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Report of the 2017 annual workshop of the European Network of Paediatric Research at the EMA (Enpr-EMA)

16 May 2017

Chairpersons: Mark Turner / Irmgard Eichler

Introduction

The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) held its 9th annual workshop on 16 May 2017 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 emphasised the need for international, global collaboration and provided a dedicated session on interaction between the EU and the US for global paediatric research.

The opening addresses by Guido Rasi, Executive Director of the EMA, and by Mark Turner, Chair of Enpr-EMA, highlighted the successes of the Paediatric Regulation ten years after its implementation, e.g. the number of children involved in clinical trials has increased in recent years and more than 900 paediatric investigation plans (PIPs) have been agreed. However, many of these plans face difficulties regarding the conduct of the clinical trials, which makes it necessary to modify and/or delay the plans. In order to improve the conduct of paediatric trials it is crucial to run them internationally, supported by global paediatric research networks and collaboration of regional regulators.

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Session 1

Update on Enpr-EMA activities in 2016/17

- Paediatric Regulation: Submission of comments during the public consultation of the 10-year report on the Paediatric Regulation.
- Dialogue with ethics committees: Two virtual meetings with the European Network of Research Ethics Committees (EUREC) have taken place. Among other things it is planned to establish a training plan to increase paediatric expertise in ethics committees.
- Publicity/awareness: A first virtual Enpr-EMA awareness seminar has been conducted to publicise Enpr-EMA's work.
- Communication between networks and the EMA's Paediatric Committee (PDCO): The opportunity for regular meetings of Enpr-EMA networks with the PDCO at their plenary meetings has been set up. Two of such meetings have taken place.

Sustainability is one of the biggest challenges for networks. It will be increasingly important to promote global collaboration, to increase predictability and reliability of network service provisions and to promote the added value of research networks.

A pan-European paediatric clinical trials network (funded by the Innovative Medicines Initiative (IMI)) will be launched in the near future. It will be crucial for Enpr-EMA to foster collaboration with this new network, and also with the Institute for Advanced Clinical Trials for Children (I-ACT), which was recently launched in North America.

Session 2:

Updates from the Working groups

Working group on GCP training across multiple specialties and countries

The objective of this working group is to review the training available to paediatric research nurses across Member States, and to identify potential training needs.

A questionnaire based survey was designed. The survey was distributed to 75 research centres in 15 countries. 343 completed questionnaires were received covering all main paediatric research specialties. A clear need for more training was identified, especially at the beginning after taking up a post as research nurse. It would also be beneficial to implement a European standard job description for research nurses.

Based on the results of the survey a manuscript for publication is being drafted and will soon be finalised. The manuscript will give insight into different roles of research nurses in different countries, their training opportunities and needs.

Moreover, funding and training of research nurses were identified as crucial points for improving paediatric clinical research in Europe. Often the availability of only short-term contracts hinders the recruitment of research nurses. Increased core funding would be needed in order to be able to offer nurses more attractive career options.

Future tasks include:

- Submission for publication of the manuscript on training needs of research nurses.
- Gathering information on training curricula across Member States in order to propose a core curriculum for research nurses.

Presentation - Session 2.1: Working Group on GCP training

Working group on ethics

The objective of this working group is to develop pragmatic responses on how to disseminate examples of good practice to Ethics Committees.

The group finalised and published the informed consent for paediatric clinical trials in Europe 2015 toolkit, a table including 27 national consent and assent requirements listed by individual country. This toolkit will be updated on a regular basis.

Comments were submitted in August 2016 during the public consultation of the 'ethical considerations for clinical trials on medicinal products conducted with minors'. The comments included suggestions as to how to make the guidance document more easily readable for children and their parents, as well as specific content-related comments (e.g. provisions for access to medicine after trial completion). These are expected to be published by the European Commission in the near future.

A widely harmonised template for Informed Consent / Assent documents was created based on different national versions and presented with the request for comments. After further input and feedback received, it will be published on the Enpr-EMA website (currently planned for autumn 2017).

Future tasks include:

- To allow Enpr-EMA secretariat regular updating of the ethics toolkit (informed consent for paediatric trials in Europe 2015) all stakeholders are requested to check and inform the secretariat about changes or mistakes.
- Collaboration with EUREC and establishing a joint Enpr-EMA/EUREC group in order to develop an agenda for transnational harmonisation of paediatric expertise in ethics committees.
- Collaboration with young people's advisory groups (YPAG) to create a model for e-consent forms.

