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Human Medicines Research & Development Support Division

Report of the 2016 annual workshop of the European Network of Paediatric Research at EMA (Enpr-EMA), 2 & 3 June 2016

Chairpersons: Mark Turner / Irmgard Eichler

Introduction

The [European Network of Paediatric Research at the European Medicines Agency](#) (Enpr-EMA) held its [8th annual workshop](#) on 2 June 2016 at the premises of the European Medicines Agency (EMA) in London, UK. Enpr-EMA is a network of research networks, investigators and centers with recognized 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 enforce interaction and communication between all stakeholders: networks' representatives, pharmaceutical industry, regulators and patients/parents organizations. This year's event offered a panel debate on how ethical aspects in relation to clinical studies in children will be handled in the context of the implementation of the new European Union [Clinical Trial Regulation](#).

Session 1

The morning session started with a review by the Chair of Enpr-EMA Coordinating Group (CG), Mark Turner, on the 2015-2016 activities, including:

- Expansion of the network: Medicines for Children Research Network (MCRN) - Hungary (a multispeciality national network) has joined Enpr-EMA.
- Establishment of a new Enpr-EMA working group on clinical trial design for paediatric studies with antibiotics
- Increase visibility and awareness of Enpr-EMA:
 - Publications achieved by the working group on Ethics Committees and the working group on public-private partnership :

[Successful private-public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines](#)

[Pharmaceutical Industry and Pediatric Clinical Trial Networks in Europe – How Do They Communicate?](#)

[Informed consent for paediatric clinical trials in Europe](#)

- Submission of comments on the proposed changes to the U.S. Common Rule related to paediatric research, focused on the informed consent and the importance of having an international perspective in the revision process of the common rule (working group on Ethics Committees).
- Development of a framework for networks to promote early interaction with industry, regulators, young people and families: an SOP has been drafted and discussed during the meeting (working group on how to organise multi-stakeholder meetings).
- Improved involvement of patients/families: [Joint EFGCP/DIA/EMA Better Medicines for Children](#) Conference to be held at the European Medicines Agency on 10-12 October 2016. The focus will be on *optimisation of drug development for the benefit of children*, where children and families will be the key actors.
- Promotion of shared practise within EU and other parts of the world: EPCTRI - European Paediatric clinical trials research infrastructure – has been adopted on the European Strategic Forum for Research Infrastructure ([ESFRI](#)) [Roadmap 2016](#).
- Challenges encountered in the past year included:
- Contrast between volume of work, in terms of number of children recruited for clinical trials part of agreed PIPs, and lack of site capacity
- Sources of funding, that need to match the different healthcare systems

[Presentation: Report from the coordinating group \(CG\) Update on Enpr-EMA activities, achievements and challenges](#)

Session 2: Working Groups updates

Working Group on dialogue and interaction with Ethics Committees

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 the [Informed consent for paediatric clinical trials in Europe 2015](#) toolkit, a table including 27 national consent and assent requirements listed by individual country. The working group published a [paper](#) in May 2016.

The group submitted comments on the proposed changes to the U.S. Common Rule Implications for Paediatric Research. The comments focused on two points relating to paediatric research:

- The value of taking an international perspective when revising the Common Rule;
- Informed consent.

During the discussion, future tasks were proposed and agreed:

- Take part in the revision of the [Ethical considerations for clinical trials on medicinal products conducted with the paediatric population \(2008\)](#) that will be opened from June to September 2016, in collaboration with EFGCP CMWP ([European Forum for Good Clinical Practice, Children's Medicines Working Party](#)) and EMA.

- Work on the development of partly harmonised templates of informed consent / assent, in the context of the harmonisation of the application process that will be implemented with the new [Clinical Trial Regulation](#).
- Improve dissemination of information through industry associations in order to face the major challenge of the lack of information regarding the different national requirements for informed consent.

[Presentation: Dialogue and interaction with ethics committees](#)

Working group on How to organise multi-stakeholder meetings when encountering difficulties with implementation / conduct of clinical trials agreed in PIPs"

The group is working on a SOP/guideline on conducting meetings on generic issues in paediatric drug development. The working group highlighted the importance of identifying and anticipating possible issues related to the conduct of paediatric clinical trials. The draft procedural steps were presented and discussed. Industry expressed concern regarding the confidentiality of information shared during these meetings. Regulators clarified the general focus of these meetings, which would be addressing generic issues and not discussion confidential, proprietary information. Industry also proposed to focus on multi-stakeholder oriented meeting, including families/patients representatives as critical sources of contribution on the topics. Based on the discussion points, future tasks will include:

- Implementing a framework to address generic issues during the study preparation at early stage, by identifying therapeutic-specific needs and develop a strategy on how to address them;
- Look at lessons learned from the meeting on Type 2 diabetes;
- Find inputs from the interactive framework guideline currently under development by EMA;
- Run a pilot meeting with the topic still to be agreed upon by the coordinating group.

