Report from the 2023 Annual Workshop of the European Network of Paediatric Research at the EMA (Enpr-EMA)

Date: Tuesday, 10 October 2023

The European Network of Paediatric research at the European Medicines Agency (Enpr-EMA) held its 15th annual workshop on the 10th of October 2023 at the premises of the European Medicines Agency (EMA) in Amsterdam and online via Webex.

The 2023 annual workshop marked the return to face-to-face meetings after the restrictions due to the COVID-19 pandemic and brought together more than 100 participants comprising representatives of the networks, patient and parents organisations, healthcare professionals, academia, industry representatives and international regulators. The workshop was opened by EMA's Executive Director, Emer Cooke. The topics of the workshop ranged from updates from Enpr-EMA's working groups (WG) and network activities to discussions about best practices regarding de-centralised elements of clinical trials and the involvement of patients and young people in the planning of clinical trials. Furthermore, the revision of the ICH E6 guideline on good clinical practice and the proposal for a new EU pharmaceutical legislation (presented by the European Commission) were discussed.

Chairpersons: Pirkko Lepola, Gunter Egger

Session I - Enpr-EMA activities 2022-2023

Annual report from the coordinating group:

Pirkko Lepola, the chair of Enpr-EMA's coordinating group (CG), presented a report of Enpr-EMA's activities and achievements during the past year.

Presentation: Enpr-EMA annual report 2022-2023 (P. Lepola)

Update from Enpr-EMA working groups (WG):

WG on off-label evidence

The WG has published an article advocating the repurposing of medicines based on existent knowledge and published data:

"Off-label is not always off-evidence: authorizing paediatric indications for old medicines" published in The Lancet Child & Adolescent Health, June 2023[1].

It was noted that the European Commission's proposal for the revised pharmaceutical legislation included a strengthened legal basis (Article 48) that would allow not-for-profit entities to submit data for repurposing of medicinal products. The Dutch paediatric network (PEDMED-NL) is developing a decision model for evidence generation to indicate the kind of data and the analyses that would be needed along with the steps to submit a regulatory dossier to the authorities, to increase the level of scientific evidence that could support regulatory approval and ultimately the inclusion of the paediatric indication in the product information.

Presentation: Update from Enpr-EMA off-label working group (S. de Wildt)

WG on international collaboration

Regulatory authorities and national networks from Europe, USA, Canada, Japan, Australia and the UK, are represented in this WG that was created to address cross-jurisdiction challenges in the conduct of global paediatric clinical trials.

Aiming to boost international collaboration and global development, the group has been involved in describing the regulatory and ethics requirements for the conduct of paediatric clinical trials in each of the jurisdictions represented in the WG. Two manuscripts covering separately the regulatory authorisation and the ethics revision, are being prepared and will be submitted together for publication in a regulatory science journal early in 2024.

Presentation: Update from Enpr-EMA working group on international collaboration (T. Lacaze)

WG on paediatric research nurses

Research nurses from various countries across Europe form this working group with the aim to promote and develop the role of the paediatric research nurse in clinical trials across Europe. In order to gather data to understand the career pathway, development opportunities, employment conditions and training needs of research nurses in different regions and countries, two surveys have been launched targeting research nurses and research nurse managers, respectively.

The survey results will be analysed next year and will guide further actions of the group to improve the role of the paediatric research nurse. These activities are expected to include the further development of a network of paediatric research nurses, building a peer support forum to improve relationships and collaboration, and promoting training activities.

Presentation: Update from Enpr-EMA working group on paediatric research nurses (P. Dicks)

WG on paediatric clinical trial site standards

Following the workshop on paediatric trial site suitability criteria co-organised by Enpr-EMA and conect4children (c4c) in October 2022, two workstreams were created within this working group to reach a common understanding on the definition, need and recognition of such criteria.

Workstream 1 has aimed to establish a common understanding of what quality of paediatric sites means, the reasons why paediatric site standards are needed and how to identify them across different

[1] de Wildt SN, Foeldvari I, Siapkara A, Lepola P, Kriström B, Ruggieri L, Eichler I, Egger GF. Off-label is not always off-evidence: authorising paediatric indications for old medicines. Lancet Child Adolesc Health. 2023 Jun;7(6):371-372.

jurisdictions, paediatric age ranges and sponsors, providing a set of minimum criteria and a developmental pathway towards the aspirational requirements.

