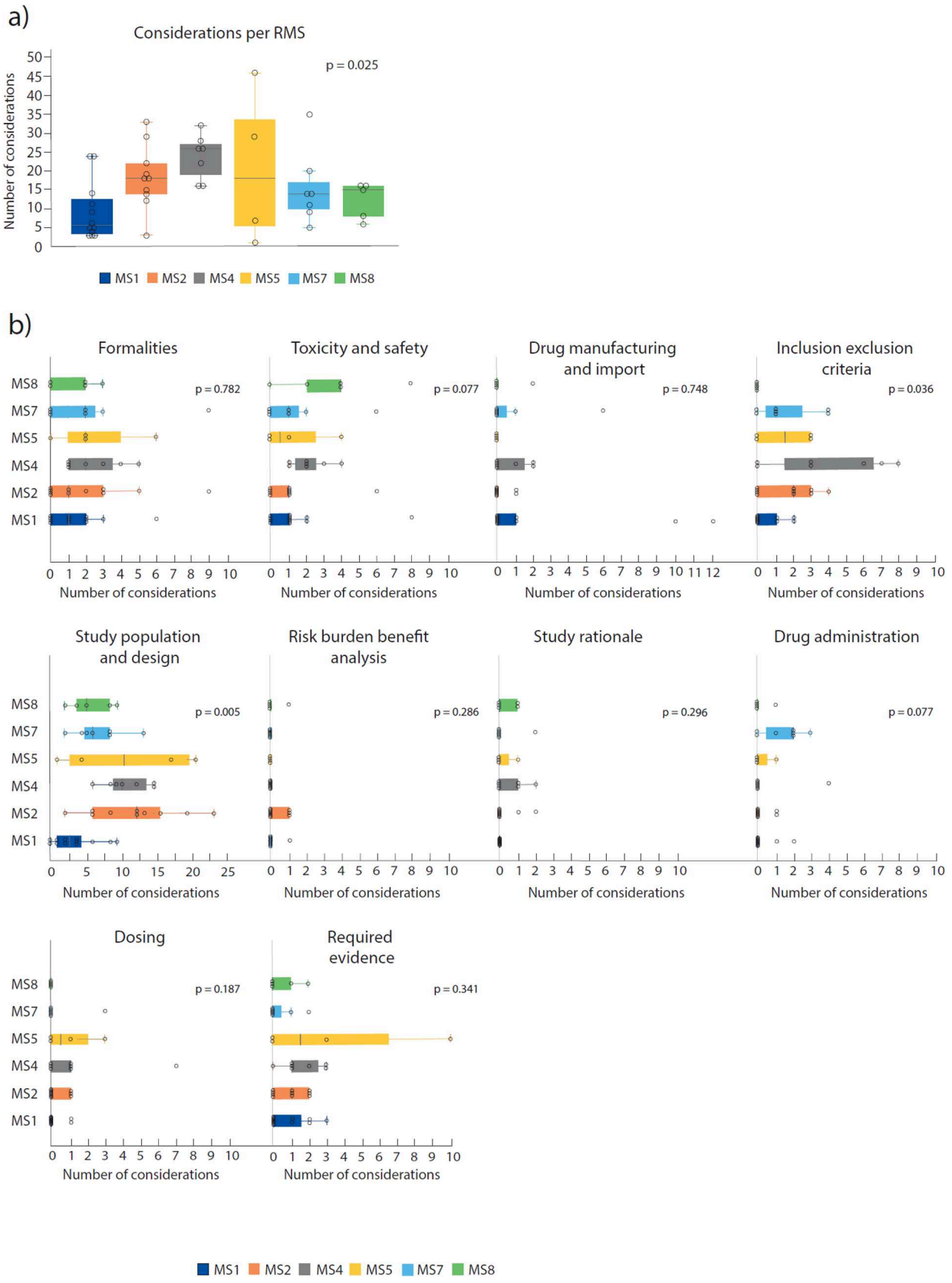
Detailed examination of considerations regarding required evidence (Fig. 4) revealed that in 20 out of 55 Phase I/II CTAs (36.4%), MSs raised concerns about the evidence supporting the CTA. Of the 37 considerations raised, 9 pertained to insufficient non-clinical data, primarily focusing on the absence of juvenile animal studies or concerns about the validity and translatability of the pre-clinical models used. Among the remaining clinical data considerations, 12 specifically addressed diseases typically occurring in childhood or adolescence. The MSs' concerns manifested in several distinct patterns: some required justification for why no PIP had been developed, while others questioned the adequacy of adult safety and efficacy data. Most commonly, it was considered too early or not favourable to conduct the trial in minors, independent of the therapeutic area and the existence of a PIP (three out of six CTAs with this consideration had a PIP, with two of these three CTAs being aligned with respective PIP key elements).

