Report from the 2022 annual meeting of the members and Coordinating Group of the European network of paediatric research at the EMA (Enpr-EMA)

Date: Tuesday 4 October 2022

The 2022 annual meeting of Enpr-EMA was held virtually as in previous years, due to COVID-19 pandemic restrictions. Coordinating group (CG) members, Enpr-EMA members, and members of the Paediatric Committee (PDCO) and the European Medicines Agency's (EMA) Paediatric Medicines Office attended the meeting. The programme covered updates on the achievements and deliverables of the Enpr-EMA working groups (WG) and network activities, a report from the workshop organised the previous day (3 October 2022) in conjunction with conect4children (c4c) on paediatric trial site suitability criteria, a panel discussion on Health Technology Assessment (HTA), a presentation on the role of academic clinical trials in paediatric development, and an update on the implementation of the Clinical Trials Regulation. Additionally, a closed meeting of the members and observer members of the coordinating group took place to hold the election of the chair of the coordinating group, along with the endorsement of new and updated Enpr-EMA membership applications.

Chairpersons: Pirkko Lepola, Gunter Egger

Morning Session

Report from the Coordinating Group

Pirkko Lepola, the chair of Enpr-EMA's CG, presented a report of the activities performed by the group during the past year. Despite challenges due to the COVID-19 pandemic, geopolitical conflicts and the constraints in human resources, 2022 has resulted in various achievements, including the dissemination of information on workshops, scientific meetings, conferences, public consultations and training opportunities. Additionally, the reactivation of pre-existing working groups and the creation of new ones have expanded the possibility of new deliverables such as planned surveys and scientific publications covering the following topics: requirements for paediatric clinical sites, regulatory process and approval for paediatric clinical trials across six jurisdictions, role and status of research nurses in Europe, patients' rights and cross-border access to clinical trials, and off-label evidence of medicines for paediatric use. One article published by the Enpr-EMA working group on ethics was highlighted:

- "Informed consent and assent guide for paediatric clinical trials in Europe" (Arch Dis Child. 2022 Jun;107(6):582-590) (WG on ethics).

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In addition, the growing number of networks that have become members of Enpr-EMA since its creation and the need to adapt Enpr-EMA to these evolving times by revising membership categories, self-assessment forms and the composition of the coordinating group were highlighted.

Thanks were given to all Enpr-EMA members and participants for the work done during the last year.

Presentation: Report from CG 2022 (P. Lepola)

Report from Enpr-EMA/c4c workshop on paediatric trial site suitability criteria

Gunter Egger, the co-chair of Enpr-EMA's CG, informed the members about the outcome and conclusions of the workshop on quality criteria/standards for paediatric clinical trial sites. This workshop, co-organised by Enpr-EMA and conect4children (c4c), had taken place the previous day. Participants represented various Enpr-EMA and c4c members, along with invitees representing pharmaceutical industry, patients and academia.

The workshop was based on the work on this topic that had been performed by c4c and by Enpr-EMA's working group on international collaboration in parallel work streams. C4c has been dealing with the clinical trial sites' perspective by surveying clinical trial sites that are linked to c4c, while the Enpr-EMA working group has focused on the pharmaceutical industry's perspective by conducting a survey among pharmaceutical companies and contract research organisations (CROs) on the required characteristics from the sponsors' point of view.

The objective of the workshop was to start and catalyse a discussion around site suitability criteria amongst all stakeholders, to reach a common understanding on the need for such criteria and what they would be used for, how a set of criteria could be reached by sites and recognised by industry, as well as considering the possibility for endorsement of such criteria.

It was reported that participants at the workshop agreed on the need to define some type of quality criteria or standards, with the aim to speed up trial set-up, support site selection, ensure high quality data and to enhance the development of sites. Moreover, it was stated that a collaborative approach, with the participation of clinical sites, networks, patients, and industry, would be needed. Several participants volunteered to be involved in follow-up activities. Therefore, a follow-up meeting will be organised early in 2023 with the aim to set up a working group to define quality criteria, map existing standards and ultimately develop a roadmap/recommendations document for paediatric clinical trials site standards.

