Report from the 2025 Annual Meeting of the European Network of Paediatric Research at the EMA (EnprEMA)

Date: Thursday, 20 November 2025

Location: EMA, Amsterdam and online

The 17th Annual Meeting of the European Network of Paediatric Research at the EMA (EnprEMA), held in Amsterdam and online on 20 November 2025, brought together over 180 stakeholders from research, healthcare, industry, patient organizations, and regulatory bodies. Participants received updates and engaged in discussions on regulatory developments, innovations in paediatric clinical trials, ethical principles, and collaborative initiatives. The meeting highlighted ongoing work in areas such as the European Health Data Space, artificial intelligence, trial methodologies, and patient and family involvement, reaffirming a shared commitment to harmonised, patient-centred paediatric research across Europe. Chairpersons: Pirkko Lepola, Gunter Egger

Session I – Accelerating data use

European Health Data Space (EHDS)

Daniel Morales presented an overview of the European Health Data Space (EHDS), which was established by EU Regulation in March 2025. It creates a harmonised framework for the use and sharing of electronic health data across EU Member States. The EHDS enables patients to access and control their electronic health records, supports secure cross-border data sharing and supports secondary use for research, innovation, and policy.

Implementation is phased, with full application of all requirements expected by March 2031.

Key actors include data users, data holders, and Health Data Access Bodies, which will issue data permits and provide secure processing environments. Individuals will retain the right to opt out of secondary data use.

Strict safeguards for privacy and data protection were highlighted.

The presentation further provided updates on related initiatives supporting the EHDS vision, including DARWIN EU®, the HMA-EMA RWD Catalogues, and the HealthData@EU pilot. which enables generation of high-quality evidence, enhance transparency, reproducibility, and findability of RWD based research.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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The discussion emphasised the need for organisations to prepare for the new framework, with suggestions to develop guidance for investigators and ensure paediatric-specific considerations are incorporated into future EHDS data models and processes.

Presentation: https://www.ema.europa.eu/en/documents/presentation/presentation-european-health-data-space-d-morales_en.pdf

EMA Reflection Paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

Gabriel Westman presented the European Medicines Agency's (EMA) reflection paper on the use of artificial intelligence (AI) in the medicinal product lifecycle, outlining technical foundations, regulatory principles, key methodological challenges, and practical applications of AI.

The paper emphasises that applicants and marketing authorisation holders are responsible for ensuring that AI models are suitable for their intended regulatory context, with a focus on transparency, methodological robustness, and alignment with EU legal and ethical requirements. It advocates a risk-based approach, considering the AI model's architecture and context.

Furthermore, specific methodological risks were discussed - such as overfitting, data leakage, and insufficient generalisability - along with the importance of interpretability and explainability.

The presentation also illustrated current AI applications in regulatory practice at the Swedish Medical Products Agency, including pharmacovigilance triage, document harmonisation, and generative AI tools to support regulatory analysis.

Artificial Intelligence (AI) in paediatric research. Data protection and ethics and use of data from minors for further research.

Julian Isla discussed how AI could support paediatric clinical research by enhancing system efficiency and strengthening patient engagement. The presentation noted a decline in clinical trial activity in Europe, partly due to regulatory complexity and differing expectations between Europe and the U.S.

The intervention further highlighted uneven integration of patient perspectives across the clinical research and regulatory landscape. While the European Medicines Agency has established structured mechanisms for patient involvement, similar approaches are applied less consistently across health technology assessment bodies, ethics committees, national regulators, and other stakeholders. This observation underscored the importance of greater alignment.

The presentation also examined the potential role of AI in advancing paediatric and rare disease research. A range of applications was described, including digital twins for in-silico control arms, generative AI tools for transforming unstructured clinical data into analysable evidence, AI-supported protocol design, automated patient-matching systems, and tools intended to reduce administrative burden. The discussion emphasised the need for robust governance, transparency, and early integration of paediatric needs in clinical development and decision-making.

