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Human Medicines Development and Evaluation

Report on second workshop of the European Paediatric Research Network (EnprEMA), 16 March 2010

Background

On 16 March 2010 the European Medicines Agency (EMA) convened a one-day follow-up workshop on the European paediatric research network. One of the objectives of the Paediatric Regulation (EC) No 1901/2006, as amended, is to foster high quality ethical research on medicinal products to be used in children. This should be achieved through efficient inter-network and stakeholder collaboration. To meet this objective, a European paediatric network of existing networks, investigators and centres with specific expertise in performing drug trials in the paediatric population has to be established.

Following the outcome of the first workshop with participants of 38 networks and/or clinical trial centres in February 2009, two working groups with members of identified networks were established and were tasked to elaborate

1. The structure for the operation of the European Paediatric network.
2. Recognition criteria for existing networks which will have to be fulfilled to become a member of the European paediatric research network at the EMA (EnprEMA).

Both groups achieved their respective tasks and in February 2010 the recognition criteria elaborated were put on the Agency's website for public consultation.

The aim of the second workshop was to discuss with the networks the proposals elaborated by the two working groups, and to come to an agreement on the recognition criteria and the structure for the operation of EnprEMA. Twenty-two networks were represented by 27 participants (see List of participants). In particular the other Agency network, the European network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was represented, and for the first time commercial partners with the European Clinical Research Organisations Federation (EUCROF).

Operational structure of EnprEMA:

The morning session was dedicated to discussing the structure for the operation of EnprEMA. The [implementation strategy](#) for EnprEMA adopted by the EMA Management Board proposed to create a 'Coordinating Group' which would 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.

The chair of working group presented their proposal for the composition of the Coordinating Group:

- The Coordinating Group should a) be as diverse as possible, b) inclusive to represent various types of networks: networks focusing on specific therapeutic areas, specific needs/age subsets (e.g. neonatal /adolescent networks) or specific activities (e.g. pharmacovigilance), as well as organisational networks (e.g. national networks linking together either several clinical trial centres or community paediatricians), accommodating for regional differences throughout Europe with regards to how the medical care of children is organised.
- According to the implementation strategy the total number of members shall not exceed 20, including one member representing the EC and 2 members of the Paediatric Committee. Thus the Coordination Group will consist of 17 members of existing and recognised networks. The working group could not agree that initially all networks meeting the recognition criteria would automatically become members of the Coordinating Group, whereas other networks would then have to group themselves to be represented, once the maximum number had been reached. Instead the working group proposed the following composition:

- 4 members representing national networks
- 10 members representing diverse therapeutic areas (either existing and recognised European networks or learned societies if the latter have access to clinical trial centres with the following proposed as necessary:
 - Oncology
 - Diabetes/Endocrinology/Metabolic disorders/Gynaecology
 - Gastroenterology/Hepatology
 - Allergology/Immunology/Transplantation/Rheumatology
 - Haematology /Haemostaseology
 - Respiratory diseases /Cystic Fibrosis
 - Cardiovascular diseases/Nephrology
 - Psychiatry/Neurology
 - Infectious diseases/Vaccinology
 - Intensive Care/Pain/Anaesthesiology/Surgery
- 3 members representing special activities/ age groups:
 - 1 member from European neonatal network
 - 1 member representing European paediatric pharmacists
 - 1 member representing special activities, such as pharmacovigilance and long-term follow up, and community paediatricians

Once networks have published evidence that they fulfil the recognition criteria, the final composition of the Coordinating Group should meet the above criteria. It is proposed

- to define so called “subgroups”, i.e. representatives of networks which have grouped themselves to be jointly represented within the coordinating group.
- to invite “subgroups” to meet at least once yearly at the EMEA, e.g. the afternoon before the day of the annual workshop, to promote and allow inter-network exchange.

The Implementation strategy states that membership of the Coordinating Group will be for 3 years only to ensure sufficient renewal and involvement of various members. This was agreed upon in principle; however, the working group proposed to replace only some members of the Coordinating Group initially to ensure continuity.

Outcome of the discussion with the participants:

1. Composition of the Coordinating group:

The proposed composition of the Coordinating Group was extensively discussed. The final agreement was to have 4 instead of 3 members representing special activities/age groups:

- 1 member from European neonatal network
- 1 member representing European paediatric pharmacists
- 1 member representing pharmacovigilance,
- 1 member representing community paediatricians/primary care physicians.

Regarding pharmacovigilance and long-term follow up, participants were informed about the European Agency's Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). This is a project intended to strengthen the post-authorisation monitoring of medicinal products in Europe by facilitating the conduct of multicentre independent safety studies, and studies focusing on long-term efficacy. Although not the primary focus, ENCePP also includes paediatric centres. A close collaboration and link between EnprEMA and ENCePP is welcome to avoid duplication.

With regard to the grouping and the final number of members representing various therapeutic areas, the consensus was to wait and re-discuss who can be members of EnprEMA once networks have submitted their self-assessment. Flexibility of the composition was agreed.

