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Ethical considerations for paediatric trials

How can Ethics Committees of the Member States and the Paediatric Committee at the European Medicines Agency work together?

Report on an international meeting at the European Medicines Agency
30 November – 1 December 2011

Executive Summary

The meeting brought together 25 Ethics committee members representing 15 Member States, more than 20 European regulators, members of paediatric research networks and clinical researchers. There were also more than 40 pharmaceutical companies. Other participants with experience in paediatric ethics came from the US and Canada. The report provides the outcome of the meeting, the view of Ethics committees represented and other members dealing with paediatric trials. The actions suggested refer to objectives and activities of Ethics committees in collaboration with the EMA and its Paediatric Committee, while some refer only to either the EMA or Ethics committees. The follow-up activities have been reviewed with the help of some meeting participants.

Trials with children, from newborns to adolescents, are necessary to provide safe and effective medicines to them. Medicines have not been studied sufficiently in the past in children, but the situation has changed since the implementation of the US and then EU Paediatric Regulation in 2007. The safe and well-defined environment of a trial protects children participants from harm better than off-label use. Trials are necessary to generate evidence-based reliable information on safety and efficacy of medicines.

The Paediatric Committee evaluates the design of future paediatric trials proposed in Paediatric Investigation Plans (PIPs), including some ethical aspects. The main ones are how to minimise the burden on participating children and how to ensure that the trial is scientifically sound, the latter being a pre-requisite for ethical acceptability. Before a paediatric trial is authorised in the EU, a favourable opinion has to be given by an Ethics Committee with paediatric expertise, taking into account the risks and benefits of research and other aspects such as the study design, the use of placebo and the monitoring of safety during and after the trial. Despite having distinct roles and responsibilities, Ethics committees and the Paediatric Committee evaluate many common elements.

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During the meeting, Ethics committees and the EMA Paediatric Committee examined how they could work together efficiently, when reviewing the design and conduct of paediatric trials. All are interested in direct communication on specific cases of paediatric research and, at a European level, in dialogue and exchange of ideas to improve research ethics. Opportunities for research into ethical issues of paediatric trials were identified, as well as for improving information produced by the EMA and that to Ethics committees. The involvement of children and young persons should be developed throughout design, conduct and interpretation of paediatric research. Some practical actions were outlined as joint activities of Ethics committees and the EMA / PDCO. Overall, it was agreed that there should be more opportunities to share with the public and explain our experience on ethical aspects of paediatric trials, including in scientific meetings.

The shared ethical responsibilities for progress in science and health of children was acknowledged by the paediatric Ethics Committees, patients /families, the European network for paediatric research at the EMA (Enpr-EMA), the EMA / PDCO, paediatric clinical trialists, and pharmaceutical companies.

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The agenda of the meeting, presentation slides and recordings of the meeting are available here: http://bit.ly/yMWZym ("All documents").

The following text is a summary of the presentations and the discussion.

1. Sessions 1-3

Session 1: Background and meeting objectives

This session introduced the roles and responsibilities of the EMA Paediatric committee (PDCO) and of the Ethics committees (EC) in Europe.

- The Paediatric Committee (presented by **Daniel Brasseur**, Chair of the PDCO) has a key role in implementing the Paediatric Regulation (EC) No 1901/2006. The Regulation came into force on 26 January 2007, and required that all new and many authorised medicines have to be evaluated by the PDCO for potential use in children and be developed with a view to being authorised in children. The PDCO must ensure that clinical research conducted with children is of high scientific and ethical quality, in order to increase availability of medicines that are appropriately authorised for children, and to increase transparency and produce better information on medicines for children.
- The legal and regulatory framework for pharmaceutical products (presented by **Agnès Saint Raymond**, EMA) includes the Paediatric Regulation, the Directive on Clinical Trials 2001/20/EC

(GCP for trials using medicinal products), the ICH guidelines (E6 and E11) and some Commission Guidelines. A specific document the "Ethical Considerations for clinical trials with the paediatric population" [AHG2008], was published in 2008 and was intended to be a practical aid for Ethics Committees. Feedback on this document was sought from Ethics Committees to make it more useful. In addition, the EMA has also produce an analysis of trials performed in "third country", because of an increase in numbers and geographic dispersion. Such trials submitted for marketing authorisation may raise concerns as to the application of standards and ethical principles, the global distribution of research burden, the role of Ethics committees and how patients' views are heard. In such trials, participants and even more so minors, may be more susceptible to influence and vulnerable, for reasons of poverty, young age, lack of access to care and understanding of research. Investigators may also be influenced and subject to conflicts of interest for reasons of fewer opportunities for research and access to innovative treatments. The EMA has published a "Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU regulatory authorities" [EMAGCP2012], which aims to strengthen processes and provide assurance to the public that clinical trials used in marketing authorisation applications meet the ethical and GCP standards, no matter where in the world they have been conducted.

