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Report of the tenth annual workshop (2018) of the European Network of Paediatric Research at the EMA (Enpr-EMA)

7 June 2018

Chairpersons: Mark Turner / Irmgard Eichler

Introduction

The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) held its 10th annual workshop on 11 June 2018 at the premises of the European Medicines Agency (EMA) in London, UK.

Enpr-EMA is a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children, with the aim to foster high-quality ethical research in children, providing expertise and support regarding quality, safety and efficacy of medicines to be used in children. The main objective of the annual workshop is to foster interaction and communication between all stakeholders: networks' representatives, pharmaceutical industry, regulators and patient/parent organisations.

This year's workshop marked the 10th anniversary of the network. The opening addresses by Enrica Alteri, Head of the Human Medicines Research & Development Support Division of the EMA, and by Mark Turner, Chair of Enpr-EMA, highlighted the successes of Enpr-EMA. In the ten years Enpr-EMA has grown substantially and includes now 46 network members, with new specialty networks in therapeutic areas where none existed 10 years ago and has expanded beyond Europe with networks from US, Canada and Japan.

The development of and access to authorised medicines for children requires input from various groups, including industry, academia, learned societies, networks, the newly established European Reference Networks, patient and young person advocates, regulators, HTA bodies. To bundle resources most efficiently, close communication and collaboration among those various groups is essential. This year's Enpr-EMA workshop brought together all stakeholders to discuss a holistic approach to paediatric research and how to best link together the various existing initiatives and stakeholders, to optimise the development and access to better medicines for children, while avoiding duplication and wasting resources.

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Session 1

Report from the coordinating group (CG): Update on Enpr-EMA activities, achievements and challenges.

The following achievements of Enpr-EMA and benefits it can offer to industry where highlighted:

- Expert advice on standard of care, identification of unmet needs and advice on the feasibility of clinical trials.
- Speeding up of recruitment through better access to patients.
- Platform for multi-stakeholder meetings.
- European voice in terms of raising awareness of challenges and difficulties related to paediatric trials.
- Identification of solutions.

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

Session 2

Update on Enpr-EMA Working Groups

An overview of the activities of Enpr-EMA's working groups and their achievements was provided. The working groups' activities are driven by needs and contributions of multiple stakeholders and pursue concrete outcomes.

Working group on Good Clinical Practice (GCP) training

The main task of the group is to identify models, gaps and needs related to training for paediatric clinical research nurses across different EU Member States.

The outcome of a questionnaire based survey across Europe was presented..

Some relevant points for discussion were identified such as the impact of self-funded courses in some countries, the low number of nurses taking patient consent and the different roles of research nurses across countries.

The results of the survey was published in BMJ Paediatric Open (https://bmjpaedsopen.bmj.com/content/1/1/e000170). About 40 European paediatric research nurse networks and groups expressed an interest in working with Enpr-EMA, considering it as a central resource where to find and share information.

Information on paediatric research nurse networks and groups was published on the Enpr-EMA website: Table of European Paediatric Research Nurse Networks and Groups.

Facilitation of connection between the various groups and networks will be the next action point.

Presentation - Working group 6: educational training of research staff involved in paediatric clinical trials / GCP training across multispecialty and countries (G. Veal)

Working group on ethics

The role of the group is to develop pragmatic responses and develop proposals to disseminate examples of good practice to ethic committees.

The original plan, i.e. to develop a harmonised Informed Consent / Assent form across all EU countries, was changed as it was not possible to do so for all EU countries and for all age groups. Instead, Consent / Assent information as a Guidance Document was developed, including input and recommendations from the European Young People Advisory Groups network (eYAGnet). This document will be published on the Enpr-EMA website by Q2 2019). The usefulness and functionality of the tool "Readability Scoring" function has been evaluated. The result was that it could be used together with the feedback of children and young people, but should not be used by itself.

In addition, a new collaboration has been initiated with EUREC, the European Network of Research Ethics Committees.

During the following discussion, the importance of collaborating with National Competent Authorities (NCAs) was highlighted.

Presentation - Working group 4: Dialogue and interaction with ethics committees (P. Lepola)

Working Group on Young Persons Advisory Groups

The role of the group is to include young people and their families in the set up and organisation of clinical research. The group aims to give young patients a voice, respect their needs and improve the acceptability and understanding of trials.