Presentation - Session 2.2 - Working Group on Ethics (Pirkko Lepola)

Working group on young patient advisory groups

The objective of this working group is to engage and involve young people and family members in the set up and organisation of clinical research. Based on the feedback from two surveys 42 networks and groups could be mapped within the European Patients' Academy (EUPATI). There are disease focussed support groups and not disease specific YPAGs.

Various groups have been able to connect through Enpr-EMA, which led to collaboration and the sharing of good practices on e.g. training courses and materials. This collaboration has been formalised through the establishment of a European YPAG, 'eYPAGnet'. eYPAGnet has been accepted as a Category 4 member of Enpr-EMA. This new network is expected to act as a single point of contact for all YPAGs in Europe.

Moreover, principles on the involvement of young patients / consumers in EMA activities have been agreed by the EMA in collaboration with the Enpr-EMA Working Group and are planned to be published soon.

Future tasks include:

- Creation of a business model for eYPAGnet.
- Interface creation between eYPAGnet and patient support groups.

Presentation - Session 2.3 - Working Group on Young People Advisory Groups (Pamela Dicks)

Working group on public-private partnership

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

The group has created a guidance document outlining the recommended model for network consultations in relation to the PIP process, which is planned to be published on the Enpr-EMA website. The recommended approach includes four different time points for network/industry communication in relation to the PIP process with the following services that networks can provide (1) scoping / exploration, (2) doability / targeting, (3) feasibility / implementing, (4) reporting / safety follow-up.

After a pilot phase a decision will need to be taken on the usefulness of continuation and pricing of the services outlined in the model.

Future tasks include:

- Publication of the consultation recommendation document and testing of the model during a pilot phase.
- Survey among companies which took part in the pilot phase regarding usefulness.

Presentation - Session 2.4: Working group on interactions networks-industry-regulators (Susan Tansey, Pirkko Lepola)

Working group on paediatric clinical trials for antibiotics

The objective of this working group is to facilitate the harmonisation of the design and conduct of paediatric trials for the investigation of antibiotics.

The group is creating a summary document of the key design components of paediatric trials for antibiotics based on the available evidence and expert opinions. The outcome is planned to be published in a scientific journal and will support the drafting of the paediatric addendum to the EMA guideline on the evaluation of medicinal products indicated for the treatment of bacterial infections. It is expected that the first draft of the paediatric addendum will be released for public consultation by August 2017.

Future tasks include:

- Publication of summary document on trial design.

Presentation - Session 2.5: Working group antibiotics (Laura Folgori)

Examples of interaction of investigators – sponsors - regulators

Accelerate and multi-stakeholder interaction in paediatric oncology

Accelerate is a multi-stakeholder initiative comprising members of industry, academia, parents and regulators in order to improve the development of medicines for children with cancer. The initiative has defined five objectives/wishes: (1) paediatric development should be based on the mode of action rather than on the adult indication; (2) prioritisation of developments should be done based on needs, feasibility and expected benefit; (3) reduction of delays of initiations of paediatric developments; (4) inclusion of adolescents in adult trials; (5) new incentives and rewards.

The group recently published a paper on ‘Implementation of mechanism of action biology-driven early drug development for children with cancer’ and another one entitled ‘Joint adolescent-adult early phase clinical trials – new strategies to improve access to new drugs for adolescents with cancer’.

A paediatric pre-clinical platform was launched to provide an opportunity for interaction between all stakeholders on topics requiring discussion in drug development for children with malignancy. In close

collaboration with regulators the first multi-stakeholder paediatric oncology strategy workshop (cancers with anaplastic lymphoma kinase aberrations) was held at the EMA in January 2017.

Presentation - Session 2.6: Examples of interactions - Accelerate (Gilles Vassal, Gustave Roussy)

Paediatric Rheumatology InterNational Trials Organization (PRINTO)

PRINTO is an international not for profit, non-governmental research network with the goal to facilitate the conduct of clinical trials and foster outcome standardisation studies in children with paediatric rheumatic diseases. PRINTO collaborates with the pharmaceutical industry very early on during the development and has, together with the US Pediatric Rheumatology Collaborative Study Group (PRCSG), been involved in many successfully completed trials that were part of agreed Paediatric Investigation Plans (PIPs). PRINTO has taken up an important role in fostering discussions on clinical trial methodologies and outcome standardisation. It is considered important to strengthen the role of academia and independent research organisations and their options for communication with regulators.

