Report from the 2021 annual meeting of the members and Coordinating Group of the European network of paediatric research at the EMA (Enpr-EMA)

Date: Tuesday 28 September 2021

The 2021 annual meeting of Enpr-EMA was held virtually due to restrictions related to the COVID-19 pandemic, as was also the case for the meeting the previous year. Invitees included the Coordinating Group (CG), Enpr-EMA members, and members of the Paediatric Committee (PDCO) and the European Medicines Agency's (EMA) Paediatric Medicines Office. The meeting covered various aspects ranging from the latest updates regarding the evaluation of the Paediatric and Orphan Regulations and the global EU pharmaceutical strategy, presented by the European Commission, to other current topics such as Real World Evidence contributing to drug development, COVID-19 therapeutics and vaccines for paediatric use, and the upcoming implementation of the EU Clinical Trial Regulation and Clinical Trial Information System. Additionally, an update on the achievements and deliverables of the Enpr-EMA working groups (WG) and network activities was presented.

Chairpersons: Pirkko Lepola, Gunter Egger

Morning Session

Report from the Coordinating Group

Pirkko Lepola, the chair of the Enpr-EMA CG, summarised the activities of Enpr-EMA during the past year, which despite challenges due to the impact of the pandemic on some of the working groups, resulted in various achievements, including the following publications:

- "Preparedness of medicines' clinical trials in paediatrics. Recommendations by the Enpr-EMA working group on trial preparedness" and its related article: "Recommendations by the Enpr-EMA Working Group on preparedness of clinical trials about paediatric medicines process" (ArchDisChild. March 2021) (WG on trial preparedness).
- Assent / informed consent for paediatric clinical trials: Guidance document published in February 2021. A related manuscript was submitted in July 2021 for review and publication (WG on ethics).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

- Two manuscripts are being drafted regarding the process of clinical trial application approval across six jurisdictions, and one survey about site requirements to industry partners is in planning stage (WG on international collaboration)

Further activities covered dissemination of information related to workshops, conferences, public consultations, training opportunities and other initiatives; issuing consolidated Enpr-EMA responses to public consultations; and global collaboration and representation of Enpr-EMA in scientific meetings and conferences.

Thanks were given to all Enpr-EMA members and participants for the work done during the last year. Moreover, new members of the CG and a new member network (AEPC (Association for European paediatric and congenital cardiology) Task Force on Clinical (Drug) Trials) were welcomed.

Presentation: *Update on Enpr-EMA activities 2020-2021 (P. Lepola)*

Update on membership criteria and conflict of interest declaration

Gunter Egger, the co-chair of the Enpr-EMA CG, informed the members about the up-coming new version of the self-assessment form. The form was updated to reflect the reduction of membership categories from four to three categories, as adopted by the CG earlier in the year. The updated form is now available on the Enpr-EMA website.

The purpose of the self-assessment form is to capture information on the state of the member networks and their services, and also to serve as an application form for new members. Members were reminded that the information, which is publicly available via the Enpr-EMA network database, needs to be updated every two years. Further instructions in this regard will be sent to all members later on.

Moreover, members were informed that the Conflict of Interest declaration (CoI), which in line with transparency policies is required for members of the CG and members of the working groups, is also being updated in order to streamline the process. Further information will be provided in this regard.

Update on EU evaluation of Paediatric and Orphan Regulation

Fabio D'Atri of the European Commission's DG SANTE presented an overview of the evaluation of the Orphan and the Paediatric Regulation and the work on the ongoing revision of the Regulation.

An evaluation of the Regulations for rare diseases and medicines for children was performed and published in August 2020, the conclusions of the evaluation showed that, overall, the two Regulations had fulfilled most of their objectives, identifying nevertheless some weaknesses. In view of these limitations, both legislations are being reviewed with the common objective to increase development in areas where there are high unmet medical needs, ensure availability and timely access for medicines, advances of science and simplification of the regulatory procedures. In order to achieve these objectives, different options are being evaluated in an impact assessment and publicly consulted by means of an open public consultation completed in July 2020 and ongoing surveys and interviews. Preliminary feedback showed, among other topics, interest in increasing dialogue and discussions for establishing priorities and criteria related to unmet medical needs, a request for the simplification of PIP procedures and for the revision of the rewards. Responses to the consultation have been published[1]. The aim will be to deliver a proposal for the revision of the legislations by the end of 2022. The proposal by the Commission will then be negotiated with the European Parliament and the Council and it can be considered that the two revised legislations may be adopted in 2023-2024.