3.5 Analysis of CTAs with PIPs

Among the analysed CTAs, 28 were associated with PIPs, of which 22 (78.6%) were aligned to their respective latest PIP Opinion. Supplementary Figure 4 shows the temporal context between CTA submission and PIP agreement. During the assessment process, MSs made various references to PIPs: 10 RFIs mentioned PIPs (7 of which requested to provide the full version of the respective PIP without asking specific questions about content or implementation of the PIP), and 4 final assessment reports included PIP references. In 11 assessments, NCAs questioned trial characteristics that had already been defined in the approved PIP. Regarding outcomes, 14 trials were authorised, while 3 trials with PIPs were not authorised, with 2 of these being only partially aligned to their latest PIPs (Supplementary Table 4). In 2 cases, the conditions of authorisation substantially altered the original PIP. Therefore, most PIP studies were authorised with their elements as originally decided by the PDCO.

3.6 Analysis of Adult-Adolescent CTAs

Of 38 identified adult CTAs that included participants aged < 18 years, 12 were Phase I/II trials—9 involving only adolescents and 3 also including younger children. In 11 of these 12 CTAs, the inclusion of adolescents was either questioned, rejected, or required to be delayed (Fig. 5). During consolidation, some of these considerations were accepted while others were not incorporated, indicating divergent views.


a)
Considerations per RMS
p = 0.025
Number of considerations
MS1 MS2 MS4 MS5 MS7 MS8
b)
Formalities
p = 0.782
Toxicity and safety
p = 0.077
Drug manufacturing and import
p = 0.748
Inclusion exclusion criteria
p = 0.036
Study population and design
p = 0.005
Risk burden benefit analysis
p = 0.286
Study rationale
p = 0.296
Drug administration
p = 0.077
Dosing
p = 0.187
Required evidence
p = 0.341
Number of considerations
MS1 MS2 MS4 MS5 MS7 MS8

◂**Fig. 2** Analysis of considerations across Member States (MSs). (a) Number of considerations per Clinical Trial Application (CTA) by Reporting Member State (RMS). Box plots show the median, interquartile range and outliers for each MS. (b) Detailed breakdown of number of considerations by evaluation criteria across MSs per CTA. Box plots show the median, interquartile range and outliers for each criterion. (a, b) Each MS is consistently represented by the same number

In most cases, the inclusion of adolescents was approved, albeit sometimes required to be delayed, while 2 cases led to rejection or mandatory delay in one MSC.

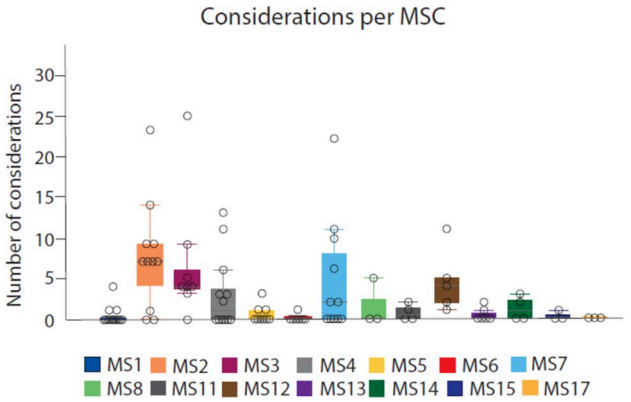


Fig. 3 Number of considerations per Clinical Trial Application (CTA) by Member State Concerned (MSC). Box plots show the median, interquartile range and outliers for each Member State (MS). Each MS is consistently represented by the same number

