Report from the 2019 annual face-to-face meeting of Enpr-EMA members and the Enpr-EMA Coordinating Group

14 October 2019

In 2019 the annual face-to-face meeting of Enpr-EMA was held as a meeting of the Coordinating Group (CG) and Enpr-EMA members rather than a wider workshop, considering the Agency's business continuity related to the relocation. The meeting saw the election of a new chair of Enpr-EMA's CG and focused on the network's role in the light of a changing research environment.

Session 1 - Update on activities

Chairpersons: Mark Turner / Gunter Egger

Report from the Coordinating Group

Mark Turner, the outgoing chair of the Enpr-EMA CG, summarised the activities of Enpr-EMA. Mark highlighted that Enpr-EMA was driven by the needs and contributions of multiple stakeholders, and it serves as platform for discussion that can identify and address needs, engage multiple stakeholders and different perspectives. He also pointed out the challenges of agreeing, specifying and delivering on concrete tasks within an agreed timeframe.

Presentation: *Update on Enpr-EMA activities, achievements and challenges (M.Turner)*

Report from the working groups

An overview of the activities of Enpr-EMA's working groups (WG) and their achievements was provided.

Working group on public-private partnership

The aim of this group is to facilitate communication between medicine developers and networks in order to enhance collaboration on paediatric trials.

The group had published the results of a survey among networks and pharmaceutical companies: 'Pharmaceutical Industry and Paediatric Clinical Trials networks in Europe- how do they communicate?'

As a follow-up action, the group had developed a guidance document for network consultation, 'network consultation recommendation', which was published on the Enpr-EMA website, outlining the recommended model for consulting paediatric research networks, particularly on developing and conducting paediatric investigation plans (PIPs).

The action to conduct a pilot with interested companies was no longer deemed necessary as the companies previously interested in such a pilot were partners of the IMI2 consortium conect4children (c4c) and therefore receive similar services via the consortium. For all other companies the network consultation recommendations were public and ready to use.

In conclusion, all tasks of this WG had been completed and it was agreed to close it. All WG participants were thanked for their efforts.

Presentation: *WG on public-private partnership (P. Lepola)*

Working group on ethics

The aim of this group is to develop pragmatic responses to ethical issues in the context of paediatric trials and to disseminate examples of good practice among ethic committees.

The original plan to develop a harmonised Informed Consent / Assent template for use across EU countries had been changed as it was not deemed feasible. Instead, a Guidance Document related to Consent / Assent information had been developed, including input and recommendations from the European Young People Advisory Groups network (eYAGnet). This document is in the process of being finalised and will be published on the Enpr-EMA website. In addition, a manuscript for a scientific journal has been prepared and is planned to be submitted for publication by the end of 2019.

Similarly to the previous deliverable of the WG, a tool kit and comprehensive multinational overview on informed consent and assent requirements for paediatric clinical trials in Europe that is published on the Enpr-EMA website, the planned guidance document would also be a living document, to be updated as necessary. In this context all Enpr-EMA network members and stakeholders were reminded to inform the Enpr-EMA Secretariat about necessary updates to the published overview on informed consent and assent requirements.

In addition, it was reported that, building on the recently initiated collaboration with the European Network of Research Ethics Committees (EUREC), Pirkko Lepola had presented Enpr-EMA and the work of the ethics WG at the European Network of Research Ethics and Research Integrity (ENERI) Boot Camp in March 2019. Further collaboration between Enpr-EMA and EUREC is planned in order to exchange views on important issues to consider in the assessment of paediatric trials.

Presentation: *WG on ethics (P. Lepola)*

Working group on young persons advisory groups

The aim of this group is to establish a European network of young persons advisory groups (YPAGs) in order to give young persons/patients and their families a voice in the setting up and organisation of clinical research, respect their needs and improve the acceptability and understanding of trials. Building on the work of this WG, the European Young People Advisory Group network (eYPAGnet) had been established and became a Category 4 member of Enpr-EMA in 2018. The network had substantially grown with 9 new YPAGs established in 8 European countries.