[1] https://ec.europa.eu/health/medicinal_products/consultations/impactassessmenteulegislation_en

Update on EU pharmaceutical strategy

Fabio D'Atri presented an overview of the Pharmaceutical Strategy for Europe, which was adopted in November 2020 with the objective to create a regulatory framework that supports industry in promoting medical research and technologies. It covers the whole lifecycle of medicines based on four pillars: learning from COVID-19 towards a crisis-resistant system, ensuring accessibility and affordability of medicines, supporting sustainable innovation, and reducing shortages. In order to achieve these objectives, the EU pharmaceutical legislative framework is currently undergoing a revision. A consultation on the roadmap for this revision, highlighted the necessity to better conceptualise 'unmet medical needs' and to develop a core set of shared criteria between regulators, Health Technology Assessment (HTA) bodies and payers, and to promote early interactions with these bodies to ensure that sufficient data are generated for pricing and reimbursement decisions. The involvement of patients and taking into account their perspective has been recognised as a key factor. Further steps involve targeted consultations with stakeholders, along with an open public consultation that was launched on 28 September. Members are invited to consider submitting their comments to the EC public consultation by 21 December 2021. A legal proposal amending the general pharmaceutical legislation is due in Q4 2022.

Presentation: *Revision of the legislations on medicines for children and rare diseases – Pharmaceutical Strategy (F. D'Atri)*

Afternoon session:

EU-Initiatives progress update:

Conect4children (c4c)

Mark Turner presented an overview of the structure, objectives and future plans of c4c, a private-public partnership between academia and pharmaceutical industry for a pan-EU paediatric clinical trial network under the EU Innovative Medicines Initiative (IMI). The main scope of the project includes strategic feasibility, conduct of paediatric clinical trials, data standards, as well as education and training. Achievements from last year comprise the establishment of a panel of experts involved in strategic feasibility activities, having received over 25 requests for advice, and the organisation of a multi-stakeholder meeting. In terms of trial conduct, 20 national hubs have been engaged, counting with 240 sites, 3 non-industry trials are open and 5 industry trials at feasibility assessment stage. Data standards have also advanced through the integration with the Clinical Data Interchange Standards Consortium (CDISC) and the creation of a paediatric data dictionary. Education and training initiatives have been made available via the c4c Academy. C4c would like to share its experience of strategic feasibility advice with the PDCO, which was welcomed.

Steps for the transition to a new business model and legal entity after the IMI project period ends in 2024 have been initiated.

Presentation: *A pan-EU paediatric clinical trial network, c4c (M. Turner)*

Global initiatives progress update:

Multi-Regional Clinical Trials (MRCT) Center

Dominik Karres provided an update about the MRCT initiative on promoting global clinical research in children, an initiative whose objective is to identify solutions to regulatory, ethical and operational challenges encountered while developing medicines for children.

Three working groups have been established to focus the discussion on: 1) Decision making for children's participation in biomedical research, 2) Benefit/risk considerations for pediatric research, 3) Challenges in implementation of global pediatric clinical trials. In all three groups patient engagement has been identified as a fundamental element for the development of novel medicines, including above all representativeness and transparency in the process.

Among the planned project deliverables are guidance documents and other resources to assist in youth engagement and overall in the conduct of paediatric clinical trials; a legal landscape analysis of the consent and risk benefit; the establishment of principles towards paediatric regulatory convergence; educational materials and publications. Enpr-EMA members stressed that taking into account the perspectives of different geographical regions in addition to Europe and the U.S. is of great relevance and benefit.

5 webinars are planned to be held. The first webinar on 6th and 7th of October 2021 will build on lessons learned during the COVID-19 pandemic, with attention to timing and infrastructures needed for initiating clinical trials in children. The dates and topics of subsequent webinars in the series will be confirmed in the near future. Additionally, a conference on "advancing international paediatric clinical research" will be held on the 10th and 11th of May 2022.