Comments showed that there is uncertainty and a lack of clarity on the definition of risk and its categories (minimal to more than minor increase over minimal). With respect to age of consent (legally required process, as opposed to assent), which is established by national laws, some EU Member States allow adolescents to take decisions for themselves on clinical care. Although there are differences with decisions on clinical research, it was suggested that adolescents should be able to consent to research, based on a continuously maturing capacity to understand research and to make a fully informed decision. Regarding the EU guideline, the "Ethical considerations" may not have reached Ethics committees, and may be too long to be practical. Overall more communication was expected from EMA aimed at Ethics committees, if EMA guidelines and documents are meant to help Ethics committees. The EMA acknowledged that Ethics Committees are managed at national level but that in the best interest of children participating in research, there is a need to reach out to Ethics committees, who in turn could also improve their functioning by developing an effective organisation at European level. A direct exchange between Ethics Committees and the PDCO is desirable, in order to compare experience in evaluating paediatric clinical research proposals and handling ethical issues in paediatric trials.

Session 2: How are paediatric trial proposals evaluated?

The session reviewed how the PDCO and ECs work to identify and address ethical issues of paediatric trials, and where there are opportunities for collaboration.

- A survey [Altavilla2011] of the involvement of Ethics committees in paediatric research in Europe performed in 2009 (**Annagrazia Altavilla**, Marseille) has suggested to increase awareness of ethical issues related to paediatric research, even though, Ethics committees do already involve paediatric expertise in the vast majority of paediatric trial reviews.
- The PDCO approach to the evaluation of Paediatric Investigation Plans was presented by **Marek Migdal** (PDCO). Pharmaceutical companies submit proposals for PIPs, which are structured according to a Commission guideline [OJ2008]. The PDCO then discusses scientific questions, such as the (unmet) paediatric needs and potential paediatric use for the medicine, the relationship between relevant adult and paediatric data, which type of data should be generated through paediatric trials so that the medicine could be authorised and the needs met. The paediatric medicine development is presented in a PIP by the development strategy and by synopses of

paediatric trials rather than detailed protocols. The PDCO discusses the scientific robustness of the approach and the acceptability of the burden for the children, as well as potential harms and benefits. For example, the approach for sampling or analysing pharmacokinetic and pharmacodynamic data may be agreed by the PDCO. However, the PDCO does not assess information on the qualification of investigators and sites, the exact volume of blood samples and information sheets for participants and parents or legal guardians. The PDCO deals with uncertainties when agreeing a proposed PIP, often years in advance of the paediatric trials, when the adult development is still ongoing. Modifications of an agreed PIP are possible, and required when new data emerge, indicating to change the strategy.

- Young persons as research subjects present "old problems" with respect to ethical, moral and philosophical issues (lecture by **Inez de Beaufort**, Rotterdam). Without belittling these problems in paediatric research, the debate has to take note of the scale of ethical issues when seen globally, where children are ignored in daily life ever so often. In medicine research, underprotection is of similar concern for children, but additionally their overprotection is of concern because administering treatments that have not been subject of research is unethical, prima facie. Indeed, debating and justifying paediatric research requires to balance dignity, non-malevolence, beneficence and solidarity. Requiring minimal burden in non-therapeutic research raises a number of issues (such as the possibility for exceptions, the understanding of "minimal", the presence of both non-therapeutic and therapeutic elements in a given trial, the attempt to stretch the notion of "benefit"). "Minimal burden" seems a principle that, were it applied literally, would lead to such additional issues and to overprotecting children. The debate on paediatric research includes views that there is a duty (of children) to contribute to research, that research can be therapeutic in a moral sense, and that children can show solidarity, even to those with other diseases (cf. works of John Harris). Other views are that exceptions to minimal risk and burden might be justified by assent and the exceptional value (indispensable necessity) of the study to improve medical care for children [Westra2011]. For the future, differences of assent should be subject of research, scientific standards should be scrutinised, children's views and experiences should be sought, focus groups with paediatricians, parents and children should be considered, the burden to children should be investigated and awareness of other groups of patients should be raised.