Recent activities included the implementation of standard operating procedures for financial management, membership and communications, the launch of a website (www.eypagnet.eu), and the establishment of an advisory board, that had its first meeting in May 2019. The network had already

received several requests from developers to review informed assent templates and study protocols. Other activities included YPAG involvement in c4c activities, contributions to the work of other Enpr-EMA WGs (on ethics, trial preparedness, and parents & patients), one book chapter in "Ethics of research involving minors" and several scientific publications.

During the discussion it was recommended that eYPAGnet should reach out to coordinators of European Reference Networks (ERNs) and to patient organisations to raise awareness on eYPAGnet and to increase their reach among patients. Moreover, it was decided that eYPAGnet would share expertise and collaborate with the WG on parents and patients.

WG participants were thanked for their efforts and congratulated on the establishment of eYPAGnet. As eYPAGnet had been successfully established and was operational as a member network of Enpr-EMA it was decided that this WG should be closed because its objective had been fulfilled.

Presentation: *Young persons advisory groups (P. Dicks)*

Working group on parents and patients

This WG was established in 2019 with the aim to provide Enpr-EMA with the patients' perspective and to act as a consultative platform for topics such as patient involvement, data sharing, and multi-stakeholder collaboration.

A core group/steering committee was set up involving patient representatives and regulators from the EMA Committees and the Patient-Consumer Working Party (PCWP) with experience in regulatory activities and medicines development in the paediatric population. Expansion of the WG to include further patient representatives, and collaboration with eYPAGnet is planned. The group had identified inefficient use of research data and lack of interoperability of data as major hurdles to efficient clinical research in children. As the group's first task it was agreed to map and assess data collection practices in paediatric research networks and to develop a guidance document to facilitate data sharing in paediatric clinical research, taking into account the FAIR Guiding Principles for scientific data management.

Presentation: *WG on parents and patients (D. Athanasiou)*

Working group on research staff

The aim of this group is to identify needs related to training for paediatric clinical research nurses across EU Member States. The group reached out to key European research nurse networks and carried out a questionnaire-based study to learn about the roles and training needs of paediatric research nurses. Following previous publication of the results of the survey in BMJ Paediatric Open (https://bmjpaedsopen.bmj.com/content/1/1/e000170), the data were also presented on behalf of EnprEMA at the STTI (Sigma Theta Tau International Honor Society of Nursing) European nurses conference. Information on paediatric research nurse networks and groups was published on the Enpr-EMA website: Table of European Paediatric Research Nurse Networks and Groups.

In carrying out the study the WG found that research nurses would benefit from enhancing connections. Consequently, the WG managed to bring together European network by identifying key research nurse groups in paediatrics across Europe. A total of 40 groups / clinical centres expressed an interest in working with Enpr-EMA.

It was agreed that a research nurse group under the umbrella of Enpr-EMA could provide a useful central resource for sharing information between interested parties at a European level.

In February 2019 the inaugural teleconference of an Enpr-EMA research nurse group with nurses from more than 10 European countries was held. Three topics of mutual interest were identified:

- Training needs and access to training resources across Europe
- Standardisation of research nurse practices across Europe
- Investigation into cultural differences in the role of the research nurse across Europe

Moreover, it was agreed that awareness about Enpr-EMA and its initiatives needed to be raised among research nurses. Another difficulty identified was that in some European countries dedicated associations for research nurses did not exist. The group will work on providing potential solutions for these issues.

Due to other commitments Gareth Veal had to step down as the lead of this WG. Vincent O'Mahony from the Irish Paediatric Clinical Research Network volunteered to take over, with the support of the lead research nurse of the Scottish Children's Research Network and the TEDDY network.

Presentation: *WG on educational training for research staff (G. Veal)*

Working group on clinical trial preparedness

The aim of this group is to create a guidance document on trial preparedness and increase the ability to complete high quality clinical trials in a timely manner.

The WG achieved the following action points:

- Revision of the current regulatory guidance and literature, capturing trial preparedness factors and proposed solutions as well as collecting information on past initiatives related to this topic;
- Analysis of a written survey and interviews with relevant stakeholders (industry, CROs, patients/parents; health care professionals, regulators) on good practice and lessons learned to build on experience already made in order to identify the main barriers in paediatric clinic trial characteristics leading to delays, or impairment of study feasibility;
- Preparedness guidance document published on Enpr-EMA website for consultation until 15 November 2019 in order to solicit additional feedback from stakeholders.