Workstream 2 has worked on identifying existing quality criteria and standards for paediatric clinical sites and has mapped how these criteria apply to different types of trials, based on literature search and categorisation of the evidence.

The research conducted by both workstreams has demonstrated that clinical trials in children introduce additional complexities compared to clinical trials in adults, requiring that stakeholders and clinical sites involved in paediatric clinical research meet unique requirements. The publication of recommendations for quality criteria on the Enpr-EMA website and in a scientific journal article is envisaged for 2024, along with the creation of a plan for dissemination and implementation.

Presentation: Update from Enpr-EMA working group on paediatric clinical trial site standards (R. Fernandes, S. Corriol-Rohou)

Presentation: Update from Enpr-EMA working group mapping existing quality criteria for sites (P. Skovby)

WG on cross-border access to paediatric clinical trials

The main goal of this working group is to develop consensus guidance to facilitate the inclusion of paediatric patients in cross-border clinical trials in Europe (i.e. where a child travels to another country to participate in a clinical trial). The aim is to avoid discrimination based on language, culture, or other factors. This may be especially relevant for children living with rare diseases.

To achieve this goal, the working group aims to identify current practices regarding inclusion and exclusion of potential child participants from abroad in a clinical trial by collecting paediatric clinical study data from the period 2017-2022. Additionally, the group will analyse if there are explanatory reasons from a scientific and ethical perspective and identify good practices.

The activities conducted so far include the evaluation of published clinical trial protocols to assess study design and eligibility criteria in terms of mother tongue and country of residence of the patient, along with the collection of information through ongoing surveys targeting clinical trial sites and patient organisations. Interim results were presented during the meeting. The data showed low numbers of patients recruited from other countries and identified several cases of discrimination based on language. It is planned that in 2024 the group will continue the data collection and analyses to extract the reasons for discrimination, and to identify and publish recommendations for good practices.

Presentation: Update from Enpr-EMA working group on cross-border access to paediatric clinical trials (B. Nafria)

Decentralised elements in clinical trials - paediatric perspective:

A recommendation paper on decentralised elements in clinical has been published by the Accelerating Clinical Trials in the EU (ACT EU) initiative.

Representatives from Enpr-EMA and PDCO had participated in the drafting group and made comments on the draft prior to publication. It was thus assured that the decentralised clinical trials (DCT) recommendations also apply to the paediatric population. The Paediatric Committee (PDCO) and Enpr-EMA will continue to be involved in ongoing discussions to further improve the DCT paper and ensure incorporation of specific paediatric recommendations, if found relevant.

The use of decentralised elements in clinical trials allows more flexibility for the trial participants (e.g. via home health visits, electronic informed consent) and permits the collection of real time data (e.g. via wearable devices).

It was stated that a risk-proportionate approach should be followed for the implementation of decentralised elements in clinical trials and, crucially, that it should be participant-centred via the involvement of patient organisations and investigators at the planning stage.

The specific characteristics of the paediatric population pose unique challenges to the design and implementation of decentralised elements in clinical trials that require specific training and adaptation, such as the need to adapt the study methods, technologies and language to the different subsets of the paediatric population, the specificities for the informed consent process considering legal implications with minors and the involvement of parents or legal representatives.

Presentation: EU recommendations on decentralised elements in clinical trials (M. Al)

Presentation: Paediatric considerations on decentralised trials (T. Lacaze)

Session II - Regulatory activities and pharmaceutical legislation

Good clinical practice, ICH E6 (R3) update from ACT EU (priority action 4 - PA4):

The ICH E6 good clinical practice (GCP) guideline addresses international ethical and scientific quality standards for the design, conduct, and reporting of trials, providing a unified standard for the ICH regions to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

Revision 3 (R3) of the guideline is ongoing, to improve clarity and readability, to facilitate innovation in clinical trial design, the use of new technology and operational approaches, and to set a foundation for feasible expectations around the responsibilities of sponsors and investigators in a digital ecosystem. Moreover, Annex 2 of the guideline will include additional considerations on the application of GCP principles to decentralised elements, pragmatic elements and real-world-data sources in clinical trials.

The revision document was released for public consultation in Europe in May 2023. Furthermore, a multistakeholder workshop was conducted as part of ACT EU priority action 4 (PA4). The comments received are in the process of being reviewed by expert groups, with the aim to identify major trends to bring them forward to the ICH E6 (R3) expert working group (EWG) for further discussion. The adoption of the draft guideline (principles and Annex 1) is planned for summer 2024.