Presentation: Report from site standard workshop (G. Egger)

Report from the Working Groups (WG):

WG on international collaboration

The group includes representatives of networks and regulatory agencies from the EU, US, Canada, Japan, Australia and the UK with the objective to establish international collaboration to facilitate the development of paediatric clinical trials.

The group (including representatives from the EU, the US, Canada, Japan, Australia and the UK) has been collaborating globally on two main topics, (1) to facilitate the understanding of the requirements concerning the regulatory authorisation and the ethics review approval for conducting paediatric clinical trials in each of the six jurisdictions, and (2) to identify the criteria that sponsors require sites to fulfil for the conduct of paediatric clinical trials.

It is anticipated that the manuscripts about the requirements for the submission packages and approval of clinical trial applications by national competent authorities and ethics committees will be submitted for publication in a scientific journal in Q1 2023.The identification of the industry required criteria for the clinical sites to participate in paediatric clinical trials has been performed by disseminating a global survey and by conducting follow-up interview among representatives of the pharmaceutical industry and contract research organisation (CRO). This work complements the research performed by c4c internally on the identification of site standards (see report from joint Enpr-EMA/c4c workshop above). A publication in a scientific journal is envisaged.

WG on paediatric research nurses

Research nurses from various countries across Europe have joined this working group in recent months. The primary objective of the group is firstly to understand the current situation of the research nurses' roles in terms of conditions, career pathways, development opportunities and training needs; secondly to promote the development of this role and to increase career opportunities.

To do so, a survey to investigate the current situation of the research nurses' roles is under design phase and will be tested within the working group, bringing to light the need to have the questions answered by two profiles, nursing work managers and individual clinical nurses. Therefore, the survey will be divided into two sets of questions directed to each of these roles. The following steps will also include the translation, the development of the appropriate software and the dissemination of the survey for which the support of Enpr-EMA and its members will be sought.

The second objective of the group is to develop a platform for training and peer support for the research nurses across Europe. Discussions are ongoing with c4c to investigate the possibility of collaboration with their learning academy. So far, the fact that the training material on the platform is provided only in English has been identified as the main challenge. Translation options are being investigated.

Presentation: WG on research nurses (P. Dicks)

WG on cross-border access to paediatric trials

The group on cross-border access to paediatric trials is a newly formed working group with members from different countries and areas (e.g networks, industry).

The main objective of the group is to develop guidance to facilitate the inclusion of paediatric patients living with rare diseases, or specialised medical conditions, via cross-border access to clinical trials in Europe avoiding language discrimination and cultural barriers. Publication of such guidance is targeted for 2024 and will be opened for public consultation. The group aims to identify and analyse from a scientific and ethical perspective cases of discrimination against paediatric patients, reviewing the current evidence on cross-border clinical trial access in the EU and frameworks on its implications. To this aim, two surveys will be distributed in parallel to clinical trial sites and to patient organisations with the purpose of identifying cases of discrimination. Moreover, a search will be performed in clinical databases to evaluate patient facing materials used in clinical trials such as patient reported outcome measures, quality-of-life questionnaires and scales to evaluate their adaptations to the local languages. Currently, the surveys are under development, with the input from focus groups in different countries, including ethics committee and patients' organisation members. It is expected that the surveys will be delivered during next year so that results are available by the end of 2023.

Following the presentation of the group's objectives a discussion ensued regarding potential issues that patients could face regarding the access to clinical trials and innovative medicines in cross-border settings, ranging from language difficulties, cultural differences, economic barriers such as insurance

coverage and differences in licensed products per country. This revealed the need to act in multiple areas, such as translations, sharing good clinical practices, promoting hybrid designs of trials, etc.

Presentation: WG on cross-border trials (B. Nafria)

WG on off-label evidence

The group has studied the off-label use of medicinal products in children and to promote the assessment of off-label evidence and if appropriate authorisation of paediatric indications by regulators.

A manuscript on this topic has been prepared and will be submitted for publication soon.

