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Report on annual workshop of the European Network of Paediatric Research at the EMA (Enpr-EMA), 26 & 27 June 2014

On 26 & 27 June 2014 the European Medicines Agency (EMA) convened the annual two-day workshop of the European network of paediatric research at the EMA (Enpr-EMA). 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 on quality, safety and efficacy of medicines to be used in children.

Day one of the workshop was dedicated to strengthen the links and communication between all stakeholders: patient/parent organisations, network representatives, pharmaceutical industry staff responsible for paediatric studies and regulators. The open meeting was followed by the Enpr-EMA members meeting.

Day two was dedicated to the Enpr-EMA coordinating group meeting to analyse the outcome of day one, and to discuss and define priority tasks for the year 2014-2015.

Day 1

The morning session started with a report by the chair of Enpr-EMA coordinating group (CG), Dr Mark Turner, on the activities in the past year, including:

- Early involvement of networks in PIP development encouraged in guidance for applicants on EMA website (PIP application guidance for industry; Question 31);
- Development of a fully searchable network database allowing the identification of Enpr-EMA registered networks in several ways (http://enprema.ema.europa.eu/enprema/);
- Increase visibility of and publicity for Enpr-EMA: Abstract "*Enpr-EMA, A Platform For Disseminating Good Practices About Paediatric Medicines Research Across Europe And With International Partners*" accepted by European Academy of Paediatric Societies at annual meeting 2014;
- Set up of several ad hoc Working Groups to develop pragmatic responses to some of the most important needs identified during last year's meeting;
- Initiating international collaboration with clinical paediatric research initiatives in the US;

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- Initiating ad-hoc participation of industry representatives in coordinating group meetings, to be implemented in Autumn 2014;
- Continuing support of new specialty networks in the fields of gastroenterology, cardiology, and diabetes/endocrinology.

Challenges encountered in the past years included:

- Advocacy at EU level (Parliament, Commission) regarding paediatric specific needs and challenges related to paediatric trials, including need for dedicated funding of paediatric specific research.

The following session was dedicated to the working groups and the presentation of their activities over the last year:

The working group on "**How to establish communication between Enpr-EMA networks and industry**" and the WG on "**Sharing Good Practice within Enpr-EMA and with Industry Partners**", with the aims to facilitate communication between Industry and Enpr-EMA networks, decided to join together. A survey was developed and distributed to collect good practice examples from both network members and Industry colleagues. A total of 89 responses were received (19 network responses / 70 industry responses) and analysed. Next steps will be to finalise the report for wider dissemination, and to develop a dissemination strategy to distribute and share good practice. It was also suggested repeating the survey in 12 months. (Update on working groups 3 and 5)

Working Group "**Dialogue and Interaction with Ethics Committees**" was tasked with gathering examples of good practice when Ethic Committees (ECs) consider trials relating to children and young people and to develop proposals to disseminate examples of good practice to ECs. A report with 7 short term and 5 long term recommendations was presented to the Enpr-EMA coordinating group in January 2014. After CG meeting, it was decided to develop a table showing requirements/regulations regarding consent of children across EU Member States as a practical deliverable, since there was consensus within the group that consent and assent present the greatest challenge in achieving ethical approvals across Member States. The table of EC details for informed consent for paediatric trials provides data including legislative surroundings of the informed consent requirements for pediatric clinical trials, listed by country. Next steps will be to finalise the table with more accurate country-specific data, to add country-specific additional information, if existing (i.e. templates or direct web-links to regulations and guidelines) and to publish the table after it has been circulated to Enpr-EMA networks for comments. (Update on working group 4)

The working group "**A framework for networks to interact with industry and regulators when implementation/conduct of clinical trials agreed in PIPs is no longer possible**" identified 2 key priority needs:

1. To provide unbiased expert advice to Industry and PDCO before a paediatric investigation plan (PIP) is approved while maintaining a clear(er) mechanism for avoiding conflicts of interest. To ensure clear, detailed, up to date and accurate conflicts of interest (CoI) statements in the public arena for all experts or network members, will require a much easier, harmonised individual expert CoI submission process available in public domain: individuals should be to be able to produce one CoI form for use across multiple agencies – employer, national organisations, European/ international organisations/ Government.
2. To define what to do when completing PIP is not feasible, i.e. to define mechanisms to bring stakeholders together to design feasible trials (assuming CoI issues resolved). The use of multi-stakeholder meetings was proposed to bring all stakeholders together when problems are identified. Industry consultation with Enpr-EMA networks should be enhanced when PIP feasibility issues occur.