It was highlighted during the meeting that although the consultation period is closed, there were still opportunities for cooperation regarding considerations for the paediatric population (e.g. quality-criteria for paediatric clinical trial sites). These could be taken into account for the creation of training materials and case examples complementing also the work done within the ICH paediatric group.

Presentation: Good clinical practice – ICH E6 (R3) update from ACT EU (PA4) (K. Pietsch)

Support for academic sponsors, update from ACT EU (priority action 2 - PA2):

ACT EU priority action 2 (PA2) aims to identify and address gaps, issues and bottlenecks of regulatory and operational nature that present challenges for non-commercial sponsors in the conduct of multinational clinical trials.

As part of the initiative, the feasibility of creating a regulatory helpdesk and facilitating access to scientific advice is being assessed. A multistakeholder platform will be established under ACT EU to facilitate dialogue and collaboration, through workshops, consultations and surveys. Strategic advice to the platform will be provided by an advisory group formed by representatives from industry, patients' organisations, healthcare professionals, academia and funders. A call for nominations was launched in October 2023. Enpr-EMA members were encouraged to put forward their application so that paediatric representatives could be part of this advisory group.

Currently the ACT EU initiative is working on identifying the most pressing challenges for performing non-commercial multinational clinical trials. In this context Enpr-EMA members highlighted difficulties with navigating the regulatory landscape, finding funding opportunities, CTIS functionality, ethics, and patient engagement as the most pressing hurdles for academic sponsors performing multinational paediatric clinical trials.

Members were also informed of the upcoming ACT EU multistakeholder workshop on methodology guidance taking place on the 23rd of November 2023.

Presentation: ACT EU action plan to support non-commercial multinational clinical trials (G. Capone)

Reform of the EU pharmaceutical legislation and its impact on paediatric & orphan medicine development:

Directive 2001/83/EC and Regulation (EC) 726/2004 on the rules for authorisation of medicinal products and the establishment of the EMA structure and composition, as well as the Paediatric and Orphan Regulations are being revised into a new Regulation, a new Directive and Council Recommendation on Antimicrobial Resistance (AMR), with six main objectives: to improve access to medicines, to avoid shortages, to increase affordability, to create a competitive regulatory framework, to ensure environmental sustainability, and to combat AMR.

Fabio D'Atri explained that in the proposal for the new pharmaceutical legislation, the paediatric provisions are included within a Regulation and a Directive, maintaining a structure of obligations and rewards. The main changes compared to the current Paediatric Regulation aim to facilitate the processes for the Paediatric Investigation Plan (PIP) application, to decrease delays in the development of paediatric medicines and to increase the development of medicines for rare diseases and areas where there is an unmet medical need. The proposed changes include clarifications on the timing of the submission of PIPs; the introduction of a step-wise PIP; more flexibility in PIP Key Elements; the requirement to submit PIP applications for conditions of unmet need on the basis of the product's mechanism of action; the introduction of a cap of maximum five years for deferrals; and the introduction of clear steps for the repurposing of medicines, with the possibility for academics to submit data to extend the label of existing products.

Moreover, the changes foreseen to the regulation of medicines for rare diseases were explained. This includes changes in the criteria for granting the orphan medicine designation, the criteria to define unmet medical needs and the established incentives. The objective of these changes is to increase regulatory support for developers in the early phases of development, with the aim to accelerate EMA assessment and European Commission (EC) authorisation later on.

Furthermore, a reorganisation of EMA's structure and its committees is envisaged in the new legislation proposal, with paediatric expertise to be present across the committees and working parties. Furthermore, an extended role for the Enpr-EMA network is foreseen as a multistakeholder forum to permit discussions on unmet medical needs and prioritisation of paediatric research and development.

The next steps of the revision process include the discussion at the Council and EU parliament in 2024, with the expectation to reach an agreement in 2025, with a foreseen transitional period of around 18 months.

Presentation: Reform of the EU pharmaceutical legislation and its impact on paediatric medicine and orphan medicine development (F. D'Atri)

Session III - Highlights from Enpr-EMA networks in 2022/23 and work plan 2023/2024

Highlights in 2022-2023 of Enpr-EMA and its member networks:

Paediatric clinical trials need paediatric clinical trial budgets:

Stavros Koulizakos and Jenny Kindblom presented the results of the study 'Paediatric clinical trials need paediatric clinical trial budgets'[2], describing the experiences with budget preparations in paediatric clinical trials, where 10 industry trials were analysed comparing the initially proposed budget with the finally agreed one, the results showing the difference between them and that paediatric trial costs are often misrepresented.