4 Discussion

4.1 Summary of Main Findings

This comprehensive analysis of paediatric CTAs under the new CTR reveals several important findings. The marked variation in both the number and nature of considerations raised by different MSs, particularly when acting as MSCs, suggests that despite the CTR's aim for harmonisation, national interpretations of requirements remain diverse. This inconsistency directly impacts children by creating inequitable access to clinical trials depending on their country of residence within the EU.

While the vast majority (90%) of CTAs were authorised, which indicates general support for paediatric trials by authorities, a notable disproportionality was observed for oncology trials—constituting 10% of authorised CTAs but 40% of non-authorised CTAs, despite well-documented high unmet medical need in high-risk malignancies [14, 15] and widespread off-label use in this field [4]. The predominant reasons for rejection included toxicity concerns, unfavourable risk-burden-benefit analysis, and insufficiency of required evidence.

Three key challenges emerged from our analysis. First, MSs demonstrated differing levels of required evidence, with 36% of assessments raising concerns about insufficient clinical and preclinical data without specifying toxicity or efficacy concerns. Through personal communication with MSs, it became apparent that approaches to evidence prerequisites vary considerably: some demand robust Phase II or even Phase III adult clinical data and/or juvenile preclinical toxicity studies, while others conduct case-by-case assessments. Second, significant variation exists in how MSs consider PIPs during CTA assessments. Sometimes, CTA assessment were detached from their respective PIPs and/or trial characteristics defined in the PIP questioned in the

Table 3 Significance and feasibility of considerations raised by MSs in their role as RMS across authorised phase I/II paediatric CTAs

Member state	Easy to implement *n* (%)	Easy to implement and protocol change requested *n* (%)	Difficult to implement *n* (%)	Difficult to implement and protocol change requested *n* (%)	**Total**
MS1	85 (68.5)	12 (9.7)	21 (16.9)	6 (4.8)	**124**
MS2	103 (55.7)	39 (21.1)	23 (12.4)	20 (10.8)	**185**
MS4	117 (66.9)	32 (18.3)	18 (10.3)	8 (4.6)	**175**
MS5	47 (56.6)	13 (15.7)	17 (20.5)	6 (7.2)	**83**
MS7	61 (57.5)	26 (24.5)	9 (8.5)	10 (9.4)	**106**
MS8	31 (48.4)	10 (15.6	16 (25.0)	7 (10.9)	**64**
Total	**444 (60.2)**	**132 (17.9)**	**104 (14.1)**	**57 (7.7)**	**737**

Considerations were classified into four categories: 'Easy to implement' (minor clarifications or questions easy to answer); 'Easy to implement and protocol change requested' (no substantial protocol changes required); 'Difficult to implement' (clarifications requiring more extensive responses); and 'Difficult to implement and protocol change requested' (changes substantially altering the study protocol). Only MSs that participated in more than two trials as RMS are included. Each MS is consistently represented by the same numer

CTA Clinical Trial Application, *MS* Member State, *n* number of considerations, *RMS* Reporting Member State

Table 4 Significance and feasability of considerations raised by MSs in their role as MSC across authorised Phase I/II paediatric CTAs

Member state	Easy to implement *n* (%)	Easy to implement and protocol change requested *n* (%)	Difficult to implement *n* (%)	Difficult to implement and protocol change requested *n*(%)	**Total**
MS1	4 (66.7)	0 (0.0)	2 (33.3)	0 (0.0)	**6**
MS2	49 (58.3)	18 (21.4)	8 (9.5)	9 (10.7)	**84**
MS4	19 (50)	11 (28.9)	6 (15.8)	2 (5.3)	**38**
MS5	4 (80)	1 (20.0)	0 (0.0)	0 (0.0)	**5**
MS7	22 (40.0)	11 (20.0)	10 (18.2)	12 (21.8)	**55**
MS8	2 (50.0)	1 (25.0)	1 (25.0)	0 (0.0)	**4**
Total	**100 (52.1)**	**42 (21.9)**	**27 (14.1)**	**23 (12.0)**	**192**