[Presentation: Standard Operating Procedure for meetings about generic issues in paediatric drug development convened by Enpr-EMA](#)

Working group on GCP Training across multispecialty and countries

With the objective of reviewing current requirements, level and consistency of training received by nurses involved in CTs across EU countries, the working group has developed a questionnaire to generate data and gather information on what research nurse training currently exist in the EU, and to identify differences and gaps across countries. The questionnaire was circulated among Enpr-EMA networks for comments, finalized and sent to 28 identified organizations, covering 12 countries and three specialties (oncology, haematology and neonatology). 201 completed questionnaires have been received to date. The analysis of this data was presented during the open workshop. One relevant result showed that 1/3 of research nurses felt they would benefit from additional trainings and proposed several training areas of interest, including IT, sample handling, clinical trial setup, finance, research governance.

Future tasks include:

- Identification of other target organisations in countries underrepresented in the dataset obtained for circulation of the questionnaire;
- Analysis of collected data and sharing information with Enpr-EMA networks;
- Publication in appropriate journal;

- Discussion on the proposal of the applicability of a questionnaire-based survey to other healthcare areas, targeting groups of professionals rather than only individuals.

[Presentation: Educational Training of Research Staff Involved in Paediatric Clinical Trials / GCP Training across multispecialty and countries](#)

Joint working group on public-private partnership

The group was task with identifying strategies on how to disseminate good practise examples of interaction between industry and Enpr-EMA networks. To this end, the group analysed the data collected in the two surveys sent to the networks and industry in 2013 and 2014. The results were published on *Applied Clinical Trials* in January 2016: [Pharmaceutical Industry and Paediatric Clinical trials networks in EU-how do they communicate?](#) The results allowed the working party to create specifications for an “ideal paediatric clinical trial network” including the desired capabilities and services identified by the companies. Finally, the working party formulated a table of recommendations for all the parties involved in the survey.

The working group is currently developing a guidance for industry to engage with Enpr-EMA and its registered networks when planning paediatric development plans in the European Union., It is planned to publish this guidance for network consultation on the EMA website, with the objective to promote early engagement with networks and provide industry with a multi-phase model of interaction.

Future tasks include:

- Finalise and implement the guidance model;
- Draft an advertisement to publise the guidance, circulate it to industry and Enpr-EMA for comments and finalise it.

[Presentation: Working Group on public-private partnership](#)

Working Group on young patient advisory groups

The group has completed two surveys. The first survey targeted Enpr-EMA networks, with the scope to review the already established Young Person Advisory Groups (YPAGs) and create a database useful for EMA and Pharma. 15 responses have been received. Data were analysed and presented. The second survey targeted non-Enpr EMA members, with the scope to identify other YPAGs within existing organisations, such as disease specific support groups, patients groups, or associated with charities. 6 responses have been received so far. Data were analysed and presented.

Future tasks with the first survey include:

- Draft a short report to be published on EnprEMA website;
- Create an online portal to access existing YPAGs with guidelines and young people’s agreement;
- Host a workshop for enpr-EMA and non-enprEMA networks.

Future tasks related to the second survey include:

- Identify additional non-EnprEMA members through EURORDIS, EUPATI and other associations;
- Identify target patients organisations in collaboration with EMA in order to catch young groups within those.

Action plan:

- Similar to initiatives in North America to build a network of young advisory group across Europe, starting by collecting information from the already existing advisory groups and develop a standardised procedure for a more European-oriented approach;
- Develop training packages for other parties involved (cross-population approach);
- Reflect on the proposal to create a funding group to sustain the database and keep it updated;
- Gather feedback from other working groups on possible strategies.

[Presentation: Young Persons Advisory Groups Terms of Reference and updated Work Plan](#)

Afternoon session

The afternoon session started with a report on the activities of the [International Neonatal Consortium \(INC\)](#), including:

- Completion and publication of a survey by the association of neonatal nurses to gauge nurses' perceptions of neonatal clinical trials
- Draft a white paper to assist regulators in preparing guidance on clinical pharmacology considerations for the design of neonatal trials (INC's clinical pharmacology workgroup). The finalised article has been submitted to *Paediatric Research*. It has been suggested that the proposed model could be applicable to other age-groups paediatric patients and other therapeutic areas
- Dissemination of data and information on neonatal drug development through publications (4 articles published in 2015 and 1 currently in press)
- Several workgroup projects ongoing (protocol for treatment of seizures, development of a definition for BPD and development of a guide for normal lab values and ranges)
- Upcoming workshops: [Sept 2016 at EMA](#) and Spring 2017 at FDA

European networks

As a key example of network's good practice, the Austrian [OKIDS](#) model, experience and achievements were presented, with particular focus on the financial model adopted by the network, based on a public-private partnership which involves several parties (academia, industry, politics and parents/patients). OKIDS became category 1 network at Enpr-EMA in May 2015.