Young persons' advisory groups are children and adolescents from 11 to 18 years of age with an interest on health research and who have received training on multiple disciplines related to clinical research. Among others they comment, for example, on the design of clinical trials and language used in consent/assent forms and study protocols to make them better understandable for young people,. As paediatric clinical trials are usually international, a common collaborating environment at European level is important to promote research, share tools and educational materials and support new initiatives. In 2017 a European Young People Advisory Group network (eYPAGnet) was established.The group's activities include:

- A strategy paper where standard operating procedures are described has been written and is planned to be published on the networks' website.
- Membership procedures with an application process planned to be opened in July 2018.
- Development of a website, planned to be launched in July 2018.
- Development of a standardised common curriculum to train Young People Groups around Europe.
- Publicity work and organisation of meetings at national, European and international level.
- Development of a business model for sustainability (work in progress).

The network has a single point of contact coordinating all queries and activities at European level. The services provided range from pre-marketing to post-marketing activities.

Presentation - Working group : young persons advisory groups (P. Dicks, B. Nafria, S. Gaillard)

Working Group on clinical trial preparedness

The aim of this working 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 group promotes the dialogue among the different parties conducting clinical trials and develops preparedness orientated strategic guidance.

The group has achieved the following action points:

- Revision of the current regulatory guidance and literature, creating a spreadsheet capturing all trial preparedness factors and proposed solutions;
- Collection and list of other past or ongoing initiatives related to this topic;
- Analysis of a survey and 13 interviews with all 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;
- Draft of preparedness guidance document planned to be finalised by December 2018.

Presentation - Enpr-EMA work group on clinical trial preparedness (A. Siapkara)

Working Group on public-private partnership

The role of this working group is to facilitate the communication between industry and networks.

The group has 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 has finalised a guidance document for network consultation to be published on the Enpr-EMA website. The document includes four points: for network/industry communication in relation to the PIP process:

- Scoping / exploration;
- Doability / targeting;
- Feasibility / implementing;
- Reporting / safety follow-up.

Presentation - Working group: Public-private partnership (S. Tansey)

Update on networks:

As every year a few networks were invited to present their network and its activities.

European networks

Task-force in Europe for Drug Development for the Young (TEDDY) and European Paediatric Translational Research Infrastructure (EPTRI)

TEDDY is an independent multidisciplinary network that aims to facilitate the performance of good quality paediatric studies and research. It encompasses 50 partners from 21 EU and non-EU countries.

EPTRI is a framework for a new translational paediatric research infrastructure conceptual design.

Presentation - TEDDY network (D. Bonifazi and A. Ceci)

European Child & Adolescent Psychopharmacology Network (ECAPN)

The aim of ECAPN is to foster, facilitate, and conduct high-quality translational and clinical research in the field of child and adolescent psychopharmacology. The members include mainly European networks and some non-European ones.

Presentation - European child and adolescent psychopharmacology network (ECAPN) (A. Zuddas)

European Academy of Paediatrics Research in Ambulatory Settings Network (EAPRASnet)

EAP was stablished in 2009 and it is the paediatric section of UEMS (Union Européenne des Médecines Specialistes).

EAPRASnet aims to promote the health of children and young people in Europe. Its mission is to improve the standards in training, service and research and to represent the professional interests of paediatricians in the EU.

Presentation - European Academy of paediatrics research in ambulatory settings network (EAPRASnet) (A. Hadjipanayis)

Central European Paediatric Oncology Early Trial Alliance (CEPOETA)

CEPOETA is a non-profit organization that supports clinical research in pediatric oncology, focusing on innovative clinical trials for children and young adults. It provides an international framework of experts and provides access to new innovative drugs. Currently, it includes representatives in the Czech Republic, Slovakia, Slovenia, Hungary, Romania, Macedonia, Bulgaria and Serbia.

Presentation - Central European Pediatric Oncology Early Trial Alliance (CEPOETA) (R. Demlova)

North American networks

Duke Clinical Research Institute

Duke Clinical Research Institute's mission is to develop and share knowledge that improves the care of patients around the world through innovative clinical research.