Presentation: https://www.ema.europa.eu/en/documents/presentation/presentation-restoring-agility-ai-future-paediatric-research-europe-j-isla_en.pdf

Session II – Enhancing trial design and conduct

Translational research from lab to patients. Latest innovations by EPTRI (European Paediatric Translational Research Infrastructure)

Donato Bonifazi presented the European Paediatric Transnational Research Infrastructure (EPTRI), a nonprofit network of 26 institutions across 14 countries supporting paediatric research and the development of medicines and medical devices for children. EPTRI provides an integrated pathway from preclinical research to clinical data, supported by partnerships with European research infrastructures.

The presentation highlighted EPTRI's policy engagement, and efforts to secure dedicated funding for child-focused research.

Case studies showcased work on medulloblastoma, PBPK modelling, wearable biosensors, and innovative clinical trial designs using Bayesian methods, extrapolation and real-world data approaches.

Ongoing initiatives include the AMIGO project proposal for the IHI call 2026, which aims to create an EU-wide federated AI platform linking paediatric clinical data from paediatric hospitals to accelerate precision medicine, reduce time-to-label for paediatric indications, and enable new opportunities for drug repurposing.

Presentation: https://www.ema.europa.eu/en/documents/presentation/presentation-translation-research-lab-patients-latest-innovations-eptri-d-bonifazi_en.pdf

Innovative trial designs in practice

Marius Thomas, Dieter Haering, and Gina Calarco Smith presented case studies on innovative paediatric clinical trial designs, focusing on Bayesian and adaptive methodologies.

The first case study focused on the NEOS trial in paediatric multiple sclerosis, a two-year, double-blind, triple-dummy phase III study employing a non-inferiority design with an active comparator. The trial applies Bayesian meta-analytic predictive methods to incorporate prior data from adult studies, thereby reducing the required sample size and avoiding the need for placebo or low-efficacy control arms.

The second case study focused on the EXPAND trial in paediatric epilepsy, which uses a combined phase II/III adaptive design incorporating multiple randomisation points and an interim analysis for dose optimisation. A randomised withdrawal phase enables participants to act as their own controls, thereby reducing placebo exposure. The design is supported by home-based EEG monitoring and comprehensive patient and family education, facilitating adherence and improving data quality. This approach aims to enhance trial efficiency while maintaining acceptability for children and caregivers.

The presenters also highlighted that patients and families prioritise minimising risk, timely access to therapies, and limiting procedural burden, while sponsors and regulators must balance these needs with statistical rigor, particularly in rare diseases where feasibility constraints and small sample sizes present unique challenges. Participants emphasised the value of strengthening the involvement of patient advocates within trial management structures and highlighted the importance of appropriate evidence integration, transparent justification, and early dialogue with regulators when proposing innovative trial methodologies.

Presentation:

https://www.ema.europa.eu/en/documents/presentation/presentation-case-study-novel-pediatric-trial-design-study-evaluate-efficacy-safety-tolerability-brivaracetam-g-calarco-smith_en.pdf

https://www.ema.europa.eu/en/documents/presentation/presentation-case-study-leveraging-external-data-efficient-pediatric-study-design-multiple-sclerosis-d-hearing-m-thomas_en.pdf

Session III – EnprEMA activities 2024/25 and new initiatives

Annual Report from the coordinating group: EnprEMA activities, achievements and challenges

Pirkko Lepola and Isabel Sanchez presented an overview of EnprEMA's achievements and key activities from the past year. The report highlighted the renewal of the Coordinating Group and the appointment of a new EnprEMA Chair. It also outlined the network's broader efforts, including information-sharing initiatives, responses to stakeholder requests for collaboration and feasibility assessments, as well as the organisation of network and working group meetings and the preparation of publications.

Presentation: https://www.ema.europa.eu/en/documents/presentation/presentation-enpr-ema-annual-report-2024-2025-p-lepola-i-sanchez_en.pdf

Update from selected EnprEMA working groups

Working group on paediatric research nurses

The working group on paediatric research nurses has undertaken an analysis of the role of research nurses across the European Union, with a focus on career pathways, professional development opportunities, employment conditions, and the structural factors contributing to persistent vacancies. This initiative aims to advance and strengthen the role of paediatric research nurses across the European Union.

Pamela Dicks presented the results of two surveys that were distributed to research nurses and research nurse managers. The analysis revealed consistent issues across countries, including contract instability, insufficient salary levels, challenges in retaining experienced staff, limited formal recognition of the profession, unclear role definitions, and restricted opportunities for career progression.

