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Report on annual workshop of the European Network of Paediatric Research at the EMA (Enpr-EMA), 28 & 29 May 2015

On 28 & 29 May 2015 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, networks' representatives, pharmaceutical industry staff responsible for paediatric studies and regulators.

Day two was dedicated to the Enpr-EMA members meeting, followed by the Enpr-EMA coordinating group meeting to analyse the outcome of day one, and to discuss and define priority tasks for the year 2015-2016.

Day 1

Introduction

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 (Presentation - Update on Enpr-EMA activities, achievements and challenges (Mark Turner)):

- Enpr-EMA expanded with the addition of 5 new networks that joined as Enpr-EMA registered category 3 networks:
  - EPLTN (European Paediatric Liver Transplantation Network);
  - PEDDCReN (Paediatric European Digestive Disease Clinical Research Network);
  - ESPNIC (European Society of Paediatric Neonatal Intensive Care) Medicine Research Network;
  - ECAPN (European Network Child & Adolescent Psychopharmacology Network).
  - INFANT (Irish Centre for Foetal and Neonatal Translational Research Cork University)

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- And 1 national network as Enpr-EMA registered category 1 network:
  - OKIDS (Medicines for Children Research Organization – Austria)
- A framework was established to allow a representative of EFPIA as well as of EUCOPE (to represent SMEs) to become an observer in the Enpr-EMA coordinating group for selected ad-hoc topics to improve communication and collaboration between networks and industry.
- Increase visibility of and publicity for Enpr-EMA:
  - The European consortium Coordinating Action Systems Medicine (CASyM) selected Enpr-EMA as good examples of projects relevant to systems medicine and featured Enpr-EMA on the Systems Medicine Web Hub; the information was subsequently distributed through various channels, including Twitter (@sysmednet), Facebook, Google+ and LinkedIn. http://www.systemsmedicine.net/posts/enprema
  - Poster presentation *"Enpr-EMA: a platform for disseminating good practices about paediatric medicines research across Europe and with international partners"*, at the annual conference of the European Academy of Paediatrics (EAPS 2014),on the work undertaken by the Enpr-EMA Working Groups on some of the pressing issues related to research in paediatric medicines http://www2.kenes.com/eaps/Pages/Home.aspx
- Working groups' deliverables (please see below)
- Participation at the meeting convened by American Academy of Pediatrics on development of a global paediatric clinical trials network
- Discussions with EFPIA and IMI on development of a Pan-European paediatric clinical trials network
- Preparing a proposal to add a European Paediatric Clinical Trials Research Infrastructure to the research infrastructure roadmap that will be published by the European Strategic Forum for Research Infrastructure in 2016.

Challenges encountered in the past years included:

- Marketing the work of networks and Enpr-EMA
- Educating colleagues and the public about clinical trials
- To priorities and find sufficient time and energy for activities

Working groups

The working groups presented their activities over the last year:

The joint working group on "**How to establish communication between Enpr-EMA networks and industry**" and on "**Sharing Good Practice within Enpr-EMA and with Industry Partners**", developed a survey 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. A report summarising the results has been finalised and submitted for publication in a scientific journal. Upon acceptance, the report will also be published on the Enpr-EMA website. To further disseminate the findings and recommendations, the report will also be sent to EFPIA and EUCOPE as well as to the SME office at the EMA for dissemination among their members. As next task, it is planned to utilise results to develop guidelines for new networks and make recommendations to current networks; and to repeat the survey in 3-5 years. In the discussion, it was also proposed to

potentially benchmark against US networks. (Presentation - Working group on public - private partnership (Susan Tansey))

Working Group "**Dialogue and Interaction with Ethics Committees**" developed a table "Informed Consent and Assent Tool Kit for Paediatric Clinical Trials in Europe" showing requirements/regulations regarding consent of children across EU Member States. The table lists the legislative surroundings of the informed consent requirements for paediatric clinical trials of 27 EEA countries: 25 EU Member States and 2 EFTA countries (Norway and Iceland). This table will be published on Enpr-EMA web-site once it has been accepted in a scientific journal. The groups currently finalises this manuscript. (Presentation - Working group on dialogue and interaction with Ethics Committees (Allison Needham, Pirkko Lepola)). As next task, it is proposed to group those countries with similar requirements and to create a "master consent/assent form" including all requirements (varying from one country to the other) to choose from, e.g., a drop down list. Another proposal for a future task was to develop general guidance criteria, which could be used by ethics committees, for how to evaluate paediatric study protocols.