Presentation - Session 2.7: Examples of interactions - PRINTO (Nicola Ruperto)

European Cystic Fibrosis Society Clinical Trial Network (ECFS-CTN)

ECFS-CTN aims to intensify clinical research in cystic fibrosis and to bring new medicines to the patients as quickly as possible. The network consists of experts in delivering clinical trials in cystic fibrosis, who have experience regarding the most suitable trial designs and study sites, and have an overview of the whole pipeline of treatments under development. ECFS-CTN involves patient groups in discussions about prioritisation of medicines, and explores new alternative designs for trials in this rare disease. It was stressed that companies should contact ECFS-CTN (and networks in general) even before the formal PIP procedure starts in order to make the best use of the network's expertise.

Presentation - Session 2.8: Examples of interactions - ECFS (Tim Lee)

Paediatric European Network for Treatments of AIDS (PENTA-ID)

PENTA-ID undertakes independent clinical trials to address questions about antiretroviral therapies in HIV infected children and provides training programmes for health care professionals. In recent years the network has widened its scope to include also paediatric infectious diseases other than AIDS, with a focus on neglected and complex diseases. PENTA-ID has been involved in several research proposals to the European Commission. In 2015 a spin-off company (PENTA-ID Innovation) was set up to provide services to commercial entities.

Presentation - Session 2.9: Examples of interactions - PENTA (Carlo Giaquinto)

Session 3

Selected topic discussions

Update on national networks

- **Spanish Paediatric Clinical Trials Network** (RECLIP) & **Spanish Translational Research Network in Paediatric Infections** (RITIP)

  The Spanish networks were launched in 2016 and conduct clinical trials in all paediatric therapeutic areas.

  Presentation - Session 3.1: Updates on networks - Spanish network (Cristina Serén Trasorras)

- **Nordic investigators network for Paediatric Medicines** (NordicPedMed)

  NordicPedMed was launched in 2017. The network represents joint operations of the Nordic national paediatric clinical trial networks of Denmark, Iceland, Finland, Norway and Sweden. The fact that the Finish network was the only established network in the Nordic countries when collaboration was agreed allowed for the use of the same common infrastructure, IT tools and databases across countries. This is seen as a great advantage over already established networks that decide to collaborate at a later time when each network already has their own structure and tools in place.

  Presentation - Session 3.2: Updates on networks - Nordic network (Kalle Hoppu)

- **Irish Clinical Research Network for Children**

  The Irish Paediatric Clinical Research Network is currently being established (name may change). It will bring together all of paediatric research in Ireland and will have a national coordination hub at Clinical Research Coordination Ireland (CRCI). This will incorporate a number of research centres and networks in Ireland including the Irish Centre for Fetal and Neonatal Translational research (INFANT), the National Children's Research Centre (NCRC) and the Health Research Board Mother and Baby Clinical Trials Network.

  Presentation - Session 3.3: Updates on networks - Irish network (Geraldine Boylan)

Update on international networks

- **Pan-European Paediatric Clinical Trials Network** (an IMI 2 project)

  The Innovative Medicines Initiative 2 (IMI 2) programme aims to create a large collaborative, sustainable, multi-specialty pan-European network to facilitate the development and availability of new medicines and other therapies for the entire paediatric population, and the expansion of knowledge about drugs. The aim is to create the network with a lean central coordinating organisation, arranged around 'national hub coordinating centres' cooperating with multiple sites within each member state. The network will be a collaborative network comprised of a public and an industry consortium. It is expected that the participating consortia will be announced within the coming months.

- **Institute for Advanced Clinical Trials for Children** (I-ACT)

  The non-profit network was launched in May 2017. It is currently mainly a Canadian and US network and could be regarded as the North American counterpart of the pan-European Paediatric Clinical Trials Network.

- **Pediatric Clinical Research Infrastructure Network** (PedCRIN)

  The PedCRIN kick-off meeting took place in January 2017. PedCRIN brings together the European Clinical Research Infrastructure Network (ECRIN) and the European Paediatric Clinical Trial Research Infrastructure (EPCTRI) to develop capacity for multinational paediatric clinical trials. PedCRIN is funded by the EU Framework Programme for Research and Innovation (Horizon 2020).

  Presentation - Session 3.6: Updates on networks - PedCRIN (Mark Turner)

EMA framework for collaboration with academia

The Agency has developed a framework to formalise, structure and further develop interactions with the academic community in the context of the European medicines regulatory network. The framework and an action plan for the next three years were adopted in March 2017 and published on the EMA's website.