The findings also emphasise the need for a dedicated European research nurse network to facilitate the exchange of best practices, advocate for improved working conditions, and support the development of standardised job descriptions aimed at elevating the professional standing of paediatric research nurses.

Presentation: https://www.ema.europa.eu/en/documents/presentation/presentation-enpr-ema-paediatric-research-nurse-working-group-p-dicks_en.pdf

Working group on paediatric clinical trial site quality criteria

Ricardo Fernandes presented the progress of the EnprEMA working group on quality criteria for paediatric clinical trial sites.

In 2022, EnprEMA and connect4children (c4c) held a workshop to define quality requirements for paediatric clinical trial sites. Based on its outcomes, the working group established a shared definition of "quality of a paediatric site" reviewed existing standards, and produced a report outlining key criteria for paediatric sites.

The report underwent several revisions including a public consultation. The comments received ranged from minor editorial adjustments to significant conceptual recommendations. Following incorporation of

the feedback and alignment with existing guidance, such as ICH E6 (R3), the group finalised the document to prepare it for publication and dissemination. In addition, a guidance document will be published on the EnprEMA website.

Presentation: https://www.ema.europa.eu/en/documents/presentation/presentation-quality-criteria-paediatric-clinical-trial-sites-enpr-ema-initiative-p-skovby-r-fernandes_en.pdf

New initiative – European Rare Disease Research Alliance (ERDERA)

Daria Julkowska presented an overview of the European Rare Disease Research Alliance (ERDERA), a pan-European alliance dedicated to improving the lives of 30 million people with rare diseases. ERDERA aims to accelerate diagnosis, advance therapies and deepen understanding of the societal impact of rare diseases.

Its activities span the full research and innovation pipeline, including annual Joint Transnational Calls, a Networking Support Scheme, and a major Clinical Trials Call planned for 2026. ERDERA provides extensive support services through its Data Hub, its regulatory and methodological expertise hub, mentoring programmes, and an upcoming Public-Private Collaboration Accelerator. These structures provide training and facilitate capacity-building, access to data resources and repositories, advanced methodological guidance and consultancy tailored to researcher needs, along with in-house research through its clinical research network.

ERDERA also works to harmonise priorities, diagnostic pipelines, training programmes, and funding activities across European national systems, positioning itself as a major driver of rare disease research, offering integrated expertise, data infrastructure, training, and coordinated research activities to advance diagnostics and therapies across Europe.

Presentation: https://www.ema.europa.eu/en/documents/presentation/presentation-european-rare-diseases-research-alliance-erdera-d-julkowska_en.pdf

Session IV – Impact of ethics principles and public involvement

Declaration of Helsinki (DoH) 2024 in paediatrics

Dominique Sprumont highlighted the ethical and regulatory updates in paediatric drug development introduced by the 2024 revision of the Declaration of Helsinki (DoH). The new guidance calls for balancing the risks of excluding and including children in research, shifting from the principle of strict subsidiary to responsible inclusion.

The presentation further emphasised informed consent from legal guardians, respect for the child's evolving capacity, and active involvement of patients, families, and communities throughout the research lifecycle. This approach reflects the principle, reaffirmed in the 2024 DoH, that individuals who participate in research must be appropriately informed, freely consent, and be respected as active participants in decisions affecting them.

EU law now directly references the DoH and ICH GCP, embedding responsible inclusion and patient engagement in binding frameworks. In this context, Article 32 of the EU Clinical Trial Regulation should be interpreted in light of these principles to enable proportionate risk assessment and facilitate paediatric studies.

Finally, the session outlined the importance of fit-for-purpose technologies and patient-centred designs to minimise burden and enhance data quality in paediatric trials. Collectively, these ethical, regulatory, and methodological developments constitute a substantive paradigm shift that safeguards children and secures equitable access to research benefits.

Presentation: https://www.ema.europa.eu/en/documents/presentation/presentation-introducing-principle-responsible-inclusion-children-declaration-helsinki-2024-dsprumont_en.pdf

Patient and parent experience of advocacy and involvement

Maria Baselga, speaking on behalf of patients' families, shared her experience enrolling her daughter affected by a rare disease in a gene therapy clinical trial, highlighting the need for more structured involvement of families in paediatric clinical research.