[Presentation: OKIDS activity update, learnings and improvements](#)

An update of the IMI2 proposal for a 6-years project to build a pan-EU paediatric clinical trial network (EUPCTN), where Enpr-EMA would have a central role was presented. The initiative has been proposed as a solution to overcome planning and organizational challenges inherent in conducting paediatric clinical trials. EUPCTN is part of a broader initiative in North America with the objective to develop aligned processes and standards to address the needs in children globally (see below [Paediatric Trials Consortium](#)). Relevant [achievements over 2015](#) include:

- Draft of the first IMI2 Call topic text (Feb 2015)
- Enpr-EMA and PDCO endorsements (June 2015), followed by official letter by the PDCO in support of Enpr-EMA involvement in the planned IMI2 project (Aug 2015)

- Submission to EUC for feedback (Dec 2015)
- IMI2 Workshop with all stakeholders. [Future plans and timelines:](#)
- Submission of revised Call Topic Text summary to EFPIA Research Directors Group/INNOMED (June 2016)
- Submission of finalised call topic text to EUC/IMIs (Aug 2016) and publication (Oct 2016)

[Presentation: What ever happened to the IMI2 proposal?](#)

The successful IMI2 project **INNODIA** and EUCADET (European children and adolescent diabetes and endocrine trials network)-was presented.

The proposal "Translational approached to disease modifying therapy of T1D mellitus: an **INN**ovative approach towards understanding and arresting T1 **DI**abetes" has been submitted to the IMI2 call for proposals in 2014 and has received the grant agreement in 2015. Partners include 32 clinical trials centres around the EU and other stakeholders, Industry and Independent charities associations (

Action plan:

Improve engagement with EMA, academia and industry to put forward INNODIA project and accelerate drug development for T1D within innovative pathways

[Presentation: Successful IMI project: INNODIA](#)

International networks

The US-based Paediatric trials network (DUKE-PTN), which targets off-patents therapeutics, presented an update of its activities since 2010. Progresses in this timeframe include the completion of 30 projects and 18 multi-therapeutic area clinical trials, which enrolled over 100 sites and more than 5000 children. Innovative pathways have been used such as data access, education, neonatal studies, and master protocols. PTN projects were presented, in particular the clinical trials managed and meta-analysis conducted. Among the lessons learnt reported, the frequent interaction with FDA (via direct communication with relevant Divisions)/NIH has been of critical importance to meet the reported achievements.

[Presentation: NICHD - Pediatric Trials Network](#)

The US-based [Paediatric Trials Consortium](#) is a non-profit organization established in October 2015 as member of the Critical Path Institute, with the objective to prepare and oversee establishment of a North-American paediatric clinical trial network.

EPCTRI, the European Paediatric Clinical Trials Research Infrastructure has been adopted on the road map 2016 and published by the European Strategic Forum for Research Infrastructure.

[Presentation: EPCTRI: Paediatrics in 2016. Roadmap of European Strategy Forum for Research Infrastructure \(ESFRI\)](#)

Update from industry representatives

The first topic proposed by the industry representative of EUCOPE was the difficulties encountered by companies with preparing and obtaining informed consent. And the need to search of pragmatic ways to improve and make the Informed Consent "process" for patients/families more informative:

- The Informed Consent (IC) is an educational process, an informative tool that should also address common issues and misconceptions related to clinical trials (e.g. trial=experiment≠treatment).

- There is a need to increase awareness of the already available tools provided by industry and other groups (CISCRP, EFGCP, ICAN) that offer support in organising the IC process. Enpr-EMA might have an important coordinative role for dissemination of this information.
- Contentwise, the Informed Consent documentation should be streamlined and study-specific focused. by addressing relevant aspects of the specific clinical trial(s).
- To research already available data and information to better understand what should be highlighted to patients/families and in which way (e.g. there is evidence that the informed consent should be re-discussed during the trial, as a multiphasing process).
- Approach patients/families directly to ask feedback about what level of information they expect from the IC process.

The second topic for discussion was a proposal from EFPIA Paediatric working group for feasibility of Paediatric CTs presenting the wish of companies to discuss a framework for paediatric clinical trial preparedness.