Classification categories are identical to those described in Table 3. Only MSs that participated in more than two trials as MSC are included

CTA Clinical Trial Application, *MS* Member State, *MSC* Member State Concerned, *n* number of considerations

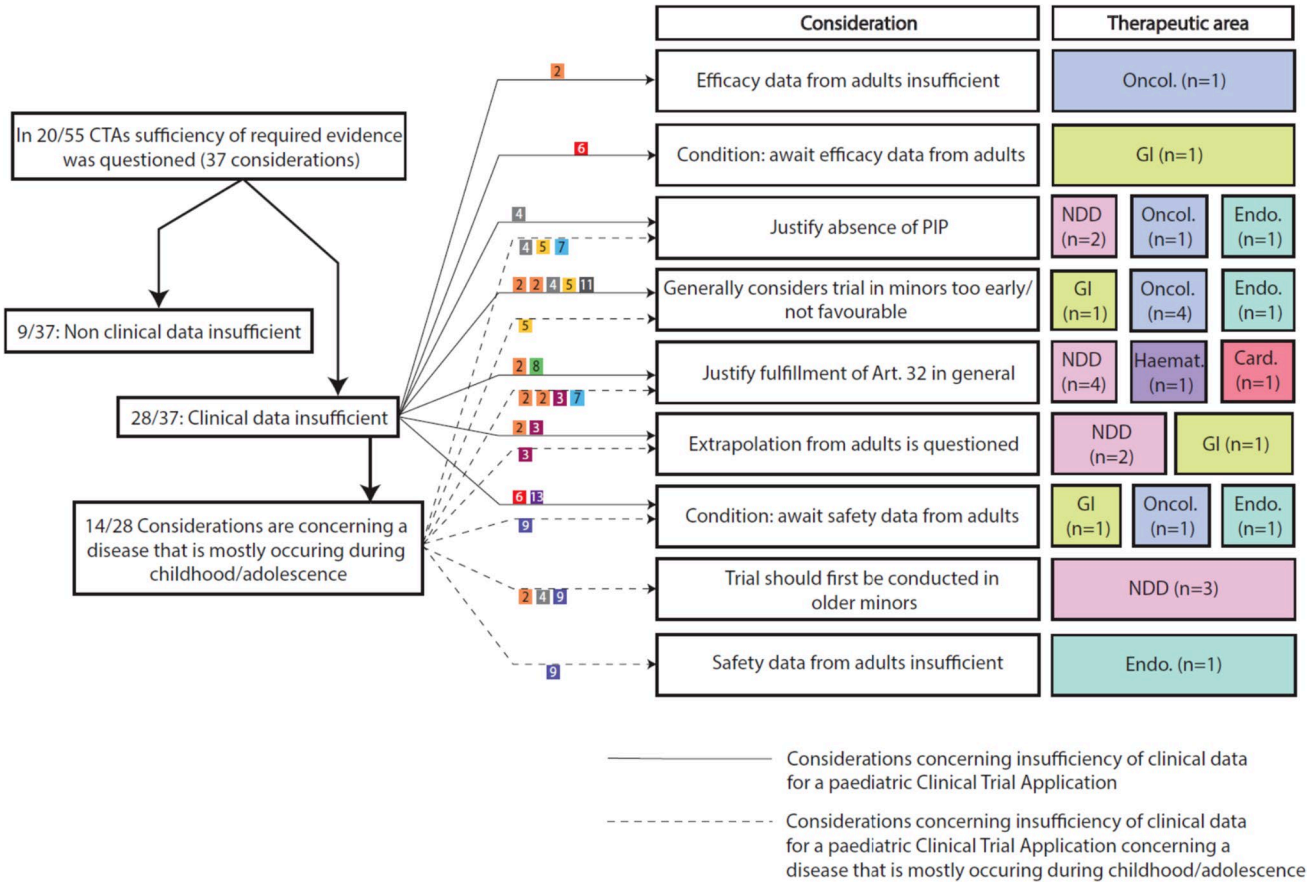


Fig. 4 Analysis of required evidence for paediatric Phase I/II CTAs. Left side shows the breakdown of evidence prerequisite considerations, from total considerations ($n = 37$) to non-clinical and clinical data insufficiencies. The right side details specific types of considerations, with numbers in coloured boxes representing MSs that raised them. Colours in the numbered boxes represent MSs and are not related to therapeutic area; colours on the right side represent therapeutic areas. Each MS is consistently represented by the same number. *Art. 32* Article 32 of the Clinical Trial Regulation, *Card.* Cardiology, *CTA* Clinical Trial Application, *Dermat.* Dermatology, *Endo.* Endocrinology, *GI* Gastrointestinal disorders, *Haemat.* Haematology, *NDD* Neurology and Developmental disorders, *Oncol.* Oncology, *PIP* Paediatric Investigation Plan