Its research includes five main areas: Clinical pharmacology, pharmacometrics, safety and ethics, devices and mentorship.

Presentation - Pediatric trials network: Duke Clinical Research Institute (C. Hornik)

Institute for Advance Clinical Trials (I-ACT for Children)

The mission of this group is to serve as a neutral and independent organisation on behalf of children, bringing a dedicated voice to the advancement of new medicines and devices. The priority areas of work include achieving a common scientific approach between the U.S. and other jurisdictions, developing patient-centred products, leveraging innovation and developing shared tools among others.

Presentation - Partnering to optimize and accelerate pediatric clinical trials (C. Hovinga)

Update on implementation of the CTR (Clinical Trial Regulation)

Several conventions and guidelines have been taken into account in order to stablish a common regulation across Europe. Four general principles have been established:

- Beneficence;
- Non-maleficence;
- Respect for the individual;
- Justice.

The key points of the Clinical Trial Regulation for clinical studies on efficacy and safety of medicinal products include:

- National decisions - one decision per Member State;
- Strict timelines;
- Similar procedure if the trial is performed in one or several Member States;
- No distinction between rules for non-commercial and commercial research.

A new trial category is defined in the regulation: low-intervention clinical trials. Low-intervention clinical trials are trials which include authorised medicinal products which are used according to the terms of the marketing authorisation. Otherwise, their use must be supported by published scientific evidence on safety and efficacy.

There will be a common portal (EU Portal) which will be managed by EMA. All applications will be submitted to this EU Portal, avoiding separate submissions to Ethics Committees or National Competent Authorities. All entries will be publicly accessible (expect for e.g. personal data, commercially confidential information). The sponsors' documents and assessment reports by Member States will be public.

The new legislation will apply when the EU Portal will be fully functional. It will facilitate paediatric clinical trials through:

- Single application for multinational trials;
- Better defined timelines for assessment and decisions;
- Possibility of multiple co-sponsors;
- Possibility of deferring informed consent in emergency cases;
- Simplified procedures for low-intervention clinical trials;
- Simplified safety reporting for low-intervention trials (SUSAR reporting tool);
- Transparency of results.

Presentation - Update on implementation of the clinical trial regulation (A. M. Janson Lang)

Session 3

Holistic approach to paediatric research – perspective of various stakeholders

The need for collaboration between all stakeholders as well as for a more holistic approach to development of medicines for children was highlighted. This holistic approach could be built by identifying each stakeholder's function, developing ways to link stakeholders and targeting real-world problems once links are working. This would lead to increased collaboration and continuous improvement.

The perspective / functions of the various stakeholders were presented during this session.

Presentation - Holistic approach to paediatric research: introduction (M.Turner)

Young people advisory and patient groups

Being involved in discussions about one's healthcare and receiving information to be able to do this is a patient's right. These groups aim to give young people a voice and to enable them to get involved. The groups have:

- Identified points for improvement: assent and consent materials are too long, complex and technical to be understood by young patients.
- Developed guidance and tools to involve patients: evaluating multimedia information resources to improve engagement of children, adolescents and their parents with trials (TRECA study) or Wong-Baker FACES® Pain Rating Scale.

Presentation - Holistic approach to paediatric research: young people and patient involvement (J. Preston)

Industry perspective

Timely completion of paediatric development programmes remains a challenge. The following challenges have been identified:

- Selection of the right scientific approach to address paediatric needs;
- Limited available data at the time of PIP agreement;
- Alignment with different stakeholders;
- Practical issues to conduct paediatric clinical trials;
- Competitive clinical trials, especially in rare diseases.

Proposal for improvement are:

- Establish early dialogue with different stakeholders.
- Ensure scientific global alignment (selection of indication, population and endpoints), by, for example, expanding Enpr-EMA beyond Europe.
- Improve trial preparedness.
- Increase innovative approaches (e.g. extrapolation, higher EnprEMA-industry collaboration).

Presentation - Holistic approach to paediatric research: industry perspective (T. Tillmann, L.R. Arfelt, M. Dehlinger-Kremer)

Paediatric Clinical Trial Networks

The perspective of Paediatric Clinical Trial Networks was presented by PRINTO (The Paediatric Rheumatology International Trials Organization).