The next steps will be to summarise and incorporate feedback received during the consultation period into a final document which will be published on Enpr-EMA website and submission of a manuscript for publication in a scientific journal.

Working group on international collaboration

This WG was established in 2019 with the aim to identify, understand, and possibly address cross-jurisdiction challenges in the conduct of paediatric clinical trials in order to boost international collaboration.

Representatives from regulatory authorities and national networks from the following five regions are part of this WG: USA, Europe, Canada, Australia and Japan.

The WG agreed as their first task to do an environmental scan

- comparing the regulatory and ethics requirements for paediatric clinical trials, as well as submission and review processes in the five regions

- in order to assist investigators and industry involved in conducting these studies and to identify regulatory challenges in conducting these trials on an international scale.

A survey based environmental scan was developed to be answered by both the regulators and the networks. This survey is ongoing.

The next steps will be to compile and summarise data in a manuscript and submission for publication in a scientific journal.

Presentation: *WG on international collaboration (T. Lacaze)*

Election of chair of the Coordinating Group

Pirkko Lepola from the Finnish National network FINPEDMED was elected as the new chair of the CG.

Enpr-EMA thanked the outgoing chair, Mark Turner, for his invaluable input and contributions to the work of Enpr-EMA.

News article: European Network of Paediatric Research at EMA elects new chair

Session 2 - Future activities:

Chairpersons: Pirkko Lepola / Gunter Egger

Enpr-EMA's place in a changing environment - networks' views

Building on the discussions following the presentation on the activities of the WG on public-private partnership, the need for oversight of the numerous currently ongoing paediatric research initiatives was expressed, such as

- interactions between conect4children (c4c) and Enpr-EMA,
- the European Joint Programme on Rare Diseases (EJP RD) which includes several work packages (WP), e.g. WP 19 (facilitating partnerships and accelerating translation) and WP 20 (validation, use and development of innovative methodologies for clinical studies), http://www.ejprarediseases.org/index.php/about/
- other initiatives (summarised in Mark Turner's presentation "Overview of European paediatric research infrastructures and initiatives" – see below).

It was highlighted by Enpr-EMA members that c4c activities were currently limited to the scope of the IMI2 consortium partners and defined tasks, whereas major groups were not served by c4c (e.g. biotech companies, other disciplines). Therefore, Enpr-EMA's role was considered important to ensure that all groups have access to support and advice from relevant networks.

It was agreed to establish a new WG addressing the need for oversight of the various ongoing paediatric research activities. Several Enpr-EMA members volunteered to become members of this new WG, to be chaired by Pirkko Lepola.

Enpr-EMA's role should be to facilitate communication between different initiatives/organisations in order to identify synergies, avoid duplication and maximise the output.

In addition, it was suggested by members that Enpr-EMA may contribute to the ongoing discussions regarding the EU Regulations on orphan medicinal products and paediatric medicines, as appropriate.

It was agreed to discuss this topic at a CG meeting once the next steps for the review have become available.

Enpr-EMA's place in a changing environment - feedback from the Coordinating Group

At the CG meeting in July 2019, members were asked for suggestions concerning Enpr-EMA's role in fostering paediatric research, driving research agendas, as well as identifying needs and gaps. The following proposals from that meeting were presented:

Advanced Therapy Medicinal Products (ATMPs)

It was noted that beside guidelines on manufacturing processes there were several topics which need to be considered to ensure correct practice with cell-based products. Some open issues, especially relevant for children who might be treated at a very young age and might benefit from repeated therapies for a long period of time, were highlighted:

- Who is the owner of autologous cells/tissue?
- Who determines the expiration date of un-manipulated cells/tissue, and of modified products?
- Who is responsible for long-term preservation/storage (e.g. who determines possibility to use cells/tissues which were stored for other purposes, e.g. cord blood cells usually collected for un-manipulated stem cell transplantation).

The ensuing discussion focused on what Enpr-EMA could contribute to these complex, legal issues from researcher's perspective, which need to be addressed together with other stakeholders.