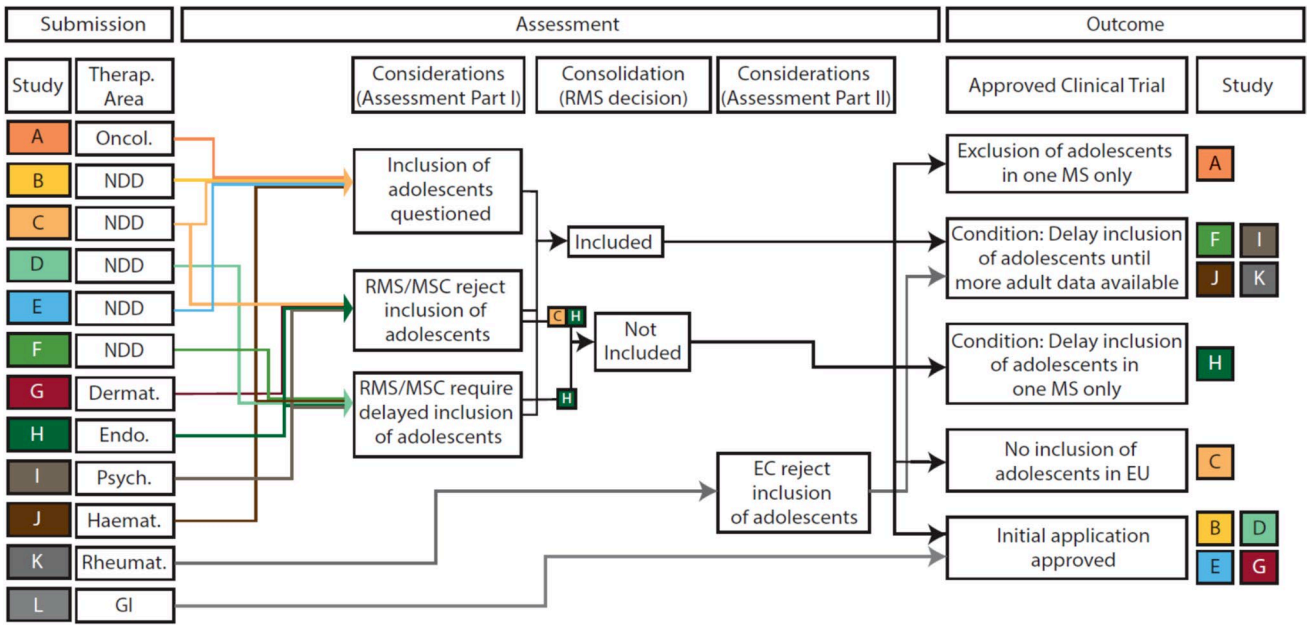


Fig. 5 Flow diagram depicting assessment and outcome of adolescent inclusion in adult Clinical Trial Applications (CTAs) ($n = 12$). Consolidation is the process of combining all raised considerations. Age of inclusion in 8 out of 12 CTAs was ≥ 12 years, except for Study D (age ≥ 8 years), studies E and G (age ≥ 6 years) and unspecified for Study C. Letters in coloured boxes refer to respective studies. *Card.* Cardiology, *CTA* Clinical Trial Application, *Dermat.* Dermatology, *Endo.* Endocrinology, *EC* ethics committee, *GI* Gastrointestinal disorders, *Haemat.* Haematology, *MS* Member State, *MSC* Member State Concerned, *NDD* Neurology and Developmental disorders, *Oncol.* Oncology, *PIP* Paediatric Investigation Plan, *Psych.* Psychiatry, *Rheumat.* Rheumatology, *RMS* Reporting Member State

CTA, while in other cases, sponsors had to justify when deviating from the respective PIPs. This inconsistency was highlighted in personal communication with NCAs: some do strictly adhere to PIP elements during CTA assessment, while others do not assess CTA differently when there is a PIP in place. Third, MSs demonstrated widespread hesitancy to include adolescents in adult Phase I/II trials, despite their physiological similarity to adults.

4.2 Comparisons with Existing Literature

Our findings align with findings from Beck et al [12], who reviewed paediatric oncology trial application assessments in Germany from 2014 to 2019 and similarly identified deficiencies regarding toxicity and safety as predominant issues, including insufficient clinical and non-clinical data. These findings suggest that the requested amount of non-clinical and clinical data was already an important issue before the CTR came into place.

The findings regarding Phase I/II adult-adolescent CTAs show that MSs, despite final approval, demonstrated hesitancy to include adolescents in these trials, potentially reflecting stringent interpretations of the requirements outlined in CTR's article 32. Given that pharmacokinetic parameters and physiology in adolescents typically closely mirror those of adults [16, 17], their inclusion in adult trials has been identified as crucial for ensuring timely access to innovative therapies [18–20]. Our findings confirm that despite this recognition and even when adolescent inclusion is favoured in PIPs, a gap remains between recommendations and widespread implementation.