She described significant burdens families face during trial participation, including relocation, emotional and financial strain, repeated procedures due to inadequate data sharing, and limited logistical and language support, particularly in international settings. Based on these challenges, she recommended early and continuous consultation with families, transparent and efficient data sharing, better coordination between trial sites and local clinicians, child-centred scheduling, availability of interpreters, and clear, compassionate communication regarding any protocol changes.

Maria Baselga highlighted that family involvement is both scientifically valuable and ethically necessary. Families provide essential insights into daily realities and patient needs, contribute to defining realistic endpoints, and enhance adherence, safety, and trust throughout the trial process. She concluded with a call for systemic change, advocating for formal family participation mechanisms, more flexible and decentralised trial models, regulatory adaptation for ultra-rare diseases, and cross-border support to ensure equitable trial access.

Session V – Regulatory updates 1 - Good Clinical Practice (GCP) - Implementation in clinical trials. ICH E6 (R3)

Peter Twomey, presented an overview of the renovation of the ICH Good Clinical Practice E6 guideline (R3), outlining its major structural, conceptual, and operational reforms, highlighting that R3 represents a substantial modernisation of earlier versions, responding to technological advances, increased methodological diversity, and stakeholder concerns that previous guidance was overly prescriptive.

The revised guideline is organised around core principles emphasising proportionality, fit-for purpose approach, thoughtfulness in the design and conduct, risk-based approaches and clarification of roles and responsibilities. It provides clearer expectations for innovative trial designs, digital processes, use of real-world data and decentralised or pragmatic trial elements. R3 also strengthens provisions relating to data governance, transparency, and the streamlining of essential records to reduce administrative burden while maintaining participant protection.

The presentation highlighted new paediatric-specific requirements, including mandatory assent from minors where appropriate, the provision of age-appropriate information, and the need for re-consent when participants reach adulthood during a trial. These provisions align European legal and ethical standards with modern expectations for paediatric involvement.

Implementation of R3 in the EU began on 23 July 2025, supported by extensive training programmes.

Overall, GCP R3 constitutes a major, future-oriented revision that strengthens ethical and scientific rigor while offering greater flexibility, proportionality, and adaptability to contemporary clinical research practices.

Presentation: https://www.ema.europa.eu/en/documents/presentation/presentation-overview-ich-e6-r3-renovation-ptwomey_en.pdf

Session VI – Regulatory updates 2 – EU Regulatory Network

Paediatric clinical trial assessments under the new EU Clinical Trial Regulation – from PIP to CTA

Laura Fankhauser presented the results from a collaborative project examining paediatric clinical trial assessments by national Competent Authorities and ethics committees under the Clinical Trial Regulation (CTR) 536/2014. The analysis revealed substantial variability in the evaluation and authorisation of paediatric clinical trials across EU Member States.

Using data from the Clinical Trials Information System (CTIS), the study found that evidence requirements - especially demands for additional non-clinical, adult, or adolescent data - were the most frequent reasons for non-authorisation. There is heterogeneity on national interpretations of Article 32 of the CTR, particularly regarding what constitutes sufficient data regarding efficacy and safety of a medicine to justify the enrolment of minors. This inconsistency resulted in differences in authorisation rates and reasons for non-authorisation.

The analysis further highlighted that although the majority of studies supported by Paediatric Investigation Plans (PIPs) were approved, the reliance on PIPs during Member State assessments was inconsistent.

Overall, the findings demonstrate significant heterogeneity in paediatric trial assessment practices across the EU and highlight the need for enhanced coordination between the Paediatric Committee (PDCO), the Clinical Trial Coordinating Group (CTCG), national Competent Authorities, and ethics committees. These efforts aim to support greater harmonisation, particularly in the context of the revised Declaration of Helsinki, which promotes the responsible inclusion of minors in clinical research.

Presentation: https://www.ema.europa.eu/en/documents/presentation/presentation-paediatric-clinical-trial-assessments-under-new-ctr-pip-cta-l-fankhauser_en.pdf

Feedback from ACT EU workshop on assessment of paediatric clinical trials/ interpretation of CTR Article 32

Anette Solli Karlsen presented the main outputs of the ACT EU workshop on the assessment of clinical trial applications involving paediatric patients that was held on the 14 and 15th of July 2025.

