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Human Medicines Development and Evaluation

Report on workshop on the European Network of Paediatric Research at the EMA (Enpr-EMA), 10 & 11 March 2011

On 10 & 11 March 2011 the European Medicines Agency (EMA) convened a two-day workshop to introduce the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) to a wider audience. 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. (Link to Enpr-EMA webpage here.)

Day one of the workshop was dedicated to discussions between networks to establish the coordinating group of Enpr-EMA, and to discussing and defining priority tasks of the co-ordinating group. Day two was organised with the assistance of TOPRA to introduce the network to all stakeholders, particularly patient organisations, clinical researchers, and pharmaceutical industry staff responsible for paediatric studies.

Launch of the coordinating group (1st day of meeting)

33 existing networks were represented by 41 participants.

Launch of coordinating group and election of chair

On the first day Enpr-EMA's co-ordinating group (CG) was officially launched and Professor Peter Helms was elected as chair of the co-ordinating group. Prof. Helms is Professor of Child Health at the University of Aberdeen and Director of the Scottish Medicines for Children Network. The CG will contribute to the short and long-term strategy of the network, discuss and solve operational and scientific issues for the network, report to the Paediatric Committee and act as a forum for communication. According to the implementing strategy for EnprEMA adopted by the EMA management board and the outcome of two previous workshops in 2009 and 2010, the total number of members of the CG shall not exceed 20, including 2 members of the PDCO.

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PDCO representatives

The two representatives of PDCO are Dr. Dirk Mentzer and Professor Dr. Paolo Rossi.

Dr. Mentzer is Vice-Chair of the Paediatric Committee at the EMA, a co-opted member for Paediatric Pharmacovigilance in the CHMP-Pharmacovigilance Working Party at the EMA, a member of the Drug Safety Commission of the German Society of Paediatrics, and a member of the International Society of Pharmacovigilance (ISOP).

Professor Rossi is Head of the division of Immunology and Infectious Disease, Children's Hospital Bambino Gesù, Rome, an elected member of the Paediatric section of the European Academy of Allergy and Clinical Immunology, a member of the Italian Society of Paediatric Research (SIRP) and a member of the Immunocompromised Host Society.

Composition of coordinating group

At present 18 networks (so-called "category 1" networks) fulfil all minimum requirements laid down in a set of recognition criteria and are thus automatically members of Enpr-EMA. The workshop participants agreed that those 18 "category 1" networks should become members of the coordinating group for one year. As within the next year an increasing number of networks are expected to fulfil the minimum criteria, the composition of the CG should be re-discussed after the first year.

In addition, the role and position of networks not actually performing clinical trials, such as TEDDY, PRIOMEDCHILD, ECRIN, etc. was discussed. It was agreed that ECRIN and PRIOMEDCHILD, providing infrastructure and funding, respectively, would not fall within the primary aim of Enpr-EMA, and therefore should not be part of the CG. However, networks with expertise in clinical trial methodology should be represented. In this context, GRIP (Global Research in Paediatrics), was introduced: an international research consortium, funded by the seventh framework programme and launched in February 2011 with focus on: 1) development of a Paediatric Clinical Pharmacology Training Program; 2) Validation and harmonisation of research tools specific for paediatrics; 3) Sharing of strategies and plans; 4) Use of ongoing/planned research studies to evaluate the feasibility of proposed research tools and strategies. Several representatives of current Enpr-EMA members are simultaneously members of GRIP and could therefore also represent GRIP within the CG, thus avoiding the need to identify an additional representative for GRIP. The workshop participants agreed that GRIP should be member of the CG and should also represent other networks with expertise in clinical trial methodology.

Interaction between Enpr-EMA and ENCePP

The need for a pharmacovigilance network as member of the CG was expressed. In this context, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), a project led by EMA, was introduced to the workshop participants. ENCePP is open to centers and networks with expertise in conducting pharmacoepidemiology and pharmacovigilance studies. As the main interests of Enpr-EMA and ENCePP differ, existing networks and centres may join both, Enpr-EMA and ENCePP.

As per Implementation Strategy the EMA is tasked to establish a resource-saving structure for the operation of Enpr-EMA, and to establish effective collaboration with ENCePP to avoid duplication of tasks. To this end, the ENCePP resource database, the electronic ENCePP register of studies, and the ENCePP Code of Conduct were presented as basis for discussion for Enpr-EMA members as well as lessons learned from the launch of EnCePP.

