European network of paediatric research at the European Medicines Agency

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# Report from the 2024 Annual Workshop of the European Network of Paediatric Research at the EMA (Enpr-EMA)

Date: Tuesday, 2 October 2024

Location: EMA, Amsterdam and online

The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) held its 16th annual workshop to discuss regulatory developments and collaboration in paediatric medicine development.

The event brought together more than 110 representatives from research networks, patient and parent organisations, healthcare professionals, academia, industry and regulators.

EMA's Chief Medical Officer, Steffen Thirstrup, opened the workshop by introducing key topics, including Enpr-EMA's latest initiatives and recent regulatory developments.

Chairpersons: Pirkko Lepola, Gunter Egger

## *Session I – Regulatory update, Clinical Trial Regulation (CTR) and Clinical Trial Information System (CTIS)*

### *Update on the reform of the EU pharmaceutical legislation:*

The European Commission has revised the rules governing the authorisation of medicinal products, including those for paediatric use and rare diseases. This revision has been incorporated into a proposal for the new pharmaceutical legislation (NPL) with a Regulation and a new Directive. Gunter Egger highlighted the objectives of these changes, which are to improve access to medicines, avoid shortages, increase affordability, create a competitive regulatory framework and ensure environmental sustainability.

The proposal for the NPL maintains the structure of obligations and rewards of the current Paediatric Regulation. It focuses on facilitating the Paediatric Investigation Plan (PIP) process, reducing delays and better addressing unmet medical needs. Proposed updates include specifications such as the possibility of a step-wise PIP approach, repurposing of medicines, the requirement to submit a PIP application for conditions of unmet medical need based on the product's mechanism of action in case

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the adult condition applied for does not exist in the paediatric population, and enhancing paediatric expertise across EMA committees.

For Enpr-EMA, the proposal also anticipates its expanded role, acting as a multistakeholder forum to facilitate discussions on unmet medical needs and the prioritisation of paediatric research and development.

The European Parliament and the European Council are currently reviewing the proposal adopted by the European Commission in April 2023. The aim is to reach a consensus that would allow for the legislation's adoption, followed by an estimated 18-month transitional period before implementation.

Presentation: *Brief update: Reform of the EU pharmaceutical legislation (G. Egger)*

## *The COMBINE project – interface between medicines and medicinal products – paediatric clinical trials perspective*

Conducting clinical trials involving combination products, such as those integrating medicinal products with in vitro diagnostics or medical devices, poses unique challenges due to the regulatory interdependencies between the Clinical Trial Regulation (CTR) and either the In Vitro Diagnostics Regulation (IVDR) or the Medical Device Regulation (MDR). These legal and regulatory complexities have contributed to delays in combination studies within the European Union (EU), making this a priority area for action among stakeholders.

The COMBINE project was established to analyse the challenges in the regulatory processes aiming to streamline and clarify the interface between clinical trials of investigational medicines, performance studies of in vitro diagnostics, and clinical investigations of medical devices. Its goal is to harmonise these regulatory pathways reducing the burden on sponsors and facilitating smoother processes.

Marianne Lunzer introduced the COMBINE project's objectives, structure and current progress.

A step-wise approach has been adopted to tackle identified issues such as heterogeneity in member state assessments, and develop solutions. This phased strategy will be followed by an implementation and a training phase, with activities scheduled from 2024 through 2025. Initial activities will focus on enhancing the coordination across member states and relevant legislations, clarifying safety reporting requirements, and addressing the interface between medical devices and clinical trials of medicinal products.

While the project is not specifically focused on paediatric populations, it is expected to benefit all demographics, including children. However, the audience strongly emphasised the need for dedicated paediatric expertise within the project. They advocated for age-specific actions to adequately address children's unique needs. The audience was assured that this valuable feedback would be shared with the project group for further consideration, with the aim of enhancing the project's focus on paediatrics.

Presentation: *The COMBINE project: Interface between medicines and medicinal products (M. Lunzer)*

## *Update on CTR implementation, including new CTIS transparency rules*

The Clinical Trials Regulation (CTR), effective since January 2022, introduced the Clinical Trial Information System (CTIS), a unified EU portal for clinical trial authorisations. Laura Pioppo and Francesca Scotti explained that CTIS simplifies Clinical Trial Application (CTA) submissions, aiming to

increase harmonisation and transparency in clinical trials across the EU. As a single-entry point for trial assessment, authorisation, monitoring, and publication, CTIS also offers a publicly accessible, searchable website to improve transparency and foster patient engagement.