The costs were categorised into three areas, (1) startup costs including contracts and budget preparation, internal agreements, applications to the authorities and preparation of the study visits; (2) study activities including informed consent forms (ICF) for both caregivers, physical examination, tests, samples, and administration of the investigational medicinal product (IMP); and (3) examinations that needed to be adjusted to the paediatric setting.

The final study cost was on average 59% higher than initially estimated, with 84% higher costs in startup, showing the same trend in all therapeutic areas and specialties. It was concluded that the study budget needs to be revised by a dedicated team and adjusted to the paediatric population as the real costs could be significantly higher than those based general trial estimations.

At the meeting it was suggested to compare the discrepancy between initially proposed budget and the finally required one also for adult trials in order to ascertain that these differences are indeed more relevant in paediatric trials than those conducted solely in adults.

Presentation: Paediatric clinical trials need paediatric clinical trial budgets (S. Koulizakos, J. Kindblom)

The conect4children (c4c) journey

Mark Turner presented the conect4children project, a private-public partnership between academia and pharmaceutical industry that facilitates the development of new medicines for the paediatric population by building up the capacity for the conduct of multinational paediatric clinical trials, implementing a new infrastructure and a new organisational model.

[2] Koulizakos S, Kjellén T, Mellgren K, Kindblom JM. Paediatric clinical trials need paediatric clinical trial budgets. Acta Paediatr. 2023 Sep;112(9):1982-1985.

The project was based on the identified needs of ensuring rapid access to experts and to sites, facilitating the involvement of patients, permitting reliable conduct of studies, providing education and training activities, and the establishment of paediatric data standards. These needs have been transformed into the following actions and activities: strategic feasibility advice, multistakeholder meetings to define unmet medical needs and to facilitate development of innovative medicines for children, support and coordination of clinical trial conduct trough a single point of contact and national hubs, a training academy to provide education and training courses to all study sites and personnel and the creation of paediatric data standards.

The model/network was initiated by the Innovative Medicines Initiative (IMI)/Innovative Health Initiative (IHI) and has been established through the following steps: defining a vision, connecting through national networks, building an expert community and collaboration with industry partners, developing a community in alignment on goals, culture, terminology, methods and processes with established priorities and detailed business processes that are tested and adapted accordingly.

The sustainability of the model after the IMI/IHI project period will be built up with the formation of a legal entity, financial plan and marketing plan.

Presentation: The conect4children journey (M. Turner)

Draft Enpr-EMA work plan 2023/2024:

Pirkko Lepola presented the suggestions for Enpr-EMA's workplan for the remainder of 2023 and 2024. Current activities of the working groups which are expected to continue during the next year include the publications on the requirements for clinical trial applications and ethics reviews in different jurisdictions; the analysis of the data collected regarding the role and current situation of the paediatric clinical study nurse; the work on guidance to facilitate cross-border clinical trials; the recommendations on paediatric clinical trial site standards; and the possibility to further advance the repurposing of medicines due to opportunities that the new pharmaceutical legislation may bring.

Moreover, new topics that were raised by the members at their meeting on the previous day were presented. These included the adaptation of Enpr-EMA to the changing environment, the need for raising awareness and mapping of existing young person advisory groups (YPAGs), the use of real-world-data in the paediatric environment, clinical trials in special circumstances, data sharing, the inclusion of adolescents in adult trials and paediatric elements in de-centralised clinical trials.

Enpr-EMA's coordinating group will decide which topics should be prioritised next year and concretise the activities to address them at their first meeting in 2024.

Presentation: Draft Enpr-EMA work plan 2023-2024

Session IV - Patient recruitment & involvement

Patient recruitment and retention

Practices to improve patient recruitment from a network's perspective:

Marek Migdal presented best practices and activities to improve the recruitment of patients in paediatric clinical trials, by sharing the example of the Children's Memorial Health Institute (CMHI), a paediatric hospital in Poland and a research institute member of 7 European Reference Networks.