It was suggested that Enpr-EMA's role could be to raise awareness among academia and other relevant stakeholders.

Opportunities for European patients in global programmes

The representative of the European Cystic Fibrosis Society (ECFS-CTN) raised the question whether European patients had equivalent access to clinical trial opportunities as other patients globally. A survey had been circulated among Enpr-EMA network members to explore their views on this topic. The responses received from 6 networks were presented.

It was concluded that the fact that only 6 networks had replied to the survey might indicate that this problem observed in the field of cystic fibrosis is not a general problem but disease specific. It was agreed to resend the survey to collect more feedback and to decide only afterwards whether this topic should be followed up by Enpr-EMA.

The discussion extended from access of European children to clinical trials to access to medicines, which differs from one country to another depending on national reimbursement and pricing systems. While differences in access to medicines via clinical trials across European countries were acknowledged as an important issue, it was agreed that Enpr-EMA's role in addressing it was limited and may be limited to raising awareness with a unified European voice.

Presentation: *Opportunities for European patients in global programmes (T. Lee)*

Cohesion in the conduct of clinical trials among Member States

Luca Sangiorgi, the representative of European Reference Networks (ERN) within Enpr-EMA, presented survey feedback from ERNs regarding what they considered to be the main barriers to cohesion of clinical trials among European countries: different regulatory and ethical frameworks, differences in data management, cost evaluation, management of biosamples and informed consent were the most frequently mentioned barriers.

It was pointed out that several ongoing or already completed initiatives attempted to address these hurdles, such as the EJP RD, c4c, collaboration with EUREC to raise awareness on paediatric specific issues.

Presentation: *Cohesion in the conduct of clinical trials among Member States (L.Sangiorgi)*

Update of labelling information based on evidence other than clinical trials

Members highlighted that for several medicines, even if not authorised for use in children, there was evidence of safe and efficacious use from clinical practice in paediatrics. Frequently, some data have been generated which either are not reflected in the labelling or are reflected differently across countries/regions. Most of these medicines are no longer covered by a patent and it is generally known that the related approaches from the Paediatric Regulation (e.g. PUMA) were rarely successful in this space. Moreover, frequently a paediatric indication for these medicines is not of commercial interest for marketing authorisation holders; consequently, they would not use existing or generate new data voluntarily to obtain such an indication. Therefore, the aim would be to encourage companies to include 'best available' evidence, including practice experience in the labelling of medicines.

The discussion centered on the question how to best "safe-guard" off-label use without promoting it. Members were informed about the European Commission Expert Group on Safe and Timely Access to Medicines for Patients ("STAMP") and its recent discussion on repurposing of established medicines/active substances (https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp_11_47_1_en.pdf). Moreover, it was mentioned that a lot of information on this topic had been collected by existing initiatives, such as the British or Dutch National Formulary for Children.

Some members expressed their interest to explore whether and how Enpr-EMA could contribute to this topic.

Presentation: *Labelling information (S. de Wildt)*

Multi-Regional Clinical Trials (MRCT) Center

Barbara Bierer, Faculty Director of the Multi-Regional Clinical Trials Center of Bigham and Women's Hospital and Harvard (MRCT Center), presented the MRCT Center and its recent initiative on promoting global clinical research in children.

It was explained that the MRCT Center was a non-profit research and policy centre focusing on addressing the conduct, oversight, ethics and regulatory environment for clinical trials. It was clarified that the centre does not conduct clinical trials but acts as a platform for those who are involved, including patients, regulators, governments, academia, etc. on an international level. The MRCT Center chooses topics where practical solutions to identified problems can be envisaged and finalises its projects by publishing position papers and recommendations. Regarding the paediatric research project, the intention was not necessarily to change legislations, but to improve paediatric research in existing legislative frameworks. The following activities were planned:

- **Legal landscape analysis:** to understand and assess the current global landscape of paediatric research regulations, with a focus on illuminating legislative and regulatory gaps and inconsistencies
- **Ethical guidance analysis:** to identify and characterise existing ethical considerations broadly and in a geographic/culturally specific manner
- **Connecting with organisations with overlapping remit or activities:** iACT for Children, Enpr-EMA, iCAN, others
- **Background review of legislative 'incentives' for pediatric studies**

The paediatric project of the MRCT Center had only recently started; the topics and their scope were being discussed by the Steering Committee. Once more details become available, further discussions with Enpr-EMA would be held to explore synergies and avoid duplication of work already done by Enpr-EMA WGs (e.g. by the WGs on public-private partnership, on ethics and on international collaboration).