The heterogeneity in PIP consideration during CTA assessment reflects ongoing debates in the scientific community about the Paediatric Regulation [21–25]. While the PIP requirement was established to advance paediatric medicine development [26] and has made a positive impact, our analysis reveals that Article 6 of the CTR, which states that PIPs should be considered during CTA assessments, is interpreted and applied inconsistently across MSs. Some MSs also acknowledged divergent interpretations of Article 32 by NCAs and ECs, highlighting the complexity of achieving harmonisation.

4.3 Clinical and Regulatory Implications

The high proportion of considerations relating to insufficient clinical and preclinical data (without specifying toxicity or efficacy concerns) points to a strong need for alignment in the interpretation of CTR Article 32. This becomes particularly relevant for conditions primarily occurring in childhood or adolescence, where the conventional approach of establishing evidence in adults first creates practical obstacles. The requirement for extensive adult clinical activity data warrants careful reconsideration, especially given for

example the questionable translatability of adult oncology data to paediatric populations [21, 27]. Conservative approaches that delay paediatric trials create another problematic cycle: off-label use following adult authorisation undermines recruitment for formal paediatric trials while reducing market exclusivity periods for sponsors. Early adolescent inclusion could accelerate trials in younger age groups and break this cycle.

As emphasised in the revised Declaration of Helsinki, children can be harmed by their systemic exclusion from medical research and clinical trials, potentially denying them early access to innovative treatments [7], especially for diseases with high unmet medical need such as high-risk malignancies [15, 28, 29]. The pronounced focus on toxicity concerns may warrant reconsideration—particularly in light of the severely limited therapeutic options available for paediatric oncology patients. Alternatively, evidence frameworks such as enhanced preclinical proof-of-concept models like ITCC-P4 or PIVOT [30, 31] might provide relevant predictive value for paediatric oncology. This area may receive further regulatory attention, as indicated by the Non-Clinical Working Party's planned reflection paper on the implementation of mode-of-action–driven oncology paediatric development plans [32].