General discussion: It was acknowledged that sick children, such as those with cystic fibrosis or with a malignant disease, know well the burdens and the procedures of care and research. It was suggested to assess the competencies of the child participant to provide assent, but this is already part of the attempts to achieve understanding of the proposed study. The involvement of children was acknowledged to be important (see below).

The representation of diverse expertise in the PDCO, including health professionals and patient organisations, and the possibility to add expertise is a unique model. The committee can form an informed view on a medicine and how it should be developed for paediatric use. Ethics committee members mentioned that, at times, they would like to have better knowledge or expertise in certain areas. The intention of the PDCO is to establish a strong co-ordination to discuss and implement the PIP in practice, between all stakeholders.

In contrast to the PDCO which sees the whole development programme, ECs see only one paediatric trial at a time, without necessarily a view of the overall development. Ethics committee representatives asked to obtain the submission of the agreed PIPs when they evaluate a paediatric trial.

On the other hand, industry representatives mentioned that they try to convince Ethics committees of regulators' requirements. It was not considered desirable that trial sponsors play a mediator's role. Ethics committees asked for direct collaboration with regulatory bodies, such as the EMA. In this context, the European Network of Research Ethics Committees (Eurecnet, http://www.eurecnet.org/)

which is being established as a platform of national associations of Ethics committees, offered to play a role.

Representatives of Ethics committees acknowledged that the particular vulnerability of children and the complexity of ethical issues in paediatric research called for special attention during the ethical review. It was suggested that local Ethics committees could be helped, possibly by a (national) central monitoring or accreditation organisation. Such a model is in place in the Netherlands for example. Universities should play an increasing role in the development of competencies in ethics.

Reasons for possible divergent Ethics committee opinions and difficulties to achieve a single opinion were explored. Randomised, placebo-controlled, double-dummy international trials may be viewed differently because the attitudes towards placebo acceptability are variable. The availability of and funding for the comparator often depends on the national health care system and this may create disparities. An asthma trial recruiting both children and adult participants may be difficult to evaluate with respect to its specific benefits for children, whereas results in adults in a first, separate trial could better inform a subsequent trial in children.

While Ethics committee rarely find it necessary to refuse a paediatric trial, they often find that the burden to children could be reduced significantly, and almost all paediatric trials are requested to be modified for one or the other ethical reason. Based on information from representatives from large Member States, no paediatric trial seems to have been refused primarily because of the proposed placebo use. For example, there are a number of medicines authorised for multiple sclerosis, which is a partly irreversible disease, and it was felt that placebo use in children was not sufficiently justified in some trial protocols; therapeutic recommendations made by learned societies may not have been reflected sufficiently in the placebo discussion. Similarly, the EMA reported a number of discussions on valid active controls in children, and related but general difficulties with non-inferiority approaches used in active-controlled designs. Paediatric trials need to be able to provide a scientific conclusion, otherwise they would be unethical. In a number of progressive paediatric diseases, including Duchenne muscular dystrophy, adult data are of little relevance for a medicine use in children.

Other ethical issues shared between Ethics committees and the EMA were competition for paediatric patients between trials, which may be worsened by systematic regulatory requirements. While pharmaceutical companies have to be treated the same way, regulators have to assess each medicine on its on merit.

Session 3: Methodology and ethical aspects of paediatric trials

The session focussed on methodological aspects.

- While a number of well-known or "classical" ethical issues and practices continue to be identified in paediatric trials, a range of new ethical issues emerge in recent research in children (lecture by **Bartha Maria Knoppers**, Montréal). The classical ethical issues have been summarised into 10 best practice recommendations for research with children [Montreal2009]. These include best practice to include children in clinical trials, and to balance the risks and benefits; best practice to seek consent for research and to explain differences to medical care to reduce therapeutic misconceptions; best practice to seek assent, respecting the child and his/her evolving capacity to decide; and best practice to ascertain confidentiality of research data, and multi-site ethical review. New pressing ethical issues include, for example, the return of research results, as among the range of available policies no paediatric-specific guideline exists so far. New types of projects emerge, such as the International cancer genome consortium and the Public population project in genomics. The use of trial-related biological samples after the trial raises ethical concerns. Such samples cannot be used in the same way as those derived from clinical care. While bio-banking on

its own is not research, new molecular methods such as whole genome sequencing may generate highly sensitive health data. International ethical norms and practices are being developed for returning research results. Research communities should take part in the public consultations, including that on European personal data protection laws.