Next steps: to finalise a detailed paper draft for consultation by Steering committee and Enpr-EMA colleagues in first instance; seek dialogue with EMA with regard to harmonised, easy expert CoI statements. (Update on working group 6)

During the follow-up discussion, industry representatives brought forward a suggestion for the PDCO and the EMA: with the support of Enpr-EMA network members to proactively identify areas where PIPs encounter major difficulties and to organise multi-stakeholder meetings, exploring together with industry potential solutions, including multi-sponsor trials.

The chair of the **joint Enpr-EMA/ENCePP working group on paediatric pharmacovigilance** presented the plan for the revision of the guideline on conduct of pharmacovigilance for medicines used by the paediatric population. The draft Concept Paper was adopted by both committees, the PRAC and the PDCO in April 2014. Next steps are to draft the revised guideline and present it to Committees before putting the draft guideline for Public consultation at end of this year.

The working group on **Neonatology,** including members of the PDCO identified several potential topics to work on, such as pre-clinical models, definition of end-points, study designs, and when to start clinical trials in neonates. FDA set up a Neonatal Scientific Advisory Panel and is organizing a stakeholders meeting later this year to examine areas of shared concerns. The proposed agenda for discussion is similar to the one elaborated by the Enpr-EMA working group. It therefore was agreed to await the outcomes of this stakeholder meeting to maximise value of efforts. The chair of the working group as well as one EMA staff member will participate at the FDA stakeholder meeting.

Next steps: to increase interest from the clinical community by e.g. presenting at the meeting at European Society for Paediatric Research. (Update on working group 7)

The mandate of the working group "**Strategies for funding and maintaining a paediatric research network**" was to compare the network mediated paediatric research activity across Europe and to develop a business case for paediatric research networks, comparing resource inputs versus outcomes with a view to encourage governments to spend more on research infrastructure. The work will be based on result of a survey conducted by the NIHR CRN (Children) sent out to 21 networks in the UK. Preliminary results were presented. Next steps are: to use that report to identify the next work plan and to send a summary of the work done so far to the Enpr-EMA secretariat for discussion within the CG and dissemination among Enpr-EMA members. (Update on working group 9)

Finally, the working group on **FP7 projects** on **off-patent medicines in children** reported on a meeting organised by the Enpr-EMA chair and hosted by the European Medicines Agency in January 2014: representatives of projects funded through the EC FP7 were invited to share experience, to identify best practices for evaluating off-patent medicines in Europe and to identify key learning points for investigators, sponsors and regulators. A manuscript summarising the progress of the FP7 projects and lessons learnt was recently accepted for publication.

Next step: to develop a list of hurdles to off-patent medicines research in order to define proposals to be considered for Horizon 2020 and to discuss with the European Commission during a PDCO meeting in Autumn 2014. (Update on working group 10).

The afternoon session was dedicated to 3 topics:

- Opportunities for Public-Private Partnerships in Pediatric Research Networks
- Network functions: sharing good practices, sustainable business plan, and relationships between network investigators
- Worldwide Involvement of Children in Clinical Research

Opportunities for Public-Private Partnerships in Pediatric Research Networks

Two industry representatives from the US informed the audience about current initiatives in the US to develop and set up a global paediatric network because of:

- difficulties in
  - accessing the necessary patient populations for studies;
  - assessing feasibility of studying indications in the designated population;
  - finding qualified sites and identifying experienced paediatric investigators;
- paediatric trials taking longer, recruiting fewer patients, but costing much more than adult trials on a per subject basis;
- the need to provide children access to authorised medicines as per legal mandate in EU and US.