The framework's overall objectives are:

- raising awareness of the mandate and work of the European medicines regulatory network to increase academia's trust in and engagement with the regulatory system;
- fostering the translation of academic research into novel methodologies and medicines which meet regulatory standards and address needs of public and animal health;
- ensuring that the best scientific expertise and academic research are available on time to support effective evidence generation, regulatory advice and guidance, as well as decision-making in regulatory processes;
- working with academia to develop regulatory science that embraces scientific progress in medicines development without compromising patient safety, such as for example, the use of novel endpoints or novel methodologies.

Along with the framework, EMA has developed an action plan which includes, among other activities, initiatives for mutual education and training, staff exchange programmes to promote mutual learning, a strategic research agenda for regulatory science and the creation of an EMA entry point for academia to receive information on available support within the EU regulatory network.

Presentation - Session 3.7: EMA framework of collaboration with academia (Isabelle Moulon)

European Reference Networks for rare diseases

European Reference Networks for rare diseases (ERNs) are recently established networks of healthcare providers across Europe. ERNs benefit from a sustainable and robust structure, being funded by EU initiatives (the third health programme 2014-2020 funding health initiatives, Horizon 2020, EU structural funds). The first wave included 24 ERNs connecting more than 900 healthcare units in 26 Member States and already covers the majority of disease groups. ERNs are expected to provide a framework for structured cooperation to maximise cross-country expertise through joint research projects and clinical trials. By consolidating knowledge scattered across countries, the ERNs will give healthcare providers access to a much larger pool of expertise. This will result in better chances for patients to receive an accurate diagnosis and advice on the best treatment for their specific condition. ERNs provide an opportunity to build top level translational and basic research around shared strategies and to disseminate research results, expertise and training opportunities across the EU. This will enable patients to find treatment for their complex and rare condition close to home rather than only abroad.

Presentation - Session 3.8: European Reference Networks (Enrique Terol)

A presentation was given on the **European Reference Network on Paediatric Cancer** (ERN-PaedCan), as an example of an ERN. ERN-PaedCan will be officially launched in June 2017 and aims to provide paramount requirements for 'cross-border healthcare' to children with rare cancers. The network has started to develop a European childhood cancer roadmap. The activities include specialised training programmes, the setting up of registries for very rare tumour entities where case numbers are too low to consider a clinical trial setting, long-term follow-up and advice for childhood cancer survivors.

Presentation - Session 3.9: Potential interaction with Enpr-EMA networks

Update on the European Clinical Trials Regulation

Regulation (EC) No. 536/2014, the Clinical Trials Regulation, was published in May 2014 and will be directly applicable in all Member States six months after the full functionality of the EU portal and EU

clinical trials database has been confirmed in the Official Journal of the EU. The Regulation is currently expected to enter into force in October 2018.

The objectives of the Regulation are to protect the rights, safety and well-being of subjects and the reliability of the data generated in interventional clinical trials with medicinal products, to foster innovation, and to increase transparency. The key changes compared to the current Clinical trials Directive (Directive 2001/20/EC) will include a single e-submission to all Member States via an EU portal, a harmonised application dossier, coordinated assessment, and one single decision per Member State. These changes are expected to significantly simplify and accelerate the clinical trial application process. Moreover, the Regulation defines a new category of low intervention clinical trials with adapted requirements.

After entry into force of the Regulation there will be a three-year transition period from the Directive to the Regulation.

Presentation - Session 3.10: Update on the EU Portal and Database (Kevin Cunningham)

A presentation was given on the Clinical Trial Facilitation Group (CTFG). The group was established by the Heads of Medicines Agencies in 2004 and acts as a forum for discussion and agreement on common principles and processes regarding clinical trial applications, substantial amendments, and safety assessment across the European medicines regulatory framework. Fragmentation of the clinical trial authorisation regime across Member states and lack of harmonisation has led to a decrease in clinical trial application in the EU between 2007 and 2014. This is why the Voluntary Harmonisation Procedure (VHP) was set up by the CTFG for multinational trials, where the assessment of clinical trial applications is led by a 'reference Member State'. The VHP could be regarded as a forerunner of the harmonised procedure that will be introduced by the Clinical Trials Regulation.

Presentation - Session 3.11: Update on EU member state harmonisation (Seán Kilbride)

Session 4

Cooperation of the EU and the US on global paediatric research

Networks' perspective

- European Cystic Fibrosis Clinical Trials Network (ECFS-CTN) and US Cystic Fibrosis Foundation – Therapeutics Development Network (CFF-TDN)

  The two networks collaborate closely and discuss strategy issues regarding e.g. trial design challenges, 'standard care' changes at monthly teleconferences between the coordinating centres. The networks are also developing 'global' standard operating procedures for clinical trials in cystic fibrosis. Through collaboration it has been possible to significantly increase the number of patients enrolled into CTN approved studies.