The CTR mandates transparency in EU clinical trials to build public trust, prevent duplication, and keep stakeholders informed about methodologies and outcomes. To support this, publication rules were introduced along with CTIS in January 2022 and subsequently refined to allow for earlier access to clinical trial documents and data. The revised transparency rules took effect with the public portal's launch in June 2024.

During the meeting, an overview of CTIS's searchable features and new functionalities was presented. Key accessible details include trial design, objectives, endpoints, eligibility criteria, contact information, and access to study documents such as the protocol, protocol synopsis, summary of product characteristics (SmPC), recruitment materials, informed consent forms, and upon trial completion, a summary of results, a lay summary, and the clinical study report (CSR).

In addition, along with the CTR, the Accelerating Clinical Trials in the EU (ACT EU) initiative was launched in January 2022, by EMA in collaboration with the Member States, the Heads of Medicines Agencies (HMA) and the European Commission to facilitate clinical trials in the EU. An overview of ACT EU highlighted its structure, achievements, and key actions, which are annually prioritised and adjusted based on stakeholder input. ACT EU's focus areas include implementation of the CTR, support for non-commercial sponsors, establishment of a multistakeholder platform, modernisation of Good Clinical Practice (GCP), data analytics, consolidated clinical trial advice, methodologies, safety monitoring, public health emergency preparedness, and the development of a training curriculum.

Presentation: *Update on CTR implementation, including new CTIS transparency rules (F. Scotti, L. Pioppo)*

## *Networks' experience with CTR & CTIS*

Anne Elsinghorst shared valuable insights on the implementation of the CTR and the CTIS from a network perspective, based on her experience as a sponsor of both single and multi-centre clinical trials.

Implementing the CTR has required not only technical updates but also adjustments to operational models and workflows. The benefits of CTIS were emphasised, notably improved transparency in assessment and approval timelines, version control and multiple access to the latest approved study documents for each country.

Challenges in the system's implementation, highlighted through various case studies, sparked audience discussion. Key issues included heterogeneity in national submission requirements, managing complex trials that involve multiple protocols and investigational medicinal products (IMPs), and difficulties with simultaneous submission of non-substantial modifications during ongoing assessments. Technical concerns were also noted, such as delayed helpdesk response times and the lack of email notifications (alerts) within the system.

Discussions confirmed that the ACT EU program and EMA have initiatives underway to address these hurdles. Planned improvements include efforts by medical ethics groups to harmonise country requirements for part II documents, relaxation of rules for non-substantial modification submissions, a fast-tracked helpdesk for non-commercial sponsors, and pre-CTA advice, particularly for complex trials. Additional improvements to system usability and functionality are ongoing.

In conclusion, the session underscored the importance of collaborative efforts and common approaches among all stakeholders to optimise the new platform and the CTR's operational framework.

Presentation: *2.5 years of CTR and CTIS: Experiences from Academic Sponsor Institutions in the ITCC network (A. Elsinghorst)*

# Session II – PDCO update, PIPs, and ethical aspects related to paediatric trials.

## *Paediatric investigation plans based on mechanism of action – regulator and academia reflections*

Gilles Vassal and Sabine Scherer presented a new key requirement of the NPL proposal based on the mechanism of action of a product. The requirement to submit a PIP would be triggered if the adult condition for which a product is developed does not exist in the paediatric population, but a different condition within the same therapeutic area in children could be addressed based on the same mechanism of action.

Currently, the development of PIPs is primarily guided by adult indications, which can result in PIPs that inadequately address the unmet medical needs of the paediatric population or lead to the granting of waivers on case the adult condition does not exist in children. The new legislative proposal seeks to shift this focus, allowing for paediatric development centred on unmet needs, even when these differ from adult indications, by utilising a mechanism of action-based approach.

Under the existing Paediatric Regulation, products for conditions not present in children may be waived from paediatric development requirements, resulting in a predominance of adult-driven research, particularly in oncology. The ACCELERATE innovation for children and adolescents with cancer initiative has been addressing this issue by establishing aggregated databases for paediatric biological tumour drug targets, creating joint academic-pharmaceutical industry platforms to facilitate the preclinical analysis of new drugs, and organising Paediatric Strategy Forums to identify unmet needs creating a collaborative approach for facilitating prioritisation discussions among stakeholders.