PhARMA (Pharmaceutical Research and Manufacturers of America) provided an unrestricted educational grant to the American Academy of Pediatrics to convene stakeholder meeting(s) including regulatory agencies for this matter. SOATT (Section on Advances in Therapeutics and technologies within the American Academy of Pediatrics), established in 2010 with members from industry, academia, clinical practice, the Food and Drug Administration, US Government agencies) is elaborating on a concept of a Global Paediatric Clinical Trials Network:

- Initial funding from a public-private partnership (industry, public/ private research institutions)
- Global: US, EU, Canada, and beyond
- 50-60 of the best children's medical centers in the world
- Global resource for advancing science of paediatric drug development and advocating for sound regulatory policy
- Cooperate and partner with existing networks
- Primary focus is development and approval of new therapies
- All disease indications, therapeutic areas; all age groups (including neonates); all phases (I-IV, registries)
- Sustainable network infrastructure /funding

Network functions: sharing good practices, sustainable business plan, and relationships between network investigators

3 priorities were defined to be part of the Enpr-EMA annual work plan:

- Describing standards for networks/ideal network (task for the Working Group "Sharing Good Practice within Enpr-EMA and with Industry Partners")
- Need for training in GCP: Companies complain that clinical studies are frequently not conducted according to GCP and to the standards required by regulatory authorities. Networks must ensure that all their member sites are well trained in GCP and deliver high quality. (Task for new working group)
- Plan for priority setting

Worldwide Involvement of Children in Clinical Research

Inspired by the successful set-up of young people advisory groups in three Enpr-EMA network members, i.e. ScotCRN, the UK NIHR Clinical Research Network: Children, and the Maternal Infant Child, Youth Research Network (CA) a similar initiative has been recently initiated in the US: KIDS (Kids and Families Impacting Disease Through Science) is an advisory group of children, adolescents and families focused on understanding, communicating and improving medicine, research and innovation for children. KIDS is a collaboration between the American Academy of Pediatrics (AAP) Section on Advances in Therapeutics and Technology (SOATT), local AAP Chapters, children's hospitals, local schools and other partners. A first KIDS Team was launched in Connecticut in September 2013 in collaboration with the Connecticut Children's Medical Center, Yale-New Haven Children's Hospital, Pfizer Inc., and local schools. It serves as model for future KIDS Teams, planned as regional groups of 10-20 to be created within local AAP Chapters or Districts. Monthly meetings are held locally at the Chapter level perhaps at local children's hospitals. Annual meeting of local and national groups at AAP National Conference and Exhibition are planned; future expansion could include an international network named International Young Person's Advisory Network (iKAN) (e.g., collaboration with the UK NIHR Clinical Research Network: Children Young Persons Advisory Group, and ScotCRN Young Persons' Group). In the discussion following the presentation, two main issues were identified:

1. Transparency with regard of funding of such Young Persons Advisory Groups (YPGs) will be of crucial importance;
2. The need for similar YPGs across Europe and how to best approach the language barriers when extending existing YPGs, who at present are all in English speaking countries, e.g. through online fora.

Next step: *IKAN* to send a survey to Enpr-EMA members to ask them:

- how an international network of these YPGs may benefit Enpr-EMA networks clinical research; and
- if Enpr-EMA networks have interest in starting a Young Person's Advisory Group locally or if they are aware of young people who would like to join such a network.

Conclusions:

Based on the discussion points and questions raised following each presentation, it was agreed:

- that the work of the several working groups helped to increase collaboration between networks and with industry and to increase awareness about Enpr-EMA among industry.
- that existing working groups should continue their work, sending a progress plan to the Secretariat by 30th September 2014 for discussion by the Coordinating Group in October 2014; and to send an update to the Secretariat by 15th December 2014 for discussion by the Coordinating Group in January 2015.
- to set up 2 new working groups:
  - Best Practices to address issues with EU multi-languages of Young Persons Advisory Groups.
  - GCP training across multispecialty and countries.

  The purpose of these 2 new working groups is to develop pragmatic responses to each need that can be implemented within six months. The focus is on what networks can do, rather than developing comprehensive guidance. As there is already good practice in many of these areas Enpr-EMA needs to focus on disseminating this good practice rather than developing new solutions.
- to continue dialogue and engage with representatives from the US regarding the planned global paediatric network and to explore ways of close collaboration. Enpr-EMA members expressed their wish to industry that European representatives of pharmaceutical companies should also start to actively engage in setting up a global paediatric research network, not only their US colleagues.

Following the open workshop the network members met for their annual face to face meeting. The minutes of this session are published on the EMA webpage dedicated to this workshop.

Day 2:

Day 2 was dedicated for the annual face-face meeting of the Coordinating Group. The agenda and meeting minutes are published on the Enpr-EMA Coordinating Group webpage