In addition, it was agreed to include one member representing expertise in clinical trial methodology. This member could also represent networks not actually performing clinical trials (such as TEDDY, PRIOMEDCHILD). In addition, the need for a close link and collaboration with the Agency network of biostatisticians was identified; the consensus was that biostatisticians did not need be represented within the Coordinating Group.

It was noted that for this type of network specific recognition criteria would have to be elaborated as the proposed ones were established for networks performing clinical trials.

During the discussion, it was emphasised that 'national' networks may be multidisciplinary in nature and are not a representation of national interests; their expertise may be in establishing collaboration of various centres with the expertise in conducting clinical trials. To better reflect this, it was suggested to use the term 'transversal' networks instead of national networks.

The question was raised whether or not pharmaceutical industry should be represented in the Coordinating Group. The final consensus was that while establishing regular communication and formal collaboration with industry is considered very important, pharmaceutical industry (including CROs) should not be part of the Coordinating Group. This was acceptable to the representatives of the European CROs Federation (EUCROF). Nonetheless, to ensure close collaboration, industry and CROs will be invited to the annual network meeting at the EMA, on the day dedicated to this activity. More frequent meetings might be considered necessary by the Coordinating Group.

2. How to establish links with emerging networks

Participants discussed whether and how to ensure that emerging networks, i.e. those being established or new networks not yet fulfilling the recognition criteria, will also be represented in the EnprEMA. A proposal was that every established network, once a member of the EnprEMA, would have to "adopt" and represent an emerging network (twinning). This proposal was agreed upon. Thus established

networks, when submitting the recognition self-assessment, will be asked to name one emerging network (please refer to next steps below).

3. The tasks of the Coordinating Group

The main tasks identified were:

- to facilitate access for industry to paediatric clinical study sites (e.g. coordinate industry requests / enquiries / feasibility) to the Networks / Centres of Excellence / experts / societies.
- to act as a platform to communicate and negotiate with industry
- to work on agreement/contracts with pharmaceutical industry regarding paediatric trials
- to identify networks which are not yet on the Agency list
- to develop common educational tools for patients/parents to increase willingness to participate in paediatric trials
- to help ensure feasibility of studies and monitor trial recruitment so that feasibility can be maintained

The list was found to be quite ambitious. It was agreed to prepare a list of priority tasks to be discussed at the first meeting of the Coordinating Group. In addition, it was felt that the Coordinating Group should avoid directing other networks. Therefore, preference should be given to expressions such as “to foster methodology adapted to need of children; to share knowledge, experience, procedures; to encourage links and collaboration”.

In this context the name of the group ‘Coordinating’ was also questioned and ‘Collaborative’ was proposed as more appropriate.

4. Duration of membership

The proposal of working group 1 was agreed to allow for continuity and retaining memory, by not replacing the whole group in one step, but rather by third for example.

5. Ways of communication

Time-saving communication ways, such as e-mails, telephone and/or videoconferences should be given preference. The Coordinating Group would meet three times a year at the EMA. In addition, one workshop should be held open to all network participants once a year, over 2 days, to provide the forum for industry collaboration on the second day.

6. Role of EMA

The EMA’s role will be

- to provide secretarial support to the activities of the network and the organisation of the meetings of the Coordinating Group
- to coordinate and promote exchange of information between the network partners
- to provide information to external partners and stakeholders.

Recognition criteria:

The afternoon session was dedicated to the recognition criteria. The chair of working group 2 informed the participants how the criteria were elaborated, using both the *Delphi* technique for the first and second round, and the *Nominal group* technique in the face-to-face meeting held in December 2009 at the EMA.

In the first round of the Delphi survey, all 62 networks identified were asked for suggestions of recognition criteria. Thirty replies (30/62, 48%) were received including one from EMA. Similar proposals were grouped within 8 categories in order to obtain a list of the most cited criteria. Only criteria that can be quantified, either qualitatively (e.g. yes or no or other scales) or quantitatively (e.g. numbers) were taken into account.

In the second round, sent again to the 62 networks, responders were asked to rank the 8 categories from 8 for the most important, to 1 for the least important. Within each of the 8 categories, responders were asked to select one or several essential items that are important to quantify the related category.

The response rate to the second round was 45/62 (73%): 41 completed the survey, 4 refused and 17 did not reply. Based on these responses, the members of both working groups were invited to a consensus conference at EMA with the goal to establish the final list of criteria. During this meeting the final list was condensed to the following 6 categories, each with several sub-categories:

1. Research experience and ability (13 subcategories)
2. Network organisation and processes (10)
3. Scientific competencies and capacity to provide expert advice (7)
4. Quality management (7)
5. Training and educational capacity to build competences (5)
6. Public involvement (3)

After the preparation of a glossary to explain the individual categories / subcategories, and a pilot test with all network members of the two working groups, the recognition criteria were put on the EMA webpage for public consultation until February.