The new legislative proposal maintains the current waiver grounds. However, it restricts the waiver ground of the condition only occurring in adults.  If a product targets a mechanism of action that, based on existing scientific data, is responsible for a different condition in the same therapeutic area in children, a Paediatric Investigation Plan (PIP) would be required for this condition.

To effectively implement this article, clarifications are needed regarding the definition of "same therapeutic area", the scope of the provision and whether if it is strictly limited to waivers based on disease or condition not occurring in children. Additional actions identified include: identifying therapeutic areas outside of oncology that could benefit from this approach, revising the class waiver list, and evaluating the challenges of implementing this strategy, particularly regarding the use of extrapolation and the potential need for standalone paediatric programs, which can be particularly challenging for very rare paediatric diseases. The possibility of adopting a step-wise PIP approach was also discussed as a means to advance this concept.

It was concluded that a significant legislative change is underway, to further develop a science-driven and patient-centric regulatory framework that better serves the needs of children.

Presentation: *Mechanism of action PIPs: Relevant and expected in oncology (G. Vassal)*

*Non-oncological MoA based PIP – Initial Deliberations from the PDCO working group discussions (S. Scherer)*

### *Update from the Paediatric Committee (PDCO) on recent developments*

Sylvie Benchetrit, Vice-Chair of the Paediatric Committee (PDCO), provided an update on the PDCO's ongoing projects and activities.

The Committee has recently focused on the step-wise PIP (sPIP) project. This initiative enables sponsors to submit a PIP application in a phased approach when critical evidence to fully define the plan's key components are not yet available. In such cases, applicants submit a preliminary development program, which based on the evidence available including essential information, such as the condition, study outlines according to the data available, and projected completion date, and expand it with subsequent modifications at agreed milestones as more information becomes available.

Launched in February 2023 with a pilot phase, the sPIP initiative has been extended into 2024 with new guidance and more sponsors applying for this process. It is a voluntary procedure to which applicants as well as PDCO have to agree and applies to defined cases, such as defined cases of new paediatric conditions with unmet therapeutic needs and innovative approaches without precedents and depends on the early submission of the application, i.e. it is an exceptional approach. By this date, PDCO had received 11 sPIPs and providing 5 opinions on these. The aim of the sPIP concept is to adapt the PIP development to the product development cycle in specifically challenging development areas. which also supports early dialogue during the medicine development. Therapeutic areas where this approach has proven particularly relevant include rare and ultra rare conditions such as genetic disorders, metabolic diseases, neurology, inflammatory cardiology, and respiratory conditions and paediatric oncology. This concept has been formally integrated into the NPL proposal.

Additionally, the importance of collaboration between the PDCO and various entities was highlighted, including expert groups, the Clinical Trials Coordination Group (CTCG), the Committee for Medicinal Products for Human Use (CHMP), and the Scientific Advice Working Party (SAWP). These partnerships promote alignment and consistency in the evaluation of regulatory applications as well as the development of guidelines. Examples of such collaborations include recommendations for the inclusion of adolescents in adult clinical trials, therapeutic guidelines, safety monitoring, and the collaboration on the development of the International Council for Harmonisation (ICH) guideline E11A concerning paediatric extrapolation.

Presentation: *PDCO update for Enpr-EMA (S. Benchetrit)*

### *Emerging ethics assessment challenges in paediatric clinical trials and revision of Declaration of Helsinki - what will change?*

Due to technical challenges, Maria Alexandra Ribeiro's talk could not take place during the meeting. However, the documentation is available in the meeting materials for further reference.

Presentation: *Emerging ethics assessment challenges in paediatric clinical trials and revision of declaration of Helsinki - What will change? (M. A. Ribeiro)*

## Session III – Enpr-EMA activities 2023/24 and new research network infrastructure.

### *Annual report from the coordinating group:*

Pirkko Lepola, Chair of the Enpr-EMA Coordinating Group (CG), presented a detailed report on Enpr-EMA's activities and accomplishments over the past year. Key highlights included information sharing

initiatives, stakeholder enquiries for network collaboration and feasibility estimations, network and working group meetings, and publications. Furthermore, it was noted that a renewal of the Coordinating Group (CG) is scheduled for the next term, along with the election of a new Chair at the next Enpr-EMA Annual Meeting in 2025.

Presentation: *Enpr-EMA Annual Report 2023-2024 (P. Lepola)*

## *Update from selected Enpr-EMA working groups:*

## Working group on paediatric clinical trial site quality criteria

Pernille Skovby and Ricardo Fernandes presented the progress of the Enpr-EMA working group on quality criteria for paediatric clinical trial sites.