The potential use of the ENCePP resource database by Enpr-EMA was discussed. It was agreed to create a temporary ad-hoc working group to evaluate whether the ENCePP database in its current version suits the needs of Enpr-EMA or whether amendments with additional fields and search functions would be necessary.

To ensure interaction between ENCePP and Enpr-EMA, close collaboration of the two secretariats will be maintained at the level of the EMA. In the future, a change to the mandate of the ENCePP Steering Group to accommodate one Enpr-EMA member as observer might be possible.

Supporting emerging networks, not yet fulfilling minimum recognition criteria

Category 1 networks were proposed to "adopt" one of the networks not yet fulfilling all minimum criteria and to represent them by bringing their concerns to the coordinating group. It was proposed

- MCRN-UK to represent RIPPS (France)
- MCRN-NL to represent the Belgian Paediatric Drug Network (BPDN)
- FinPedMed to represent the Swedish Paediatric Society (BLF)
- ScotMCN to represent IPCRN (Irish Paediatric Clinical Research Network)
- PENTA to represent PENTI
- BFMSG to represent CLG-EORTC
- GNN to represent EuroNeoNet (European Neonatal Network) and Neo-circulation (Neonatology network UK)

This proposal was endorsed by the workshop participants and the representatives from RIPPS, PENTI, and EuroNeoNet agreed. All other networks will be contacted and asked whether they also agree with this proposal.

Action points

Contacts to be made by nominated category 1 networks to confirm the above suggestion.

Identifying new networks

Several therapeutic areas (Cardiovascular diseases/Nephrology; Intensive Care/Pain/Anaesthesiology /Surgery; Diabetes/Endocrinology/Metabolic disorders; Gastroenterology/Hepatology; Paediatric Pharmacists) are currently not represented within Enpr-EMA, as either no network fulfils the minimum criteria at present, or no speciality network submitted a self-assessment report.

It was agreed to establish another temporary ad-hoc working group tasked to identify new specialist networks and invite them to join Enpr-EMA. In the meantime, existing national networks such as MCRN-UK, MCRN-NL, FinPedMed, MICYRN with several clinical studies groups and/or research institutions and hospitals covering the majority of clinical paediatric specialties would be able to cover various therapeutic areas.

Prioritising tasks for Enpr-EMA

Following discussions in two smaller breakout groups to allow more active participation in the discussion, the following tasks were identified on which Enpr-EMA should focus:

- establishing Enpr-EMA as platform for communication with industry and patient organisations; to this end developing an Enpr-EMA resource database and improving the current webpage must have priority
- collaboration with PDCO on "Model PIPs": to agree with the PDCO 3-4 therapeutic areas to start with
- define a policy of transparency and adapting the EMA policy on the handling of potential conflicts of interest with the aim to balance the need to ensure that experts involved have no interests which could affect their impartiality with the need to secure the best (specialist) scientific expertise.
- linking activities between Enpr-EMA's members
- developing common educational tools for patients/parents to increase willingness to participate in paediatric trials.
- establish time limited working groups

EMA/TOPRA meeting with industry stakeholders (day 2)

The second day was being organised with the assistance of TOPRA and was attended by more than 160 participants.

Introduction of Enpr-EMA to wider audience

The first session was dedicated to introduce Enpr-EMA to all stakeholders, particularly patient/parent organisations, clinical researchers and pharmaceutical industry staff responsible for paediatric studies.

Two introductory presentations on "The Paediatric Regulation as an instrument for European paediatric research", as well as on the organisational and functional structure of Enpr-EMA were followed by a presentation by the chair of the PDCO on "The Contribution of Regulators for a European Network of Paediatric Research" and by the chair of the Clinical Trial Facilitation Group on "Paediatric networks for clinical trials in children: regulatory authorities perspectives".

Expectations from various stakeholders

The second session was dedicated to listening to and discussing expectations of all stakeholders involved, i.e. networks, pharmaceutical industry and patient/parent organisations.

The *pharmaceutical industry* was represented by large pharmaceutical companies, as well as companies developing medicines for rare diseases and small and medium-sized enterprises (SMEs). One representative from each of those three types of pharmaceutical companies presented their expectations for Enpr-EMA.