The varying approaches to PIP integration during CTA assessment raise important questions about how MSs interpret the role of PIPs in guiding paediatric drug development. The inconsistency—where CTA assessments are sometimes detached from their respective PIPs while in other cases sponsors must justify deviations—suggests need for clearer guidance on the weight and application of PIP requirements during CTA evaluation.

For regulatory authorities, these findings identify specific areas needing guidance to support harmonisation. For sponsors, understanding this variation can inform CTA preparation and facilitate early engagement with authorities. This analysis gains particular significance given the 2024 Declaration of Helsinki revision, which recognises that excluding vulnerable populations from research may itself pose ethical concerns. As regulatory bodies develop guidance, they must balance protective measures with the imperative to advance paediatric medicine through well-designed research.

4.4 Strength and Limitations

This study represents the first systematic analysis of paediatric CTA assessments across EU Member States under the new CTR. Conducted in collaboration with the Clinical Trials Coordination Group (CTCG) and the Paediatric Committee (PDCO), the analysis benefited from access to both public and non-public data from CTIS through an EMA fellowship, enabling comprehensive evaluation of assessment practices. The focus on Phase I/II trials, which typically involve innovative treatments and complex risk-benefit assessments, provides insights into areas where harmonisation is most critically needed.

Several limitations should be acknowledged. First, the analysis period coincides with the early implementation phase of the CTR, and some observed patterns may reflect initial adjustment challenges rather than persistent systemic issues. Additionally, no comparison was possible between the transition phase and mandatory phase due to the limited number of CTAs submitted during the transition phase. Second, categorisation of assessments according to significance and feasibility involves inherent subjectivity. Third, the number of CTAs per MS is currently limited, necessitating caution in interpreting statistical results and individual MS-level findings. Fourth, the focus on Phase I/II trials may not capture assessment patterns unique to later-phase studies. Finally, structural limitations of CTIS, such as the absence of additional search categories for different age groups, made some analyses more challenging. Further analyses are warranted to evaluate whether these patterns persist as the CTR implementation matures, and structural improvements to CTIS would facilitate future monitoring efforts.

4.5 Future Directions

The implementation of the revised Declaration of Helsinki presents a promising opportunity to embrace a more enabling approach in paediatric CTA assessment, potentially closing gaps in equal access to innovative treatments across the EU for children and adolescents. An assessor's workshop held in July 2025 [10] marks a vital step toward harmonisation. Future research should include longitudinal monitoring of harmonisation progress as the CTR implementation matures, with particular attention to whether targeted guidance successfully reduces variation in evidence requirements, PIP integration and adolescent inclusion practices.

5 Conclusions

While the CTR has established a framework for coordinated assessment of paediatric clinical trials, substantial variations in interpretation persist across Member States, particularly regarding evidence prerequisites, PIP integration, and adolescent inclusion. These variations directly impact children's equitable access to clinical trials across the EU. Addressing these challenges through targeted guidance, assessor training and ongoing monitoring is essential to realising the CTR's

harmonisation goals and ensuring that all European children benefit from advances in paediatric medicine.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40290-026-00607-z.

Acknowledgements We thank Maike Maurer and Adra Ivziku for their valuable administrative support in managing project logistics and travel arrangements.

Funding Open Access funding enabled and organized by Projekt DEAL. Laura Fankhauser worked on this project during her placement at the EMA as a collaborating expert within the ACCELERATE EU-funded Aladdin Educational Programme for Paediatric Oncology, which included travel expenses (101056190). Laura Fankhauser received a Clinical Trialist Fellowship from the Dietmar Hopp Foundation (1DH2211236).