Moreover, the results of a research project by the team of the Dutch Paediatric Formulary about the medicines used in children per indication was presented. The analysis showed that only half of the products used across all indications are licensed for paediatric use, and only 14% of the cases of off-label use are supported by high quality studies, which implies a risk of therapy failure and toxicity.

The group is continuing to analyse the current situation to identify what data/evidence would need to be generated to supplement the already available off-label evidence for which products, in order to prioritise the actions and to continue supporting the efforts to include a high level of evidence data in the Summary of the Product Characteristics (SmPC).

Presentation: WG on off-label evidence (S. De Wildt)

Role of academic clinical trials in paediatric (cancer) drug approvals

Dominik Karres presented the work of the Accelerate initiative as an example of a multistakeholder working group which aims to promote innovation for medicines for children and adolescents with cancer. Historically the development of medicines in the paediatric oncology setting was reliant on off-label use and available data from academic trials. Medicine development in paediatric oncology sees less industry funding than in adult oncology and is often based on academia involvement. In order to enhance the collaboration between academia and industry for the acceleration of medicine approvals the Accelerate platform was created in 2013. A survey was launched to pharmaceutical industry and academia where differences were shown in terms of methodology for conducting clinical trials involving different aspects such as data collection, monitoring, oversight, risk management and data cleansing. Based on the data from the survey supplemented with case studies, a set of recommendations was published to improve this collaboration not only in the paediatric oncology area but also to improve the collaboration between academia and sponsors in other therapeutic areas. The recommendations included some general principles such as having an early planning and prospective collaboration, defining the type of trial and the nature of the collaboration and to continuously promote transparent communication; along with more specific recommendations on essential documents, data identification and capture, data management, trial resources having clear expectations and requirements and calling for early dialogues with regulators.

Moreover, a series of webinars will also serve to further discuss ways to improve the academia and industry collaboration to support clinical trials and medicine development in children.

Presentation: Role of academic clinical trials (D. Karres)

Afternoon session:

Health technology assessment (HTA) in childhood

Introduction to European HTA work and how HTA bodies and regulators cooperate under the HTA Regulation

Niklas Hedberg and Michael Berntgen introduced the current situation of HTA cooperation in Europe and activities at the HTA/regulatory interface. European collaboration on HTA started in 2005 with the initiation of the EUnetHTA (European Network for Health Technology Assessment) project, a network established to create an effective framework for HTA collaboration across Europe. EUnetHTA was financed through three consecutive joint actions with the goal of putting into practice a sustainable HTA collaboration, to strengthen the practical application of tools and approaches to cross-border HTA collaboration and to define and implement a sustainable model for scientific and technical cooperation on HTA in Europe. Learnings from this project have informed the development of the new HTA Regulation (Regulation (EU) 2021/2282), which did entry into force in January 2022 and will come into application in 2025.

EMA and EUnetHTA have been working closely on topics of mutual interest since 2010, increasing mutual understanding and building synergies. Joint activities are centred around three areas: identification of emerging health technologies, joint scientific consultation and joint clinical assessments. The value of such collaboration is being recognised in the new HTA Regulation. The implementation of this regulation is supported by activities under a joint EMA/EUnetHTA21 work plan which sets 9 priority areas, covering among others joint scientific consultation on evidence generation, exchange of information and continuous optimisation of regulatory outputs, methodologies for engagement of patients and health care professionals, and generation of patient relevant data.

The experience so far indicates that discussions across decision-makers and engagement with stakeholders are crucial to better guide on evidence requirements throughout the medicine's lifecycle. The new HTA Regulation will provide a sustainable framework for cooperation on HTA which will also facilitate this work with other decision makers.

Presentation: EU HTA (M. Berntgen, N. Hedberg)

Evidentiary challenges and novel approaches in paediatric HTA: perspectives from Canada

Avram Denburg introduced the challenges for HTA in the paediatric space and the efforts made to contextualise the value of new diagnostics, therapeutics and technologies, in terms of patients, health care providers and payers, based on evidence, economics and ethics.