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**" focused on 2 previously identified key priority needs:

1. the need for all stakeholders (industry, academic networks, regulators) to both anticipate potential problems and identify problems when they occur; and
2. the need to establish mechanism(s) to resolve problems, in set up/feasibility and for ongoing studies.

When industry finds an unanticipated problem, they are usually unaware of others experiencing similar issues. Academic networks identify unanticipated problem(s), as they have been asked to participate in multiple studies but are unable to breach confidentiality for individual studies. Therefore, the important outstanding questions are:

- How could networks disseminate the information available to them on how ongoing studies and who has the authority to notify others?
- Could this be one of Enpr-EMA's functions, e.g. by hosting generic issue consensus meetings?

Another proposal was to use scientific conferences for such generic discussions between investigators and industry. While there might be several organisations, such as learned societies, DIA, EUCROF, etc. to host such meetings, the pre-requisite is an agreed mechanism to enable multi-stakeholder discussions without breaching confidentiality. As next action point, it was agreed to develop a SOP on how Enpr-EMA could help to bring all parties involved together for discussion without breaching confidentiality, and to test it by organising such a meeting within the next 6-12 months. (Presentation - Enpr-EMA WG6: A framework for networks to interact with industry and regulators when implementation/conduct of clinical trials agreed in PIPs is no longer possible (Saul Faust))

The working group on **Neonatology** did not much progress as it was awaiting the outcomes of the International Consortium on Neonatology, launched only a week prior to the Enpr-EMA workshop. Upon availability of those outcomes, next action points will be discussed together with the PDCO neonatology working group.

The working group "**Strategies for funding and maintaining a paediatric research network**" compared network mediated paediatric research activities across Europe and tried 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 was based on results of a survey conducted by the NIHR CRN: Children, sent out to 21 networks in the UK as well as gathering information from several Enpr-EMA members. Many networks do not have any documentation on costs, rendering the development of costing templates almost impossible. The findings were summarised in a manuscript to be submitted to a scientific journal.

Finally, the working group tasked to address "**issues with EU multi-languages of Young patient advisory groups"** (YPAG)**,** established since last year's Enpr-EMA workshop, reported that at present four main YPAGs exist in the UK and North America: Children's Specialty Young Persons Advisory Group of the Medicines for Children Research Network (MCRN) in the UK, the Young Persons Group of the Scottish Children's Research Network (ScotCRN) in Scotland, KidsCan Youth Advisory Group of the Child & Family Research Institute (CFRI) in Canada, and Kids and Families Impacting Disease Through Science (KIDS) in the USA. Together, they form the International Children's Advisory Network (iCAN), a global consortium of children's advisory groups. In June 2015, representatives of those 4 groups will attend the International Research Summit of ICAN, to be held in Washington DC. (Presentation - Working group to address issues with European Union multi-languages of young patient advisory groups)

In the following discussion several networks reported on the very positive experience they made with involving adolescents and there was general agreement on the need to actively involve children/adolescents – not only parents and patient group representatives – in the development of medicines for children. Yet, at present, little is known how best to do so, and how to fund these activities. While it was suggested that industry could/should pay for such service, it was agreed that industry funding must not be for a specific drug development, but general for YPAGs activities to ensure independency. The frequently mentioned language barrier might no longer be an insurmountable hurdle, considering the widespread use of social media to chat with other young people across the globe and that most young people (whose mother tongue is not English) nowadays learn English as second language. Different cultures, however, might be a potential barrier. Networks with experience in conducting multicultural studies are encouraged to share their experience with other networks.