To summarise their views:

- There is a need for optimal collaboration between the paediatric research networks and the pharmaceutical industry to achieve the goal of " Better Medicines for Children"
- This collaboration should support
    - *optimizing paediatric investigation plans (PIPs) and study protocols*
    - *fast patient recruitment and trial execution*
    - *high quality of trial conduct and data*
    - *providing optimal care for children participating in clinical trials*
- Collaboration between pharma and paediatric scientific and medical experts requires training in the skills for medicines development

The *networks*' perspective was addressed by three presentations from three different types of paediatric networks: a large national network, an oncology network and a neonatal network.

To summarise their views:

- There is a need to facilitate a dialogue geared toward cooperation and information sharing between regulators, academia and industry
- There is a need to communicate that research into medicinal products is helpful to improve children's care
- There is a need to learn from other paediatric networks and to share expertise within Enpr-EMA
- Paediatric drug trials should follow the KISS rule: Keep It Simple and Smart
    - *Simple methods for collecting, storage and analysis of biosamples.*
    - *Simple methods for documentation of exposures, endpoints and serious adverse events.*
    - *Smart methods for drug monitoring and pharmacokinetics.*
    - *Limit/reduce bureaucracy (especially for investigator sponsored trials).*

The *parent/patients*' expectations were addressed by the secretary general of the Patients Network for Medical Research and Health (EGAN) and one PDCO member representing patients' organisations.

To summarise their views:

- Enpr-EMA must ensure that the quality standards required to become a member of Enpr-EMA, including public involvement, are implemented across all paediatric clinical trial (CT) centres in Europe
- Parents should be involved in assessing benefit/risk: loving their children considered as potential candidates for participation in a clinical trial, they may be even better suited than ethics committees.
- There is a need to increase awareness of ethics committees regarding paediatric research
- There is a need to raise awareness of politicians regarding paediatric research: the health of children is the health of future elderly people

- Patients should not only be involved as research subject, but also as information provider, advisor, reviewer, co-researcher, driving force. Patients should be involved

  Before the CT;

  - Identification of indications, therapy features, patient population
  - Patient perspective on ethical and risk/benefit dilemmas: loving their children considered as potential candidates for participation in a clinical trial, they may be even better suited than ethics committees.
  - Defining patient-oriented outcome measures

  During;

  - Managing of expectations: hope or hype
  - Patient inclusion and compliance
  - Data quality
  - Patient and public confidence in clinical research

  After;

  - Quality of life, quality of healthcare
  - Therapy compliance

Proposals for the effective use of Enpr-EMA

The third session was dedicated to discuss proposals for the effective use of Enpr-EMA.

The above presentations set the scene for the discussions in three break-out groups to discuss

1. The role of EMA staff, PDCO and PIPs
2. How industry can access and use Enpr-EMA
3. How patients can be involved in networks and in trials.

1. To summarise the discussions on the role of EMA staff, PDCO and PIPs:
   - Need to ensure regular interaction between Enpr-EMA/PDCO
   - PDCO to decide "priority list" of model PIPs
   - Need to address potential conflict of interest: experts for network/applicant/PDCO
2. To summarise the discussions on how industry can access and use Enpr-EMA:

   Expectations for Networks

   To provide scientific information in disease areas

   - Identification of therapeutic needs for future research, feed-back to PDCO on priorities
   - Help identify best standard of care in Europe

- Provide some scientific input for PIP design: both ways, to EMA and industry
- Aligning study protocols with patient needs, scientific needs, and paediatric practice (driver for feasibility)
- Provide resources for high-quality study conduct
- Provide training at sites in order to ensure high-quality study conduct
- To reach out to non-European spin-off/spin-out companies developing new molecules in order to have them studied in Europe

How and When to use Network

- Consulting role
  - Early dialogue with networks before PIP application on paediatric strategy with focus on feasibility, realistic timelines, patients availability, competing studies
  - 2nd step dialogue when finalizing PIP/studies
- Generator of facilitation tools
  - Model PIPs in collaboration with PDCO
  - Agreement on age-appropriate endpoints
  - Discussion about safety aspects

Industry input to Network

- To share expertise in study design, training to sites
- To share unpublished data with networks
- To publish available data, eg PK/PD data, or negative outcome data

3. To summarise the discussions on how patients can be involved in networks and in trials:

   The discussion focused on three topics:

   1) Added value of patient involvement
   2) How to improve interaction/communication among all parties
   3) Consideration of resources

   1) Added value of patient involvement:
      - When preparing information (informed consent and assent)
      - Need to be complete vs be understood
      - To increase public awareness of the need for CTs
      - Involvement in ethics committee
      - Benefits of real participation rather than nominal consultation?