The comments received noted that:

- providing all the information asked for in the several categories/subcategories will be very time consuming; however, many also added that
- there is a need to define minimum criteria for recognition and to differentiate between essential vs. desirable criteria
- a disclaimer on future changes to the current recognition criteria is necessary,
- newly established networks will have difficulties fulfilling all criteria.

During the discussion it was agreed:

- To develop “basic criteria” for emerging network to stimulate creation of new networks
- To establish different criteria for networks not performing trials (e.g. Priomed, Teddy)
- To maintain full transparency (in respect of the recognition self-assessment). Some participants held the view that the requirement to make the self-assessment public might result in unreliable information and proposed anonymous evaluation. However, the majority of participants endorsed

the need for transparency. It was further clarified that there will be no formal 'accreditation' process and that EMA will not audit networks. Networks will be asked to provide evidence supporting the assessment and make it publicly available.

- It was clarified and agreed that the self-assessment should be reviewed by the networks on an annual basis.

In addition the following was discussed:

- RE criterion 1.2 (Number of patients potentially eligible for clinical trials per year). Participants commented that it might be very difficult to provide an accurate number. It was suggested to ask instead for the numbers of patients and/or the proportion of eligible patients actually recruited each year.
- RE criterion 2.5 (existence of internal database for disease, condition, treatment and/or outcome): The requirement for having/accessing a database/disease registry might give rise to legal concerns and might be an insurmountable hurdle for some networks. The rationale for this requirement was to obtain information about the network's capacity to recruit patients, but not to publish a list of patients.
- RE criterion 2.4 (existence of a website): The rationale was to measure the means of internal (within the network) and external communication.
- RE criterion 3.1 (numbers of peer-reviewed publications in the last 5 years): The networks should not only state the number of publications but also provide a list of references (with impact factor); as networks may not be referred to in the publications, a description providing evidence of the contribution of the network could be added. This will allow better judgment on the quality of the network and the trials performed.
- RE criterion 4.1 (adherence to GCP: all studies conducted comply with the EU Directive on Clinical trials): this was felt to be too strict, particularly for new networks. It was proposed to delete 'all' for the time being whilst reminding that to ensure adequate protection of patients, the ultimate goal must be compliance with the EU Directive in all studies. This should be reviewed after e.g. two years.
- RE criterion 4.4 (availability of standard operation procedures): The rationale is to share experience and reduce duplication of efforts. Only SOPs on general procedures related to clinical trials, but no confidential information, will be asked for. It was reminded that to be applicable, an SOP should be generated by the users directly.
- RE criterion 5.5 (promotion of participation in clinical trials in countries with limited resources): it was proposed to request a list of countries where CTs are/have been performed in addition to the proposed yes/no answer.

The last part of the afternoon session was dedicated to defining minimum recognition criteria to become a member of EnprEMA. There was general consensus on a definition of a minimum set of criteria based on the following:

- Recognition criteria are related to quality of research
- A minimum level of quality must be provided
- The intention is to be open to new/emerging networks and organisations

The minimum requirements agreed were:

- At least 1 ongoing or completed trial (Criterion 1)

- An identified contact person (Criterion 2)
- An external or internal Advisory Board (Criterion 2)
- Internal patient database or disease registry (Criterion 2)
- Individual data protection and data security (Criterion 2)
- Access to experts/expert groups (Criterion 3)
- Capacity to answer scientific questions (Criterion 3)
- Compliance with GCP (Criterion 4)
- Compliance with Ethical Considerations (Criterion 4)
- Monitoring Capacity (internal or external) (Criterion 4)
- Quality control (Criterion 4)
- Awareness of regulatory requirements for medicines development (Criterion 5)
- Training received/given (Criterion 5)
- Involvement of patients in either protocol design, or patient information package, or prioritisation of needs for clinical trials (Criterion 6)

Next Steps and proposed timelines:

Task for both working groups:

- To define criteria for networks which are not performing trials

Tasks for EMA:

- To publish the revised recognition criteria (as agreed) on the EMA webpage (by April 2010), including the agreed minimum criteria
- To organise a T-conference with all newly recognised networks to agree on a meeting date at the EMA for establishment of the Coordinating Group.
- To organise a meeting with all stakeholders including industry over 2 days (4Q 2010)

Tasks for individual networks:

- Individual networks will have three months to do the self-assessment, with provision of evidence for all information, and to make it publicly available (proposed deadline by July 2010)
- Each recognised member should identify a network for the twinning process, including representation within the Coordinating Group (at its establishment meeting)
- To provide a list of centres which are able to perform GCP trials as of today. This list will be made available to industry as a service.

Tasks for the Coordinating Group once established:

- To confirm minimum criteria for emerging networks.

All members, in particular the Chairs of the working Groups were thanked for active participation and successful delivery of the tasks within the planned timeframe.

List of participants:

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Kalle Hoppu	Finnish Investigators Network for Paediatric Medicines
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Martine Dehlinger-Kremer	European CRO Federation
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