Improvements of paediatric treatment options in the area of rheumatology 10 years after the implementation of the Paediatric Regulation were highlighted as well as main difficulties, including too many studies for too few patients, or the ethical concerns of drug provision after completion of the trials.

PRINTO proposed:

- Early and repeated interaction with academia;
- Pre-PIP involvement of health professionals and families with clinical expertise;
- Continuous collaboration of networks with industry from PIP development to trial implementation;
- Facilitation of interaction through Enpr-EMA.

Presentation - Holistic approach to paediatric research: paediatric clinical trialnetworks (N. Ruperto)

European Reference Networks (ERN)

ERNs are virtual networks involving healthcare providers across Europe. They aim to facilitate discussions on complex or rare diseases and conditions that require highly specialised treatment, and concentrated knowledge and resources.

The first ERNs were launched in March 2017, involving more than 900 highly-specialised healthcare units from over 300 hospitals in 26 EU countries. 24 networks are working on a range of thematic issues including bone disorders, childhood cancer and immunodeficiency.

To ensure close collaboration with existing paediatric trial networks and research organisations Luca Sangiorgi was appointed to represent ERNs within Enpr-EMA.

Presentation - Holistic approach to paediatric research: European Reference Network (L. Sangiorgi)

European Society for Paediatric Research (ESPR)

ESPR works in six sections covering the key research topics in neonatology and beyond.

The mission of the ESPR is to boost scientific excellence and encourage collaboration between different specialised fields of paediatrics, maintaining paediatrics as a unified science-orientated discipline, promoting research and setting standards.

Key activities include annual large-scale research grant programmes for ESPR members, mentoring programmes bringing together senior researchers and aspiring young professionals, online training and education with world-wide participation and co-organisation of annual international congresses.

Presentation - Holistic approach to paediatric research: European society for paediatric research (K. Allegaert)

Regulators

Workshop participants were informed about the outcome of the multi-stakeholder meeting to discuss an action plan to improve the implementation of the Paediatric Regulation, which was held at the EMA in March 2018.

This meeting, organised by the EMA and the European Commission, followed the publication of the Commission's ten-year report on implementation of the Paediatric Regulation. The meeting explored opportunities regarding paediatric medical needs, timely completion of paediatric investigation plans (PIP), and processes and expectations for handling PIP applications. This workshop was a crucial step for the development of an action plan to address challenges identified with medicine development for children in Europe, which is planned to be published by mid-2018. With more than 160 participants representing all main stakeholder groups, a wide range of perspectives was heard and the breadth of the proposals for concrete actions was reflective of this wide-ranging input.

Presentation - Holistic approach to paediatric research: regulators (G. Egger, R. Bax)

Clinical Trial Facilitation Group (CTFG)

CTFG is open for exchange related to paediatric trials between PDCO delegates and assessors from clinical trial units of National Competent Authorities and colleagues from Ethics Committees.

CTFG plans future EU training workshops for paediatric clinical assessors from national competent authorities and ethics committees promoting the exchange of ideas on scientific and ethical aspects of paediatric clinical trials and harmonisation within the EU.

A training workshop for Paediatric Clinical trial assessors is planned for Q2 2019.

Presentation - Holistic approach to paediatric research: clinical trial facilitation group (A.M. Janson Lang)

Health technology assessment bodies

Health Technology Assessment (HTA) in Europe consists of systematic evaluation and assessment of the properties and effects of health technology to enable evidence-based decision making to ensure cost-effectiveness in medicine.

The European Network of Health Technology Assessment bodies (EUnetHTA) is a network of government appointed organisations (from more than 30 countries) and a large number of relevant regional agencies and non-for-profit organisations that produce or contribute to HTA in Europe.

It was reported that, at present, the experience with assessment of paediatric medicines was very limited.

Suggestions for the future were as follows:

- Define common minimum evidence needs for benefit assessment by European HTA bodies.
- Strengthen EMA-EUnetHTA collaboration and understanding of the respective evidence needs in order to allow developers to generate evidence able to address both regulatory and HTA information needs.
- Increase awareness of the specificities and possible limitations of evidence generation in paediatric medicines among HTA bodies.