Different models of networks

The afternoon session focused on various models of networks. It started with a report by the EFPIA representative on ongoing initiatives, both in the US and Europe, to establish a **global paediatric clinical trial network** to overcome industry's difficulties in finding qualified sites and identifying experienced paediatric investigators. Paediatric trials take longer than expected, recruit fewer patients, but cost much more than adult trials on a per subject basis. In Europe, an industry consortium is currently discussing and preparing an IMI2 call for a "European branch of the planned global paediatric clinical trial network" which will take into account different jurisdictions and healthcare systems across Europe. The aim of the IMI2 project is to secure funding for the next 5 years to establish "national hubs" to function as single national entry points for industry. It is planned to involve as many EU member states as possible. The national hubs will then liaise with individual sites/networks, organise ethics committees' approvals, site contracts, etc. In order to become part of the planned European/ global paediatric trial network, individual sites will have to be ready to start a trial immediately, by having necessary infrastructure, GCP training, master contract, etc. in place. An important topic for the IMI2 call will be to develop a plan on how to ensure sustainability of such a global paediatric clinical trial network beyond the 5 year funding through IMI2. Enpr-EMA will have an important role, not only as liaison with already established networks, national and specialty networks, but also by providing a neutral platform for dialogue with and collaboration between, not only the networks themselves, but

also with industry and regulators. (Presentation - Proposed global pediatric clinical research network - Overview (William R. Treem))

The Canadian network MICYRN (Maternal infant child & youth research network), a practice-based specialist network connecting 17-22 academic sites across Canada, shared their experience: All sites use a unified data provider; by benchmarking, not so good performing sites can be identified and a coaching system be introduced. It is possible to share common resources (as it is not necessary for every individual site to have full time research nurses, data clerk, etc.). There is a need to market the value of networks as well as a need to ensure physician/site receives credit for being involved in networks. Hospitals should be encouraged to market their value by being involved in networks as this adds qualification/accreditation points: through networking and by sharing good practices the quality of care provided can be improved. (Presentation - Maternal infant child and youth research network (MICYRN) (Anne Junker))

Within the Nordic Trial Alliance, a 3-year pilot project funded by the Nordic Council of ministers and NordForsk with the overall aim to enhance Nordic cooperation on multi-centre clinical trials, one work package was tasked to establish a Nordic network for clinical trials in children. To date, a report on feasibility of establishing a **Nordic Investigators Network for Paediatric Medicines (NordicPEDMED),** including Finland, Norway, Sweden, Iceland and Denmark as well as a proposal for the establishment and operation of such a Nordic Paediatric Network has been submitted. Next steps will include making the use of the existing FINPEDMED IT-infrastructure possible for the other Nordic Paediatric Networks, establishing national contact points, a Nordic steering group, as well as securing funding for NordicPEDMED activities. (Presentation - NORDIC investigators network for PEDiatric MEDicines (NordicPEDMED) - Nordic Network (Kalle Hoppu)).

FINPEDMED presented their recently implemented electronic service system, allowing easy tracking of services provided. They reported that the actual rate of trials conducted in Finland is much lower than the rate of queries for trials. Sponsors, upon receipt of answers to their query, frequently do not choose Finland for the actual conduct of the trial and do not report back why Finland was not considered. It was proposed that the performance matrix requested for investigators should also apply to sponsors. (Presentation - Finnish Investigators Network for Pediatric Medicines (FINPEDMED) - IT development for e-Services 2006-2015 (Pirkko Lepola)).