Recognising the unique challenges of conducting paediatric clinical trials, Enpr-EMA and connect4children (c4c) hosted a 2022 workshop focused on quality requirements for paediatric clinical trial sites. Building on insights from this event, the working group developed a shared understanding of "quality" for these sites and mapped existing standards, and produced a report addressing key questions, including the definition and quality criteria for paediatric sites.

A core definition of paediatric trial site has been established as a location for evaluating therapies in participants under 18 years of age. Quality requirements can be used as a specified standards or criteria covering areas like staff expertise, infrastructure, quality management, and patient engagement. The group's recommendations provide a baseline standard and an aspirational development pathway for excellence. They are meant to reflect the quality of paediatric sites, facilitating site selection while supporting the development of paediatric research infrastructure without adding regulatory burdens.

Key examples highlighted the need for paediatric-trained teams, child and family friendly environments, and age-appropriate facilities and equipment. While ICH Good Clinical Practice (GCP) and other regulatory requirements set general standards, the group concluded that additional criteria are essential to address the complexities of paediatric trials.

The final report, following review by Enpr-EMA members and a one-month public consultation, will be published on the Enpr-EMA website, accompanied by the publication of a scientific article.

Presentation: *Quality criteria for paediatric clinical trial sites – an Enpr-EMA initiative (R. Fernandes, P. Skovby)*

## Working group on cross-border access to paediatric clinical trials:

Begonya Nafria presented the progress of the working group on cross-border access to paediatric clinical trials.

In Europe, the diversity of 24 official languages and cultural backgrounds poses challenges for patients to be involved in clinical trials. Eligibility criteria based on language or country of residence can lead to unintentional exclusion of patients, raising ethical concerns.

This working group aims to develop guidance for more inclusive paediatric cross-border clinical trials in Europe by addressing language, cultural, and residency barriers.

Recommendations will be informed by studying various data:

- An analysis of trials on clinicaltrials.gov assessing language and residency requirements, specific needs for technologies as eligibility criteria or as part of the study criteria.
- Survey data on discrimination cases from clinical trial sites across Europe.
- Patient feedback on trial participation experiences and digital preferences.

Results so far highlighted language barriers as a significant reason for patient exclusion from trials.

Next steps include analysing the rest of the collected data, surveying medicine developers on managing language-related issues, and conducting interviews with researchers and parents willing to share their experiences.

The final guidance with potential solutions will be made available on the Enpr-EMA website, following a public consultation period to refine and enhance the document.

Presentation: *Language discrimination and cross border access to paediatric clinical trials - working group (B. Nafria)*

### *New research infrastructure: Conect4children (c4c) stichting*

Mark Turner presented the newly established non-profit paediatric clinical research infrastructure, conect4children Stichting (c4c-S). Evolving from the initial public-private partnership funded by the Innovative Health Initiative (IHI), c4c aims to create a sustainable paediatric research infrastructure addressing the challenges encountered in developing paediatric medicines.

Built on proof-of viability studies, c4c-S's business model emphasises a collaborative culture, consistent communication and quality management across stakeholders. The organisation operates on a request-driven model, allowing stakeholders from academia and industry to present their challenges, which c4c triages into its services. These services include expert advice related to the design and execution of clinical studies, feasibility assessments and preparedness activities, patient and public involvement, and trial support. c4c-S's benefits include shorter timelines, access to sites and experts, a single point of contact, and a commitment to quality and adaptability.

In addition to its research and development efforts, c4c-S fosters education, training, and multi-stakeholder collaboration.

As c4c-S begins operating independently, it will build on the success of its initially IHI-funded model, while continuously adapting its services to meet the evolving needs of paediatric clinical research.

Presentation: *Conect4children (c4c) stichting - From IHI initiative to sustainable paediatric research infrastructure (M. Turner)*

## Session IV: Health Technology Assessment, Real World Data

### *How can academia build capacity to optimise RWD collection in order to support health technology assessment in paediatrics*

Kelly Plueschke and Denise Umuhire gave a presentation on how Real World Data (RWD) collection can be optimised to support health technology assessment in paediatrics.

HTA plays a critical role in evaluating the clinical and economic value of paediatric medicines, complementing regulatory decision-making to ensure access to effective therapies. Real-world evidence (RWE) is increasingly recognised as a valuable tool for addressing the unique challenges of

paediatric drug development, such as limited clinical data and ethical constraints on traditional trials. By leveraging prior knowledge and innovative approaches like extrapolation, HTA and regulatory bodies can collaboratively enhance evidence generation and optimise decision-making across the life cycle of paediatric medicines.