Real World Evidence to advance clinical development:

Observational studies projects (Darwin EU & Rapid Analytics)

Francois Domergue introduced the initiatives being undertaken to make best use of Big Data in support of innovation and public health in the EU. In the field of medicines development, the term Big Data comprise two concepts: (1) Real World Data (RWD), referring to the routinely collected data about patients' health status or the delivery of health care from a variety of sources other than traditional clinical trials, and (2) Real World Evidence (RWE) being the information derived from the analysis of RWD.

The EU initiatives to use RWE in the development, authorisation and post-marketing surveillance of medicines, included the creation of a Joint HMA (Heads of Medicines Agencies)/EMA Big Data Steering Group and Work Plan and the launch of the DARWIN EU project. DARWIN EU will establish a network of data and expertise to support decision-making throughout the product lifecycle with reliable evidence from real world healthcare data. In the first place, it will be made available to EMA's committees, with possible expansion to other stakeholders. In any case, data sources used by DARWIN EU will also feed into the European Health Data Space, and will thus become available to some extent to other stakeholders in a FAIR (findable, accessible, interoperable and reusable) manner. Therefore, the benefits of the DARWIN project will reach not only the Scientific Committees but also European Commission, National governments, HTA bodies and payers, EU health agencies, EU patients and other stakeholders.

A webpage has been launched and a call for tender for a service provider for a Coordination Centre is ongoing. It is expected that DARWIN-EU will be supporting scientific evaluation of EMA's committees and NCAs in 2023, while being fully operational and integrated in 2025/2026.

Presentation: *Big Data steering group update (F. Domergue)*

Real World Evidence to contribute to drug development and access

Ralf Herold further discussed the fundamentals of RWE, as a process that evolves, learns and improves with every patient who is treated. The generation of clinical evidence is evolving from being solely focussed on clinical trials, to integrating existing data and clinical perspectives in sophisticated analyses. Strong emphasis was put on the possibility of making use of a 'methodology qualification procedure' to support acceptance by regulators and other decision-makers of RWE presented in clinical developments.

Enpr-EMA members showed high interest for the use of RWE, and some experiences were shared regarding projects performed to analyse existing data in order to generate information on the use of medicines. Some of the common barriers found were due to the heterogeneity of the data coming from the various sources. It was suggested that ideally guidance should be drawn up for data standardisation and methodology qualification.

Presentation: *Real World Evidence to contribute to drug development and access (R. Herold)*

Report from the Working Groups (WG):

Working group on research staff

Since its creation, various activities have been performed by this WG resulting in deliverables such as a questionnaire-based study to learn about the roles and training needs of paediatric research nurses across Europe, as well as about the need to harmonise approaches to training and curriculum requirements.

However, the COVID-19 pandemic has caused this working group major challenges due to re-distribution of resources and reprioritisation. A call for interest was made during the meeting; interested volunteers to become part of the group are needed who can provide research experience to drive a European network for paediatric research nurses. In the meanwhile, Pamela Dicks (ScotCRN) would coordinate the reformation of the group and the selection of a new Chair, who ideally should be a research nurse themselves. Moreover, it was decided that the group would liaise with the c4c nurses group and coordinate activities. In order to increase involvement of nurses in the WG, all Enpr-EMA network representatives are encouraged to "spread the word" and contact details of the WG leads!

WG on international collaboration

The group includes representatives of networks and regulatory agencies from the regions EU, US, Canada, Japan, Australia and UK.

The collaboration has so far resulted in two main projects:

1) To scan and analyse the requirements within the jurisdictions for the submission and approval of Clinical Trial Applications (CTA). In order to do so, a survey was distributed to the networks and regulators to collect the data, that is now being collated for the creation of two manuscripts, one on the CTA authorisation by national competent authorities and the other on the ethics committee approval process. The manuscripts will also highlight upcoming changes to the regulations. It is foreseen to finalise at least the manuscript on CTA authorisation for submission for publication in early 2022.

2) To survey pharmaceutical companies and contract research organisations (CRO) in order to determine which site quality requirements / criteria sponsors deem important when selecting trial sites to participate in paediatric clinical trials. This work aims to complement research performed by c4c and i-ACT (site quality standards). The survey will be distributed globally. The results are planned to be used for (a) publication(s) in a scientific journal and/or for publishing on the Enpr-EMA website in order to serve as guidance to paediatric trial sites.