Two aspects were highlighted as key to increasing social awareness and to maintaining the trust of patients and a high reputation of the centre as a medical research institution: firstly, the importance of site preparation in terms of infrastructure and personnel, keeping experienced and multidisciplinary staff investing in continuous learning, as well as having dedicated facilities to perform clinical trials; secondly, the involvement in different networks and activities at national and international level, as well as the cooperation with families and patients with educational and training activities adapted to the paediatric population.

Presentation: Practices to improve patient recruitment from a network's perspective (M. Migdal)

Involvement of patients & young people in the planning of clinical trials

Benefits of involving patients and young people in paediatric clinical research:

Begonya Nafria presented eYPAGnet (European Young Persons Advisory Group network) which was established in 2006 as a European network of experts in Patient and Public Involvement (PPI). eYPAGnet advocates for the needs of children and parents to be considered for the design and execution of clinical trials, by providing specific support for the designing of the studies, education and training materials, and by creating a bespoke PPI plan, along with tools to report and measure the impact of the involvement, aiming for a meaningful and respectful involvement of patients and the public in clinical research.

eYPAGnet activities are standardised across countries and languages, utilising methodology adapted to each project, consisting of a first initial assessment and the creation of a tailored PPI plan to document the ethical involvement of patients, parents, and patient organisations.

PPI ensures that trial methodologies are less burdensome for patients and their families, and that outcome measures are indeed of relevance to the patients. It increases patients' and their families' satisfaction and their trust in the clinical trial and health care.

Although it has been demonstrated that the involvement of patients and young people in the decision-making process for the designing of clinical trials has clear benefits also for sponsors, such as a reduction of the study timelines, costs and protocol amendments, YPAG and PPI activities are currently only included in the designing of very few paediatric clinical trials. Therefore, efforts will continue to raise awareness of the different YPAGs and their initiatives to facilitate impactful PPI.

Presentation: Benefits of involving patients and young people in paediatric clinical research (B. Nafria)

Improve paediatric health, medicine research, and innovation by sharing children's voices with iCAN:

Donato Bonifazi presented the International Children's Advisory Network (iCAN) and TEDDY initiatives which promote the participation of children in the decision-making process in clinical research, advocating for their right to be informed and to express their views in decisions related to their health and wellbeing. The degree of the children's involvement is dependent on their evolving capacities. Different levels of participation were mnetioned: being informed, expressing a view and influencing decisions.

iCAN is present in the US and EU, formed by groups of people including children with common goals of sharing children's views and needs, and making a difference in paediatric healthcare by giving input to study designs and materials. Moreover, the group provides educational tools, networking and

collaboration opportunities (iCAN summit). TEDDY being part of the iCAN network promotes kids' groups and their participation in decision-making processes regarding their health.

Presentation: Improve paediatric health, medicine research, and innovation by sharing children's voices with iCAN (D. Bonifazi)

Speakers:

- Al, Monique. Clinical Trials Coordination Group (CTCG), Central Committee on Research Involving Human Subjects (CCMO), Netherlands
- Bonifazi, Donato. TEDDY European Network of Excellence for Paediatric Research
- Capone, Giacomo. European Medicines Agency (EMA)
- Cooke, Emer. Executive director of European Medicines Agency (EMA)
- D'Atri, Fabio. European Commission (EC), DG SANTE
- Dicks, Pamela. ScotCRN (Scottish Children's Research Network)
- Egger, Gunter. Co-chair of Enrpr-EMA, European Medicines Agency (EMA)
- Fernandes, Ricardo. Conect4children National HUB lead and STAND4kids (Portuguese paediatric research network)
- Gaillard, Segolene. RIPPS (Paediatric Investigation into Health Products Network, France)
- Koulizakos, Stavros. Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden
- Kindblom, Jenny. Dept. of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden
- Lacaze, Thierry. MICYRN (Maternal Infant Child and Youth Research Network, Canada)
- Lepola, Pirkko. Chair of Enpr-EMA, Finpedmed (Finnish paediatric research network)
- Migdal, Marek. PDCO (Paediatric Committee) at EMA, conect4children National HUB, Poland
- Nafria, Begonya. eYPAGnet (European Young Persons Advisory Groups Network)
- Pietsch, Dong Ho Kim. European Medicines Agency (EMA)
- Skovby, Pernille. Conect4children National HUB, Denmark
- Turner, Mark. conect4children co-coordinator, University of Liverpool, United Kingdom
- Wildt, Saskia de. Pedmed-NL (Medicines for Children Research Network, Netherlands)