The access to new medicines for the paediatric population faces a multitude of challenges by the health systems and HTA bodies that range from market dynamics and political environments, regulatory requirements for evidence generation, to socio-economic considerations, child and family utilities and other externalities. Together, these challenges lead to inequities in access to medicines for children, hampering the development of innovative therapies for children. Particularly important is the adaptation of HTA bodies to the assessment of new precision medicine and innovations in clinical trial designs.

It is considered that the definition of value in HTA assessment should be widened by taking into account the life course impact of paediatric diseases, and the different perspectives of experts like health care providers and payers, patients and the public. The implementation of the HTA Regulation in

the EU is seen as a unique opportunity to incorporate paediatric-specific evidentiary and value considerations.

Presentation: Evidentiary challenges (A. Denburg)

The current paediatric challenges in the EU and perspectives

Gilles Vassal explained the current challenges regarding access to paediatric medicines in the EU and the new perspectives based on initiatives that address access inequalities, such as the Pharmaceutical Strategy for Europe and the legal framework created by the revision of the Paediatric and Orphan Regulations and the upcoming HTA Regulation.

In paediatric oncology, specific challenges regarding access to innovative therapies exist due to the rarity of childhood cancers and the fact that the paediatric oncology community is not aware of HTA requirements.

An analysis of the delays in access to new paediatric cancer medicines was presented. based on three different products that had been approved for their use in the paediatric population. The selection was based on relevance, budget impact and timeline between the authorisation of the paediatric and adult indications. The HTA reports for these products of nine EU countries were studied, followed by a survey among the national haemato-oncology societies to enquire about the actual availability of these products for prescribing and the coverage of the costs in their country.

The results showed that there was high variability regarding the outcome and the timelines of HTA assessments and regarding the eventual access to these products in the different countries. Moreover, it was reported that the ACCELERATE platform for innovation for children and adolescents with cancer proposed a number of recommendations for paediatric products. These include the suggestion for early interactions between regulators and HTA bodies along with parallel evaluations to reduce timelines, the generation and integration of Real-World-Data, performing systematic joint clinical assessments, and the setting up of joint procurement and pricing negotiations as well as the obligation to launch authorized products in all member states.

In conclusion, it was stated that paediatric health technology assessment needs to be improved and that paediatric oncology could be considered as a regulatory science laboratory for piloting changes and innovation. Moreover, it was emphasized that international cooperation of HTA bodies is crucial.

Presentation: Enpr-EMA HTA (G. Vassal)

Panel discussion

The presentations were followed by a panel discussion based on questions by the audience. During the discussion, the benefits of an early interaction between EMA and HTA bodies were highlighted in terms of aligning the clinical programme to meet both regulatory and HTA requirements as early as possible to, considering that there is a legal framework that will support these interactions with the joint scientific consultation where paediatric specificities could be discussed.

Moreover, the definition of value in the paediatric population was further discussed. Specificities of the paediatric population, such as the life course impact of paediatric diseases and also the effect on families were considered important, and their consideration could innovate the way in which HTA bodies work in terms of the assessments of medicines for the paediatric population.

Additionally, some paediatric specific challenges were discussed such as the difficulties to value the potential benefit on life years gained in survival in the context of economic models, and the difficulties

to improve the access to age-appropriate formulations raising the issue of the need to provide reliable evidence and cost implications.

Clinical Trial Regulation:

Addressing pitfalls of the Clinical Trial Regulation

Anette Solli Karlsen gave an overview of the experiences and potential pitfalls of the application of the Clinical Trial Regulation (CTR), which has been in effect since January 2021.

Important benefits of the application of the CTR are a harmonised process for the joint assessment of clinical trial applications by National Competent Authorities (NCA) and ethics committees, and the possibility to submit a single clinical trial application to all Member States (MS), facilitating the expansion to other countries and the transparency of information. The applications are submitted via the Clinical Trials Information System (CTIS), and consist of Part I, assessed on a multinational level by NCAs and ethics committees (EC) and Part II assessed by ethics committees at a national level.

Some pitfalls and solutions regarding the submission of clinical trial applications were highlighted. Moreover, an overview of useful guidelines and training resources was presented.