WG on clinical practice evidence in the labelling

The working group was formed in light of the fact that even to date about half of all medicinal products with a marketing authorisation (MA) and being on markets in Europe are prescribed to children without having a paediatric indication in the Summary of the Product Characteristics (SmPC) which results in a lack of available medicines to treat paediatric patients and the increasing off-label use of these products in children. This WG aims at building a case, step-by-step, to search for new ways to include existing data (safety, efficacy) from various sources in the labels of products used off-label in children and look for potential changes in legislation at European level to make it possible to update the SmPC of products with a European MA in adults by using published clinical data.

Therefore, a first step will be a statement paper, now under development, aiming to present a few selected products as examples with high medical need, having existing published data from various sources. The aim is also to suggest criteria for the data selection to support risk-benefit analyses for the paediatric population. This is expected to form a basis for further discussions about regulatory solutions during the next steps of the case development. Activities will continue under this premise.

EU Clinical trial Regulation (CTR)

Introduction to the Clinical Trials Information System (CTIS):

Ana Rodriguez introduced the upcoming changes to the clinical trial application (CTA) authorisation process related to the coming into application of the Clinical Trial Regulation (EU) No. 536/2014. Under the Regulation the Clinical Trials information System (CTIS), comprising the EU portal and the EU database, will be used as the tool for communication and information sharing during the review and approval process of the CTA. The EU portal has been established to be used as a single entry-point for the submission of data and information, that will also be stored and publicly available in the EU database. The process for submitting, reviewing, and authorising clinical trials will be simplified by the submission of one application dossier to all member states concerned through the EU portal obtaining a single decision.

An introduction was provided to the functionalities of the system which will go live on 31 January 2022. Further information, training resources and news on upcoming events is available on EMA's website.

Presentation: *Introduction to the Clinical Trials Information System (CTIS) (A. Rodriguez)*

COVID-19 affecting children

Update on the development of therapeutics and vaccines for paediatric use:

Laura Fregonese gave an overview of COVID-19 developments in the paediatric population. The revision of Paediatric Investigation Plans in this area has been high, counting currently with 7 COVID vaccines and 10 COVID therapeutics which have paediatric developments in place.

Presentation: *COVID-19 update on development of therapeutics and vaccines for paediatric use (L. Fregonese)*

A.O.B.:

Participants were informed about the following events of interest:

- 6th and 7th of October 2021: MRCT conference-series part 1/5: Advancing International Pediatric Clinical Research; "Informing the future from COVID-19 lessons learned"
- 11th of October 2021: European FH Patient network technical meeting on familial hypercholesterolaemia paediatric screening across Europe
- 18th and 19th of October 2021: Joint EFGCP/DIA annual conference: Better Medicines for Children; "Global Pediatric Drug Development Challenges & Solutions"
- 26th of October: CTIS virtual information day
- 29th of November 2021: MICYRN Assembly; "Research Ethics Review Streamlining Initiatives"
- 7th of December 2021: EU Big Data Stakeholder Forum

The meeting was concluded by the chairs thanking all participants for their contributions.

Speakers:

- Fabio D'Atri, European Commission (DG SANTE)
- Liliya Dimitrova, European Medicines Agency (EMA)
- Francois Domergue, European Medicines Agency (EMA)
- Gunter Egger, co-chair of Enpr-EMA, European Medicines Agency (EMA)
- Laura Fregonese, European Medicines Agency (EMA)
- Ralf Herold, European Medicines Agency (EMA)
- Dominik Karres, European Medicines Agency (EMA)
- Thierry Lacaze, Maternal Infant Child Youth Research Network (MICYRN)
- Pirkko Lepola, chair of Enpr-EMA, Finnish Investigators Network for Paediatric Medicines (FinPedMed)
- Ana Rodriguez, European Medicines Agency (EMA)
- Mark Turner, conect4children (c4c)
- Saskia de Wildt, Medicines for Children Research Network Netherlands (PEDMED-NL)
- Pamela Dicks, Scottish Medicines for Children Network (scotcrn)