PENTA-ID, a global network with great expertise in conducting both, academic and industry sponsored studies in chronic and acute infectious diseases, covering antibiotics, antivirals, and antifungals, reported on the substantial pipeline of new antibiotics and antivirals, which eventually will have to be studied in children and the challenges associated, such as the lack of observational data to power paediatric trials and lack of paediatric specific regulatory guidance. Another challenge is that treatment standards and antibiotics used differ significantly in Asia and Africa, where most paediatric infections occur and consequently in where clinical trials predominantly are conducted, compared to Europe and US. The need for general standardisation was stressed. Within PENTA-ID recently a European Paediatric Mycology Network has been established as well as a FP7 funded consortium of 20 large European children's hospitals for acute viral infections (PREPARE). This network will capture data on hospital structure and workload, and will provide the largest pan-European cohort on range of acute viral infections (influenza, RSV, enterovirus) for planned studies with new antivirals in the pipeline. (Presentation - PENTA-ID - The future (Mike Sharland)). During the discussion, the need for linking various therapeutic specialities, e.g. antifungal experts with neonatologists or oncologists, from an individual level of collaboration to the level of network collaboration was stressed. Finally, the audience was informed about the paediatric organisation PKIDs (Parents of Kids with Infectious Diseases) with the mission to educate the public about infectious diseases, the methods of prevention and

transmission, the latest advances in medicine, and prevention of the spread of infectious disease. http://www.pkids.org

The last presentation of this session introduced the **Brussels Clinical Trials Network** (ClinicoBru), a non-profit patient (adults and children) recruitment organisation co-founded by three large hospitals in Brussels in 2014. These three hospitals share the same GCP training and the same accreditation process. The organisation developed a model to improve not only collaboration and communication within one hospital (between different departments/services) but also between the three hospitals, and offers flexible research staffing service, e.g. research nurse, data clerk, etc. (Presentation - ClinicoBru The Brussels clinical trial network (Florence Bosco))

Involvement of children

The last session of the workshop was dedicated to involvement of children in research and started with a presentation on the US Kids and Families Impacting Disease Through Science (KIDS) in the USA and the International Children's Advisory Network (iCAN) . The outcome of the first International Research Summit of iCAN in June this year is eagerly awaited.

This was followed by a report on the work by GRIP (Global Research in Paediatrics) to develop guidance for 'best practices' to create Young Person Advisory Groups and the Young Person's Advisory Group Start Up Tool, which is now available online: http://ypag.grip-network.org/. The audience was also informed about another GRIP initiative to develop practical tools to assist Ethics Committees (EC) evaluating paediatric drug trials. Available guidance on key issues identified by EC's during the ethical evaluation of pediatric research are collected, synthesised, and summarised in a document outlining the specific questions that need answering and the considerations that should be made in the ethics review of paediatric clinical trial research. This tool should be tested in a pilot phase to obtain feedback before finalisation. (Presentation - Global research in paediatrics (GRiP) – Tools for Interoperability (Allison Needham, Anne Junker))

The session ended with brief information on the plan to establish a Young Persons Advisory Group within the EMA Patients and Consumer Working Party (PCWP).

Conclusions:

- Based on the discussion and questions raised following each presentation, it was agreed that Enpr-EMA's work in the next year should focus on the following areas: Network Practices, Ethics, Multi-stakeholder meetings, Neonatology, Funding / Sustainability of networks, Young people, and Training. (Presentation - Enpr-EMA Working Groups)
- Existing working groups should select a topic by mid July 2015, send a first work plan to the Secretariat for discussion by the Coordinating Group in October 2015; and send an update to the Secretariat by 15th December 2015 for discussion with the Coordinating Group in January 2016.
- The working group on "A framework for networks to interact with industry and regulators when implementation/conduct of clinical trials agreed in PIPs is no longer possible" should develop a SOP for multi-stakeholder meetings within 3 months, and organise such a meeting within 6 months.
- The working group (WG) on GCP training was broadened to WG on educational training. A new chair was nominated and several Enpr-EMA members volunteered to join. Please refer to minutes of the members' meeting on 29 May 2015 below.
- The WG on best approaches to address issues with EU multi-languages of YPAG would be merged/included in the "to be established" platform of youth group within EMA PCWG.

Day 2:

Day 2 was dedicated to

- The network members annual face to face meeting. The minutes of this session are published on the Enpr-EMA webpage dedicated to this Annual workshop
- The annual face-face meeting of the Coordinating Group. The agenda and meeting minutes are published on the Enpr-EMA Coordinating Group webpage.