It was emphasised during the discussion that it would not be helpful to tie the capacity to assent to any particular age, nor to categorise this capacity as absent or present. The lack of a legal definition of assent was noted, but should not prevent efforts made to bring children to understand why they are asked to participate in research.

- The advantages and disadvantages of various development approaches of interest for paediatric medicines were presented by **Norbert Benda** (BfArM Germany). The three pillars of scientific evaluation, independent confirmation, internal and external validity, each pose challenges for clinical trials with children. Some disadvantages are expected with any approach, including innovative designs if they do not rest on all three pillars. For example, meta-analyses and Bayesian analyses may overlook systematic differences between adult and paediatric populations; withdrawal designs address primarily treatment-experienced patients; the uncertainty around surrogate endpoints cannot be estimated in children. Therefore, the benefits and risks of study design options should be assessed, not just from a single approach, but also from alternative approaches. This allows to understand how a decrease in study burden (benefit) is related to a decrease in robustness (risk), and whether a combination of approaches could have fewer disadvantages overall.

One of the criticisms made was that stringent regulatory requirements may mean waiting for the patient's death (in order to document overall survival with robust endpoints). The EMA supports the use of validated surrogate endpoints or their development when there is not sufficient evidence yet. The PDCO considers that additional endpoints may be justified if they contribute to the validation of potential surrogates, or accepts surrogates where evidence cannot be taken from adults alone.

Arguing on how paediatric trials were conducted historically, may limit thinking about possibilities for innovation and progress. Paediatric trials are often initiated and conducted by non-commercial investigators, with limited access to methodological expertise and sufficient funding; both may result in compromising the study design (e.g., smaller sample size, shorter trial duration, undetermined effective dose in younger children, no access to modelling techniques).

- A reflection on the designs of studies with neonates (presentation by **Dick Tibboel**, Rotterdam), showed that the main reason for poor gains in knowledge is under-powering of studies in the neonatal / paediatric intensive care setting (NICU / PICU). Recent technical advances include the use of minimal amounts of blood (such as from dry blood spots) for pharmacokinetic analysis of one or several medicines. In certain situations in routine neonatal care, it is justifiable and possible to conduct observational or "opportunistic" studies, where routine assessments and sampling are systematically analysed. Ethical issues of neonatal trials are similar to that in trials with older children, but some are more acute, e.g., which information to provide when medicines are used off label, how to handle trust and therapeutic misconceptions, how to act on dissent and how to deal with "motivated" consent. In addition to the hurdles in getting physicians to conduct meaningful studies, there are hurdles to translate new knowledge into routine care, with changes in physicians' awareness and behaviour.

All agreed on the special need to progress neonatal studies. It was proposed that therapeutic drug monitoring (i.e., a pharmacokinetic assessment) using minimal approaches could be applied to every NICU patient, and that "opportunistic studies" may represent an effective new system of research integrated with care in NICUs. The EMA is interested in obtaining descriptive data, especially as almost no neonatal data are available to regulators. Regulators should not request studies in neonates with

insufficient sample sizes, which stall knowledge generation by diverting resources towards inconclusive research. The creation of a European network of neonatology had been promoted by the EMA as part of the European network for paediatric research at the EMA (Enpr-EMA), but there are still difficulties in funding and conducting clinical research in neonatology.

- Among the various issues that Ethics committees face when evaluating paediatric trials, some are quite common (**Petra Knupfer**, EFGCP). For example, protocols do not specify how the safety of paediatric participants will be monitored throughout the trial. The burden to participants (e.g., from trial-related interventions) is not described. The rationale for pivotal aspects such as the justification for enrolling children in an "adult" trial is often not available. Most often, these issues can be addressed during the evaluation by Ethics committees so that very few proposed trials receive an unfavourable ethics opinion. However, trial protocols should be improved in particular those of non-commercial sponsors, and there is interest in information exchange between Ethics committees and the EMA / PDCO. As an example, five paediatric trials were outlined, showing how a particular Ethics committee balanced potential benefits and risks or burden, and rejected some of the trials elements. Some of the issues would have deserved a scientific discussion with the PDCO. Taking a global view, it seems that paediatric clinical trials have not increased significantly in Europe, while there is evidence that they increase faster in some countries / regions that do not have ethical and regulatory oversight in place. A low number of paediatric trials may contribute to hamper progress in methodology, as expertise is built up slowly by designing trials, as alternative designs are less familiar, and as standards of paediatric care based on poor evidence are infrequently challenged.