[Presentation: How can the informed consent process better address the needs of parents/children?](#)

The main topic in the afternoon session was dedicated to Paediatric specific and ethical issues related to the implementation of Clinical Trial Regulation. Hugh Davies, Health Research Authority Ethics Advisor, talked about the EU Clinical Trial Regulation and children and young people touching on ethical and procedural issues such as:

- Debate children vs adults. The question “children are not little adults?” appears to be simplistic and requires a more in-depth discussion and a contextualisation, according to the principle of the CT Regulation to find balance between research promotion and protection of individuals
- Payments to children: whether it is ethical paying adults but not children for clinical trials needs to be further discussed
- Non-therapeutic clinical trials involving minors is a critical issue for which a clear position remains uncertain so far

The above paediatric ethical topics have not been captured into the Regulation. However, it has been pointed out that the Regulation should be seen as a legal framework rather than a tool for communicating ethical issues related to clinical trials. It is of responsibility of the Research Community and all the involved stakeholders to ensure that the clinical practice is performed under an ethical framework. Possibilities to exert influence might be:

- Ensure dissemination of appropriate information avoiding over/mis-interpretation of the CT Regulation when it will be put into practise
- Get actively involved in the revision of “ethical considerations for CTs on medicinal products conducted with the paediatric population
- Watch for the Data Protection Regulation
- Balance un-researched care and clinical research based on clinical regulation

[Presentation: The EU Clinical Trial Regulation and children and young people \(minors\) - Ethical and procedural issues](#)

Dirk Lanzerath presented the European Network of Research Ethics Committees (EUREC) which been established in 2005 as a network representative of national associations and bodies of research ethic committees (RECs), with the objectives to promote co-operation and harmonization of best practice, to

support training and provide unified material across the European ethical committees. Activities from 2006, include:

- Development and maintenance of a website (2006);
- Commentary of all EUREC members on the draft proposal of the EC on a regulation on medicinal products and CTs;
- Cooperation with EMA to implement EU regulation and to set up the EU portal;
- Cooperation with SATORI (stakeholders acting together on the ethical impact assessment of research and innovation) to analyse recent ethical review and to harmonise the ethical assessments.

Future tasks include:

- Encourage regional/local RECs to found national ethic committees, due to difficulty in identifying country representatives with national mandate;
- Keep organising workshops and web-based communication strategies to improve interaction between RECs across EU member states;
- Improve cooperation with research institutions, EMA and SATORI group and other networks;
- establish International interactions.

Presentation: Networking of European REC's

The next topic was the discussion of the Enpr-EMA contribution in the implementation of the [Clinical Trial Regulation 536/2014](#) coming into application in 2018, and focused on the aspects related to the paediatric clinical practice. One role of Enpr-EMA was proposed to contribute in the revision of the document [Ethical considerations for clinical trials on medicinal products conducted with Minors](#) open for public consultation from 1 June to 31 August 2016. The following action plan was agreed:

- To set up a small group in charge with the identification of the key issues of concern and to draft first comments which will be circulated among all Enpr-EMA members for their comments before finalising and submitting them.
- [Presentation: Paediatric specific and ethics issues related to implementation of Clinical Trial Regulation](#)
- [Presentation: Ethical considerations for clinical trials on medicinal products conducted with the paediatric population](#)

Finally, the activities related to "Involvement of children in research" were reported.

Presentation: Involvement of children - iCAN

Conclusions

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

Action point 1: Ethics

- Enpr-EMA will contribute to the document "Ethical considerations for CT on medicinal products conducted with Minors" currently open for consultation. The Ethics Committee network and EUREC are in charge with the identification of the key issues to base the comments on (deadline for draft comments: end of June 2016).

- Paediatric specific issues should be integrated in the training programs for ethics committees. EUNTC expressed interest in developing training modules for the EU. A plan will be made after the summer.

Action point 2: Young people advisory groups

- To develop an European-oriented young advisory group network to link the groups together, share good practise and provide expertise. The Enpr-EMA working group on YPAG and ICAN will collaborate in this project.

Action point 3: Network and industry interaction

- To finalise the draft guidance, including comments from pharma industry. Deadline : next CG meeting in October 2016.

Action point 4: multi-stakeholder meetings on general/non-product specific issues

- To implement the SOP for mult-stakeholder meetings, by looking at lessons learnt from the meeting on type 2 diabetes and awaiting input from the EMA's guidance for interaction with stakeholders, this is currently under development. At the same time, consider running a pilot mwwting; topic to be agreed by Coordinating Group.
- Start drafting a framework on trial preparedness after October 2016 meeting.

Action point 5: How could EMA and PDCO work better with Enpr-EMA?

- To develop a list of networks with available specific expertises to be contacted in case companies wish to discuss specific topics, to be published on EMA website. Deadline for list proposal: October 2016.
- To organise regular TC meetings among selected Enpr-EMA networks and PDCO.

Action point 6: How can Enpr-EMA work with learned society?

- Networks already linked with societies are requested to provide a list in order to identify under-represented areas. Deadline: October 2016.

Action point 7: Commenting on 10 year report on EU Paediatric Regulation

- Enpr-EMA should comment on the draft report of the European Commission which is expected to be put for public consultation.

Day 2

Following the open workshop, the network members met for their annual face to face meeting.