The workshop brought together ethics committees, investigators, industry representatives, patient organisations and regulators to address key challenges in paediatric clinical trial assessment across the EU/EEA. Discussions focused on interpreting CTR 536/2014 - particularly Article 32 - alongside the 2024 Declaration of Helsinki and reviewed early experiences with paediatric trial assessments under the new regulatory framework.

Participants identified several recurring hurdles, including dosing uncertainties, benefit–risk evaluation, inclusion of minors in general and of adolescents in trials with adults, variability in national assessment approaches, and the use of adult data for extrapolation. Ethical considerations - such as defining direct versus indirect benefit and ensuring minimal burden and risk - also featured.

Furthermore, the need for meaningful integration of patient and caregiver views in trial design and review processes was reinforced.

Overall, stakeholders agreed that improved harmonisation, streamlined procedures, and clearer communication would help reduce delays and discrepancies in trial approvals, with some proposed follow-up actions: reviewing the Ethical Considerations document; surveying national legal frameworks; initiating discussions with ethics committees on interpreting Article 32; and formalising

collaboration between CTCG and PDCO. It was reported that a formalised channel for regular exchanges between CTCG and PDCO had in the meanwhile been established.

Presentation: https://www.ema.europa.eu/en/documents/presentation/presentation-act-eu-paediatrics-trials-eu-eea-workshop-assessment-clinical-trials-solli-karlsen_en.pdf

Implementation of ICH E11A guideline on paediatric extrapolation in Paediatric Investigation Plans (PIPs)

Dominik Karres presented an overview of the implementation of the ICH E11A Guideline on paediatric extrapolation. The approach begins with establishing a robust clinical foundation to characterise differences and uncertainties between adult and paediatric populations, forming the basis for extrapolation. These uncertainties are addressed in the extrapolation plan through modelling and simulation, Bayesian statistics, and real-world data, with results interpreted against pre-specified criteria.

The presentation emphasised the importance of multidisciplinary collaboration, regulatory capacity, and a rigorous evaluation of disease similarity to determine when extrapolation is appropriate.

The implementation focuses on three pillars: capacity building through a temporary operational expert group within the regulatory network; process enhancement for clarity and consistency in scientific documents, and broad knowledge dissemination across the regulatory network.

Presentation: https://www.ema.europa.eu/en/documents/presentation/presentation-putting-e11a-practice-extrapolation-guideline-application-d-karres_en.pdf

Closing remarks

The Chairs concluded the meeting by thanking all participants for their valuable contributions and reaffirmed the collective commitment to continued collaboration in advancing paediatric medicines development.

Speakers:

- Bax, Ralph. European Medicines Agency
- Baselga Iturzaeta, Maria. Patient representative
- Bonifazi, Donato. European Paediatric Translational Research Infrastructure (EPTRI)
- Calarco Smith, Gina. ACRO – Association of Clinical Research Organizations, IQVIA
- Dicks, Pamela. Scottish Children's Research Network
- Egger, Gunter. European Medicines Agency; Co-chair of Enpr-EMA
- Fankhauser, Laura. Hopp Children's Cancer Center Heidelberg (KiTZ), Germany
- Fernandes, Ricardo. STAND4Kids – Supporting Paediatric Trials in Portugal
- Haering, Dieter. Novartis
- Isla, Julian. Foundation 29
- Julkowska, Daria. Inserm (France); European Rare Diseases Research Alliance (ERDERA)

- Karres, Dominik. European Medicines Agency
- Lepola, Pirkko. Finnish Paediatric Research Network (FINPEDMED); Chair of Enpr-EMA
- Morales, Daniel. European Medicines Agency
- Sanchez, Isabel. European Medicines Agency
- Skovby, Pernille. Danish Paediatric Medicine Research Network (DanPedMed); Paediatric Committee (PDCO)
- Solli Karlsen, Anette. Norwegian Medical Products Agency; Paediatric Committee (PDCO)
- Sprumont, Dominique. Research Ethics Committee of Vaud (Switzerland); European Network of Research Ethics Committees (EUREC)
- Thomas, Marius. Novartis
- Twomey, Peter. European Medicines Agency
- Westman, Gabriel. Swedish Medical Products Agency (MPA)