China was reported to train many pharmacologists; however, recruitment of paediatric trial participants is very difficult as a consequence of the single child policy. Third countries investigators and patients/families have a strong interest in seeing their children included in studies for various potentially conflicting reasons.

- A snapshot of the pharmaceutical industry experience, was presented through case studies of paediatric trials from PIPs. This showed how trials were reviewed in Europe from both the scientific and ethical perspectives (presented by **Martine Dehlinger-Kremer**, EUCROF). Change to information sheets, consent forms and assent documentation was often requested by Ethics committees, but there were infrequent requests to modify the study design. In some cases, attempts to make a single study design acceptable to all Ethics committees could not succeed. Participants were reminded that designs of studies agreed by the PDCO are not “set in stone” and can be changed, and this is similar for studies agreed by the FDA; this is the case in particular when the agreed study is no more appropriate, because new data have emerged.

The panel discussed:

- Development strategy: The PDCO is formalising a reflection on extrapolation from existing data (e.g., from adults), the need for additional data prospectively defined, and whether this approach with an increased risk of uncertainty is scientifically sound. The issue of vaccines, for which different immunisation schedules at national level trigger requests for multiple paediatric efficacy trials, was mentioned as evidence of the lack of scientific justification for unnecessary trials, which are ethically not acceptable.

- Risk evaluation: The process of risk evaluation is mostly informal, but a structured component analysis had been carried out by one Ethics committee. At the global level, the understanding of "minimal risk" for a paediatric trial is variable. It would be possible to develop an understanding to help balancing risks and burden against potential benefits. The PDCO would need to understand the order of magnitude of risks and burden, and for example, to know if measuring a trial endpoint justifies the need for a central venous line.

- Paediatric care: There is a lack of trials aiming to improve current paediatric care, and better networking among paediatricians is needed. Some funding may be available at EU level for off-patent medicines studies or non-patented interventions.

It was noted that PIPs are submitted late, sometimes when paediatric trials are completed or ongoing. To avoid repeating trials, the PDCO may have to accept the trials even if they are not optimal and may be rejected later at approval time. Monthly exchanges between EMA and, FDA, with observers from Health Canada and Japan, are already in place for paediatric medicines. At EU level, the principles of clinical research and ethics are shared; interactions on clinical research should be possible and would bring additional value. This meeting was taken as the first evidence that such interaction is welcomed and expected by Ethics committees and the EMA / PDCO.

2. Session 4: Looking into the future

- A brief survey of Ethics committees in Europe has been conducted by the EMA to find out how paediatric trials were assessed and where EMA could be useful to Ethics committees (presented by **Ralf Herold**, EMA). The small proportion of respondents (91 from over 800 recipients) does not allow generalisation, but provides useful examples. In addition to confirming aspects already discussed, the responses suggested that guidelines should be improved with respect to practical applicability. The EMA PDCO summary reports on Paediatric Investigation Plans are not widely known. Where available, the summary report was used by Ethics Committees to search for reviews of existing data, discussion of the statistical plan, and placebo use (if proposed), and for the rationale for requiring certain paediatric trials. Respondents indicated that there could be disagreement on some elements, in the evaluation of anticipated benefits and risks, placebo use, or the definition of the target population. Respondents were interested in receiving systematically some general information (e.g. guidelines, standard PIPs, or information on workshops, etc.) and in providing feedback to the PDCO in cases of disagreement.

The discussion touched on the following:

- Assent by children is difficult to define, but assent should be sought and documented. Efforts should be made to make children understand the trial.
- Paediatric trials with sub-therapeutic doses (“Phase 0”) could be considered but the understanding of potential benefit has to be developed.
- The ethical discussion of paediatric research should not be directed solely at the risks, but also at benefits, and research on how to balance more objectively risks and benefits should be undertaken; quantitative analyses based on utilitarian concepts may be more relevant for health policy than for clinical trials.

The next part of the meeting was held with working groups. Each working group discussed and made suggestions on how the evaluation of ethical aspects of paediatric trials could be improved, how Ethics committees and the EMA might interact to improve paediatric medicine development, how to increase paediatric research where needed, and how to advise on scientific and ethical aspects. The work groups' suggestions are included in the proposals for next steps.