As Europe prepares for the new Health Technology Assessment (HTA) Regulation (Regulation (EU) 2021/2282) is coming into effect at the beginning of 2025, there is a growing focus on using real-world evidence (RWE) and real-world data (RWD) to support HTA assessments. Enhancing capacity for effective RWD collection is critical.

The new HTA Regulation will centralise assessments, enabling coordinated evaluations across EU Member States and stakeholders. It introduces three key changes:

- joint clinical assessment,
- joint scientific consultation, and
- the identification of emerging health technologies.

The joint clinical assessment will be mandatory at the EU level, with the requirement of including this assessment within marketing authorisation applications.

Joint scientific consultation will be optional. It aims to enhance the package submitted for marketing authorisation applications by incorporating both HTA and regulatory requirements. This collaborative approach will allow for parallel assessments, optimising evidence generation and accelerating patient access to new treatments.

Real-world data can support both HTA and regulatory decision making on topics like disease epidemiology, clinical management, and drug utilisation.

The EMA shared case studies from the DARWIN EU, illustrating the effective use of RWE in paediatric settings, though current data source quality remains a challenge. Thus, continued efforts are necessary to enhance data collection. To enhance data quality and relevance, the EMA launched the Big Data initiative, including a Data Quality Framework to standardise dataset evaluations. The framework assesses five main dimensions of data quality: reliability, extensiveness, coherence, timeliness, and relevance, improving data consistency for informed decision-making.

The speakers also highlighted tools for evaluating data relevance, such as the Registry Evaluation and Quality Standards Tool (REQueST) for registry assessment; the EMA guideline on registry-based studies; and the Structured Process to Identify Fit-For-Purpose Data (SPIFD) for identifying data fit for decision making.

Additionally, the EMA catalogues of real-world data sources and studies offer transparency by allowing users to search disease-specific data sets.

In conclusion, while HTA and regulators serve different roles and mandates, they share a commitment to high-quality data for decision-making. Real-world data and evidence are invaluable in this context, and despite the challenges they present, ongoing efforts to provide guidance, such as the Data Quality Framework and various assessment tools, are crucial. Early dialogue with stakeholders is essential for understanding needs, expectations, and potential challenges in the regulatory landscape.

Presentation: *How can academia build capacity to optimise RWD collection in order to support health technology assessment in paediatrics (D. Umuhire, K. Pleuschke)*

# Closing remarks

Participants were informed about upcoming events.

The chairs thanked all participants for their contributions, emphasising the importance of continued collaboration to advance paediatric research.

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**Speakers:**

- Benchetrit, Sylvie. Vice chair of Paediatric Committee (PDCO), French National Agency for the Safety of Medicines and Health Products (ANSM)
- Egger, Gunter. Co-chair of Enrpr-EMA, European Medicines Agency
- Elsinghorst, Anne. Prenses Maxima Centrum, Utrech, Netherlands, Innovative Therapies for Children with Cancer (ITCC)
- Fernandes, Ricardo. conect4children National HUB lead and STAND4kids (Portuguese paediatric research network)
- Lepola, Pirkko. Chair of Enpr-EMA, FINPEDMED (Finnish Investigators Network for Pediatric Medicines)
- Lunzer, Marianne. Chair of Clinical Trials Facilitation Group (CTCG) (BASG - Austrian Federal Office for Safety in Health Care, AGES - Austrian Agency for Health and Food Safety)
- Nafria, Begonya. eYPAGnet (European Young Persons Advisory Groups Network)
- Pioppo, Laura. European Medicines Agency
- Plueschke, Kelly. European Medicines Agency
- Ribeiro, Maria Alexandra. European Network of Research Ethics Committees (EUREC)
- Scherer, Sabine. Paediatric Committee (PDCO), Federal Institute for Drugs and Medical Devices, Germany (BfArM)
- Scotti, Francesca. European Medicines Agency
- Skovby, Pernille. conect4children National HUB, Denmark
- Thirstrup, Steffen. Chief Medical Officer, European Medicines Agency
- Turner, Mark. conect4children co-coordinator, University of Liverpool, United Kingdom
- Umuhire, Denise. European Medicines Agency
- Vassal, Gilles. ITCC (Innovative Therapies for Children with Cancer)