Overview of European paediatric research infrastructures and initiatives

Mark Turner provided an overview of European paediatric research initiatives and groups, each with expertise in certain areas and focusing on specific topics, shaped by its sponsors and/or topic leads. It was highlighted that Enpr-EMA had a unique position to facilitate communication among the various groups and the sharing of expertise due to its legal basis in the EU Paediatric Regulation and clearly defined objective to build up the necessary scientific and administrative competences at European level, and to avoid unnecessary duplication of studies and testing in the paediatric population.

Presentation: *European research landscape (M. Turner)*

Session 3 - Organisational matters

The CG endorsed three applications for Enpr-EMA membership (all Category 3 networks):

- conect4children (c4c)
- Severe Paediatric Asthma Collaborative in Europe (SPACE)
- Stand4Kids (Supporting Paediatric Trials in Portugal)

Moreover, a new member of the CG was endorsed:

- European Network of Excellence for Paediatric Clinical Research (TEDDY)

The next CG teleconference together with all Enpr-EMA networks will be scheduled for early 2020.

Update from EMA

The members were informed about two upcoming meetings of potential interest:

- EFPIA & EFGCP Multi-Stakeholder Workshop on Paediatric Unmet Medical Needs, on 12 December 2019 in Amsterdam, the Netherlands
- DIA & EUCOPE Workshop on ATMPs, on 29 & 30 October in Basel, Switzerland

Conclusions and next steps

The chair summarised the agreed actions and next steps and thanked all participants for their contributions.

1. Agreed actions for existing WGs:

WG on public-private partnership:

- Close WG

WG on ethics:

- Finalise guidance document related to Consent / Assent information and publish it on Enpr-EMA website (by Q1/2020)
- Submit manuscript on the same topic for publication in a scientific journal (by Q2/2020)

WG on young persons advisory groups:

- Close WG

WG on parents and patients:

- Draft a survey among networks to evaluate the current situation on data management, including patient access to the data and involvement in decision making (by Q2/2020)
- Prepare report based on survey results for publication on Enpr-EMA website (by Q3/2020)
- Develop guidance document to facilitate data sharing in paediatric clinical research (by Q4/2020)

WG on research staff:

- Train and inform research nurses about Enpr-EMA and its initiatives
- Reach out to countries without dedicated research nurses

WG on clinical trial preparedness:

- Incorporate feedback received during the consultation period into a final document for publication on Enpr-EMA website (by Q2/2020)
- Submit manuscript on the same topic for publication in a scientific journal (by Q3/2020)

WG on international collaboration:

- Compile and summarise responses of the survey, prepare manuscript for publication in a scientific journal (by Q3/2020)
- Reach out to MRCT Center to explore synergies and avoid duplication of work already done (by Q2/2020)

2. Other agreed actions:

European paediatric research landscape & cohesion of clinical trials among Member States:

- Establish a new WG to develop how dialogue and exchange of across European paediatric research activities can be supported by Enpr-EMA as platform

Evaluation of EU Regulations on orphan and paediatric medicines:

- Follow-up on a potential contribution by Enpr-EMA to the evaluation of the EU Regulations on orphan medicinal products and paediatric medicines

Advanced Therapy Medicinal Products (ATMPs)

- Develop proposal how Enpr-EMA could best contribute to raising awareness (among healthcare professionals, regulators, other stakeholders) on the complex issues related to cell therapy products

Opportunities for European patients in global programmes

- Resend survey on "Opportunities for European patients in global programmes" to all Enpr-EMA networks before deciding on any further actions

Paediatric information in labelling:

- Explore whether and how Enpr-EMA could contribute to increasing paediatric information in labelling, including reaching out to existing initiatives

Network members have been identified for all actions to ensure follow-up.