  Presentation - Session 4.1: Collaboration European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN) with US Cystic Fibrosis Foundation –Therapeutics Development Network (CFF-TDN) (Tim Lee)

Regulators' perspective

- EMA and FDA conduct monthly virtual paediatric cluster meetings (together with Health Canada, PMDA (Japan), and TGA (Australia) to discuss general and product-specific paediatric drug development issues (e.g. clinical trial designs, endpoints). Convergence on approaches has been achieved in more than 70% of the issues discussed in the last three years. 25 common commentaries have been adopted between 2012 and 2017 following cluster discussions.

Joint paediatric working groups (inflammatory bowel disease (IBD), paediatric rare diseases), workshops (Gaucher disease, paediatric pulmonary hypertension, advancing the development of paediatric therapeutics), and expert meetings (e.g. diabetes, HIV, rheumatology and osteoporosis) have been organised. Additional working groups and workshops will be organised on an ad-hoc basis. Ongoing harmonisation and collaboration with international paediatric clinical trial networks and consortia is crucial in order to make paediatric medicine development faster and easier, despite legislative differences and regional requirements.

The International Neonatal Consortium (INC) is an example of successful collaboration of regulators, academia, parent and patient associations and industry. The INC aims to advance medical innovation and accelerate development of medicines for neonates.

Presentation - Session 4.2: Global collaboration between regulatory agencies with paediatric research networks (Irmgard Eichler, Susan McCune)

An EMA/FDA bilateral meeting on the future of paediatric research was organised together with the European Commission in September 2016. The discussions focused on how to further intensify collaboration, increase compatibility of paediatric drug development requirements, and identify future challenges. Both regulators aim for a convergent and harmonised paediatric development programme for each medicine through early and proactive collaboration to increase efficiency during paediatric product development. Joint outreach programmes will be important to identify high priority paediatric need areas and to facilitate related research and development.

Presentation - Session 4.3: Feedback from EC/EMA-FDA bilateral on paediatric research (Peter Karolyi)

Industry's perspective

- Collaboration with networks is crucial when planning clinical trials because clinical trial networks have an overview of ongoing trials and the latest developments in their field of expertise. Industry deems it important to be able to harmonise the timing of submission of PIPs in the EU and Pediatric Study Plans (PSPs) in the US in order to be able to better coordinate network consultations.

Young persons' perspective

- EMA and FDA reinforce collaboration on patient engagement. In June 2016 the two agencies set up a 'cluster' on patient engagement. The cluster will provide a forum to share experiences and best practices on the way the two agencies involve patients in development, evaluation and post-authorisation activities related to medicines. Among other things the areas of discussion will include how to best engage with young patients and include their views in the decision making process.

  The International Children's Advisory Network (iCAN) is a worldwide consortium providing a platform for children and families in order to make their voices heard and to involve them in the development of paediatric clinical trials. Through iCAN young people have helped to develop templates for harmonised assent forms which are suitable for children and young people.

  Presentation - Session 4.5: Interaction and cooperation between the EU and US on global paediatric research: ICAN's experience (Joana Claverol)

Conclusions

Based on the discussion points and questions raised following each presentation, the seven following action points were agreed:

Working group on GCP training across multiple specialties and countries

- Submission for publication of the manuscript on training needs of research nurses.
- Gathering information on training curricula across Member States in order to propose a core curriculum for research nurses.

Working group on ethics

- To allow Enpr-EMA secretariat regular updating of the ethics toolkit all stakeholders are requested to check and inform the secretariat about changes or mistakes.
- Collaboration with EUREC and establishing a joint Enpr-EMA/EUREC group in order to develop an agenda for transnational harmonisation of paediatric expertise in ethics committees.
- Collaboration with young people's advisory groups (YPAG), among other things in order to create a model for e-consent forms.

Working group on young patient advisory groups

- Creation of a business model for eYPAGnet.
- Interface creation between eYPAGnet and disease specific patient support groups.

Working group on public-private partnership

- Publication of the consultation recommendation document and testing it during a pilot phase.
- Survey among companies which took part in the pilot phase regarding usefulness and possibly pricing.

Working group on paediatric clinical trials for antibiotics

- Publication of summary document on trial design.

The open workshop was followed by the annual meeting of Enpr-EMA networks and the annual face to face meeting of the Enpr-EMA coordinating group on 17 May 2017. A more detailed summary of agreed action points can be found in the minutes of the annual meeting of Enpr-EMA networks.

The next annual open workshop is scheduled for 7 June 2018.