Declarations

Conflict of Interest Olaf Witt serves as advisory board member for Novartis, Ipsen, BMS Janssen and receives research grant support from Day One Biopharmaceuticals and BioMed Valley Discoveries. Cornelis van Tilburg reports serving on advisory boards for Alexion, Bayer, Novartis, and Roche, receiving travel support from Eli Lilly, lecture honoraria from Ipsen, and received research grants from BioMed Valley Discoveries and Day One Biopharmaceuticals. All activities were outside the submitted work. Laura Fankhauser, Franca Ligas, Giovanni Lesa, Anette Solli Karlsen, Marianne Lunzer, Monique Al, Sabine Scherer, Sylvie Benchetrit, Claudia Riedel, Annette Kopp-Schneider, Ruth Witt, and Dominik Karres declare no competing interests.

Availability of Data and Material The data analysed in this study were accessed through special administrator privileges in the Clinical Trial Information System (CTIS) and contain confidential regulatory information. While information about approved clinical trials are publicly available via the EMA website (https://euclinicaltrials.eu), detailed assessment data used in this analysis are not publicly accessible due to confidentiality requirements between the regulatory authorities and the sponsor of the trial.

Ethical Approval Ethics approval was not required as this study involved retrospective analysis of anonymised regulatory assessment data without access to individual patient information. The analysis was conducted within the framework of an official EMA fellowship with appropriate data access permissions.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability Not applicable.

Author Contributions Laura Fankhauser, Ruth Witt, Olaf Witt, Dominik Karres and Cornelis van Tilburg conceptualised the study. Laura Fankhauser conducted all analyses of Clinical Trial Applications in CTIS, developed and implemented the analytical methodology, created all figures and visualisations, and wrote the first draft of the manuscript. Franca Ligas, Giovanni Lesa and Dominik Karres contributed to data interpretation from the EMA perspective. Anette Solli Karlsen, Marianne Lunzer, Monique Al, Sabine Scherer, Claudia Riedel and Sylvie Benchetrit provided national regulatory expertise and contributed to data interpretation from a national competent authority perspective. Annette Kopp-Schneider performed the statistical analyses. Cornelis van Tilburg and Dominik Karres supervised the study and critically reviewed and edited all versions of the manuscript. All authors reviewed and approved the final version of the manuscript and had full access to all the data in the study. Laura Fankhauser and Cornelis van Tilburg verified the underlying data.

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Authors and Affiliations

Laura Fankhauser[1,2,3,4] · Franca Ligas[5] · Giovanni Lesa[5] · Anette Solli Karlsen[6] · Marianne Lunzer[7] · Monique Al[8] · Sabine Scherer[9] · Sylvie Benchetrit[10] · Claudia Riedel[9] · Annette Kopp-Schneider[11] · Ruth Witt[1,2,3,4] · Olaf Witt[1,2,3,4] · Dominik Karres[5] · Cornelis M. van Tilburg[1,2,3,4]

✉ Laura Fankhauser
l.fankhauser@kitz-heidelberg.de

1 Hopp Children's Cancer Center Heidelberg (KiTZ), Im Neuenheimer Feld 430, 69120 Heidelberg, Germany

2 Heidelberg Faculty of Medicine, Department of Paediatric Oncology, Haematology, Immunology, and Pulmonology, Heidelberg University Hospital, Heidelberg University, Heidelberg, Germany

3 Clinical Cooperation Unit Paediatric Oncology, German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Heidelberg, Germany

4 National Center for Tumour Diseases (NCT), NCT Heidelberg, a partnership between DKFZ and Heidelberg University Hospital, Heidelberg, Germany

5 Paediatric Medicines Office, Scientific Evidence Generation Department, Human Medicines Division, European Medicines Agency (EMA), Amsterdam, The Netherlands

[6] Norwegian Medicinal product agency (NOMA), Oslo, Norway

[7] Austrian Federal Office for Safety in Health Care (BASG), Austrian Agency for Health and Food Safety (AGES), Vienna, Austria

[8] Central Committee on Research Involving Human Subjects, The Hague, The Netherlands

[9] Federal Institute for Drugs And Medical Devices, Bonn, Germany

[10] French National Agency for Medicines and Health Products Safety, Saint-Denis Cedex, France

[11] Division of Biostatistics, German Cancer Research Center, Heidelberg, Germany