- Lobbying industry in deciding on paediatric research priorities.
- Lobbying public research programmes (e.g. areas where no paediatric development exists)

2) How to improve interaction/communication among all parties:
   - The example of HIV patients' groups (well informed patients)
   - Link Enpr-EMA with registry of existing networks/organisations at national level (e.g. in the field of neonatology)
   - Link Enpr-EMA with EMA list of European "eligible organisations" with interest in paediatrics
   - Make them operational
3) Consideration of resources:
   - How much is enough for the patients/parents and for the researchers
   - How to ensure sustainability of the system

Next Steps and proposed timelines:

- 20 June 2011: first face to face meeting of Coordinating group (CG)
- Develop mandate of the Coordinating Group
- Develop policy of transparency and adaptation of the EMA policy on the handling of conflicts of interest, to be finalised during face-to-face meeting of CG in June 2011
- Create time-limited working groups for
  - developing resource database
  - establishing collaboration with PDCO regarding development of "model" PIPs
  - identifying additional networks covering diverse therapeutic areas
- 03/2012: next Enpr-EMA workshop with all stakeholders, i.e. networks, industry and patient/parent organisations

All presentations will be publicly available on the EMA webpage (www.ema.europa.eu) as well as the TOPRA webpage (www.topra.org/Enpr-EMA-presentations).

List of networks who have submitted a self-assessment report to EMA:

http://www.ema.europa.eu/docs/en_GB/document_library/Templates_and_Form/2010/02/WC500073674.doc

Networks fulfilling all minimum criteria:

- ITCC (Innovative Therapies for Children with Cancer)
- I-BFMSG (International Berlin/Frankfurt/Münster Study Group)
- NIHR-MCRN (National Institute for Health Research-Medicines for Children Research Network – UK)
- EUNETHYDIS (European Network for Hyperkinetic Disorders)
- PENTA (Paediatric European Network for the Treatment of AIDS)
- FIMP-MCRN (Italian Paediatric Federation-Medicines for Children Research Network)
- ScotMCN (Scottish Medicines for Children Network)
- PRINTO (Pediatric Rheumatology International Trials Organisation)
- Newcastle-CLLG (Children's Cancer and Leukaemia Pharmacology Studies Group)
- ECFS-CTN (European Cystic Fibrosis Society – Clinical Trials Network)
- FINPedMed (Finnish Investigators Network for Pediatric Medicines)
- EPOC (European Paediatric Oncology off-patent medicines Consortium)
- UKPVG (United Kingdom Paediatric Vaccines Group)
- MICYRN (Mother Infant Child Youth Research Network)
- GNN (German Neonatal Network)
- MCRN-NL (Medicines for Children Research Network – NL)
- EBMT (European Group for Blood and Marrow Transplantation)
- CICPed (Paediatric Network of Clinical Investigation Centres, France)

Networks currently not fulfilling minimum criteria:

- CLG-EORTC (Children Leukemia Group of European Organisation for Research and Treatment of Cancer)
- BPDN (Belgian Paediatric Drug Network)
- AMIKI (The Paediatric Trial network Germany; emphasis on Endocrinology and Diabetology)
- EuroNeoNet (European Neonatal Network)
- JSWG of PRES (Juvenile Scleroderma Working Group of Paediatric Rheumatology European Society)
- Neo-circulation (Neonatology network UK)
- PENTI (Paediatric European Network for the Treatment of Infection)
- RIPPS (Le Reseau d'Investigations Pediatriques des Produits de Santé; France)
- IPCRN (Irish Paediatric Clinical Research Network)
- BLF (Swedish Paediatric Society)
- NCCHD (National Center for Child Health and Development, Japan)
- IPTA (International Paediatric Transplant Association)
- Futurenest Clinical Research (Hungarian paediatric network)
- ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition)
- INN (Italian Neonatal Network)