- Define requirements for and increase the use of evidence transfer (extrapolation) for benefit assessment of paediatric medicines.

Presentation - Holistic approach to paediatric research: health technologies assessment bodies (Y. Schmidt)

Ethics committees

The Ethics committees' perspective was presented by EUREC (European Network of Research Ethics Committees).

EUREC is a network that brings together already existing national Research Ethics Committee (REC) associations, networks or comparable initiatives at European level, promoting capacity building and providing assistance to local RECs to cooperate in the European Research Area. EUREC disseminates knowledge and expertise and plans to develop training boot camps for REC members.

Better knowledge of PDCO requirements and collaboration with PDCO to develop common plans for new drugs and protocols was considered essential for improving and assuring the rights and interests of minors.

Suggestions for the future:

- Develop and implement national and European standards whenever possible.
- Develop paediatric expertise and awareness of PDCO requirements, EMA guidelines and other paediatric research recommendations.
- Develop common understanding and improve competencies of REC members by training activities.
- Expand pilot projects which promote the involvement of children and adolescents in designing consent forms and recruiting materials.

Presentation - Holistic approach to paediatric research: ethics committees (M.A. Ribeiro)

Example for multi-stakeholder collaboration: Global strategies for pulmonary arterial hypertension in children

Work on global strategies for pulmonary arterial hypertension (PAH) in children was presented as an example for successful multi-stakeholder collaboration. The presentation described the clinical and pharmacological hurdles for multiregional paediatric drug development in this rare and heterogeneous condition as well as joint global actions undertaken to find solutions to overcome the manifold hurdles.

Conclusions:

Regulators, academics and industry have achieved collaboration up to a very high level and have developed a multi-stakeholder network.

The current objective is facilitating the progress for the development of alternative non-invasive endpoints.

The paediatric cardiology community is encouraged to engage and maintain and further strengthen a multi-stakeholder network to address the operational aspects identified as challenging for the conduct of paediatric trials in cardiology.

Physician researchers' contribution is needed by continuing the rational and critical study of drugs in children through conducting and/or collaborating in well-designed paediatric drug studies.

Presentation - Holistic approach to paediatric research: multistakeholder collaboration (C. Ollivier)

General discussion

The subsequent discussion focused on suggestions how to best ensure collaboration among the many different parties involved in paediatric research and how to avoid duplication to ensure most effective use of available resources for the development of paediatric medicines. Discussion points included the difficulties in prioritisation of paediatric drug development plans and of clinical trials necessitating close collaboration between academia, researchers, regulators and industry.

The complexity and difficulties due to tight timelines of PIP procedures were highlighted by industry representatives.

The importance of defining criteria for 'standard of care' as well as the wish for harmonising standard of care at European or international level was also discussed. Increased international collaboration through Enpr-EMA on this topic was suggested.

The wish for guidance for and alignment of documentation needed for scientific assessment by HTA bodies was expressed.

The need for training and systematic involvement of parents – in addition to young people - in the design of clinical trials was highlighted. There was general agreement on the importance of easily understandable assent and consent forms for patients and parents.

The need for improved communication of Enpr-EMA WG activities was stressed to make them more visible to external stakeholders.

Proposed action points

- Research nurses: Provide research nurses a European platform for dialogue and exchange.
- Health Technology Assessment: Initiate collaboration with EunetHTA.
- International collaboration: Increase international collaboration by setting up an Enpr-EMA WG on international collaboration with representatives from NCAs and networks from all 5 regions.
- Standard of care: Consider setting up a dedicated Enpr-EMA WG on standard of care.
- Setting up a dedicated Enpr-EMA WG for parents and patients.
- Inclusion of adolescents in adult trials: Identify and reach out to existing initiatives on this topic and link them to Enpr-EMA WG on trial preparedness.
- Publicity: Improve the communication of outcome of WGs to make them more visible to external stakeholders.
- Platform for dialogue: Enpr-EMA to be a platform for dialogue and exchange of various paediatric initiatives funded by EC.
- EMA/EC action plan on implementation of Paediatric Regulation: Include relevant Enpr-EMA work in the EMA/EC paediatric action plan.