The Regulation foresees a period of three years to transition from the previously applicable Clinical Trial Directive (CTD) to the new CTR. It was clarified that until January 2023, new clinical trial applications could be submitted under either legislation. Moreover, clinical trials previously approved under the CTD could continue under the requirements of this framework until January 2025. However, between January 2023 and January 2025 all non-completed trials should be transitioned to the CTR. The transition process could only be performed if there are no ongoing procedures for the particular clinical trial ongoing in any of the MS, and if there is a harmonised approved protocol for all MS concerned. Once transitioned, any further modifications should be submitted according to the CTR. Moreover, it was highlighted that also the CTR's requirements in terms of archiving, notifications and safety rules will apply. Furthermore, transparency rules will become applicable, which will lead to the making publicly available of trial related documents at the time of the submission of the marketing authorisation application. A redaction of the commercially confidential information is being foreseen as well as the possibility of requesting a deferral of such publication.

Presentation: Clinical Trials Regulation (A. Solli Karlsen)

A.O.B.:

Participants were informed about the following events of interest:

- 17th- 19th October 2022: EFGCP Better Medicines for Children Conference 2022.
- Consultation on the revision of the ICH GCP (R3) principles document.

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

Closed meeting for members and observer members of the Coordinating Group:

Election of chair of the Coordinating Group

Pirkko Lepola from the Finnish National network FINPEDMED was re-elected as chair of the Coordinating Group.

Organisational matters

Following the submission of new and updated self-assessment forms, the membership and category for the following networks was endorsed:

- NETSTAP (Network of National Paediatricians in Germany), new category (Cat 1)

- PEDSTART (French national paediatric research network), new category (Cat 1).

- ECAPN (European Child & Adolescent Psychopharmacology Network), new category (Cat 1)

- HELPNET (Greek national network), new Enpr-EMA member (Cat 2)

- JPeDNet (Japan Pediatric Society Drug Development Network), new category (Cat 3)

A.O.B.

The chair and co-chair proposed a review of the organisational aspects and the strategy of Enpr-EMA in order to strengthen the network's role in an environment that has changed considerably since the network's beginnings in 2008 and to make it most beneficial to its members as well as the PDCO. To this end, and also in order to reduce administrative aspects for members to the essential minimum it was suggested to initiate a discussion on Enpr-EMA's strategy and a revision of Enpr-EMA's documentation (e.g. self-assessment forms, mandate of the coordinating group) in 2023. The Coordinating Group members agreed that Enpr-EMA should be adapted to the changing environment. It is envisaged that the Coordinating Group will start on this initiative in Q1 2023.

For next year (2023) it was suggested to have an "open" workshop/annual meeting where also industry representatives could participate. Moreover, it was suggested to consider if Enpr-EMA could play a role in the set-up of multistakeholder meetings to discuss paediatric medical needs in different therapeutic areas, with the aim to anticipate and help the implementation of expected changes due to the European Commission's revision of the Paediatric and Orphan Regulations.

Speakers:

- Berntgen, Michael. European Medicines Agency
- Denburg, Avram. SickKids Research Institute and University of Toronto, Canada
- Dicks, Pamela. ScotCRN - Scottish Children's Research Network
- Egger, Gunter. Co-chair of Enrpr-EMA, European Medicines Agency
- Hedberg, Niklas. Dental and Pharmaceuticals Benefits Agency Sweden; EUnetHTA21
- Karres, Dominik. European Medicines Agency

- Lacaze, Thierry. MICYRN (Maternal Infant Child and Youth Research Network, Canada)
- Lepola, Pirkko. Chair of Enpr-EMA, FINPEDMED (Finnish paediatric research network)
- Nafria, Begonya. eYPAGnet - European Young Persons Advisory Groups Network
- Solli Karlsen, Anette. Norwegian Medicines Agency; Paediatric Committee
- Vassal, Gilles. ITCC - Innovative Therapies for Children with Cancer
- Wildt, Saskia de. Pedmed-NL - Medicines for Children Research Network Netherlands