2.1. Assessing risks (and benefits) before the start of the paediatric trial

The working group looked at the experience of participants as members of Ethics committee, as sponsor and as investigator. The group proposed a list of which data would be useful and should be provided in the application to Ethics committee for a given paediatric trial:

- Juvenile toxicity; acute and chronic toxicity; reproduction toxicity; cell lines and animal data related to mechanism of action (especially in oncology);
- Pharmacokinetic and pharmacodynamic data informing the paediatric use; expected cmax in children; (how) is the dose adjusted for younger children, compared to older children? Status and plans for development of assay(s) for PK and / or PD for the paediatric development. Formulation aspects including the age-appropriateness;
- As applicable, latest versions of Investigator's Brochure, and/or Summary of Product Characteristics, and Periodic or Development safety update report (PSUR / DSUR); compilation and synthesis of safety data from all sources;
- Clear overview of all trial-related, invasive procedures as well as of visits (including setting, telephone interview, hospital stay);
- Rationale for choice of comparator and placebo, with discussion of advantages and disadvantages;
- Information on how patient data protection is planned and implemented;
- Critical discussion of why a paediatric trial is needed and of the consequences of, and alternatives to conducting the proposed trial (e.g., no authorisation, uncertainties of paediatric use, risk of off-label use in the disease or any paediatric disease, change in medical care, "full" extrapolation from adults, or from children with other disease, based on which data, using modelling and simulation);

Transparency and results of any previous ethics review of the trial: The reasons for non-favourable Ethics opinion on a paediatric trial will have to be made public in the EU Clinical Trials Register.[1] Currently, it is the responsibility of the applicant (sponsor) to provide the Competent Authority with the outcome from the Ethics committee, and this is not optimal.

The data listed may be found in a number of different documents, some of which require improvement. Many of the items are in the EMA / PDCO summary report.

With respect to the interaction of Ethics committees with the EMA and PDCO, it was suggested:

- The EMA / PDCO Summary report could include an executive summary on the PIP, providing the rationale for the pivotal PIP elements;
- Provision of information from Ethics committees to EMA / PDCO on unfavourable ethics opinion, including the reasons for rejection. This would be applicable in case of scientific or ethical reasons leading to the rejection, not administrative reasons.

The working group additionally suggested:

- To foster he involvement of children and young persons in the design and review of a paediatric trial. This could improve how the trial responds to moral values and ethical principles. The knowledge, experience and views of children would have added value, e.g. on the invasiveness and burden of interventions. Focus groups could be created. Proposed trial sites could be visited.

[1] E.g. https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-001643-79/SE, scoll down to N.:

„N.	Ethics Committee Opinion of the trial application:	Not-Favourable
N.	Ethics Committee Opinion: Reason(s) for unfavourable opinion	<empty>
N.	Date of Ethics Committee Opinion:	2012-04-03“

These data are part of the list of fields that are defined by the European Pharmaceutical legislation (EudraLex - Volume 10 Clinical trials guidelines, http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm) to be made public, and thus to be collected.

In November 2010, the „EudraCT - List of additional fields contained in EudraCT (reasons for negative opinions of the Ethics Committee)“ has been defined and this is a part of EudraLex - Volume 10 (http://ec.europa.eu/health/files/eudralex/vol-10/2010_10_14_final.pdf).

- The involvement would not be limited to information sheets and practical aspects of a trial, but could also shape the research agenda. This would allow integrating the value systems of children (e.g., choice of endpoints, patient-related outcomes and assent process).
- How to involve children can be built on some experiences or projects (e.g., [Montreal2009]).

2.2. Addressing the vulnerability of children through trial design choices

This topic could best be addressed through a European-wide network of ethics committees sharing their experiences, exploring different views and analysing data on how to protect children participants from potential harm. Such protection could include stopping rules and risk monitoring, but other choices of trial design and conduct can also serve this objective. From the perspective of clinicians and investigators, the European network of paediatric research at EMA (Enpr-EMA) is expected to foster scientific excellence and harmonisation in Europe across disciplines. In addition, the EMA / PDCO Summary report on a Paediatric Investigation Plan would be helpful to Ethics committees with respect to children's vulnerability. It would be useful to develop, with experts from Enpr-EMA, a checklist of practical measures required in paediatric trials in order to monitor, evaluate and communicate risks. Ethics committees clearly see their role as independent advocate of children. The involvement of parents, who are in their own right independent advocates of children, should also be encouraged.

2.3. Different approaches of ECs and EMA / PDCO to the assessment of benefit / risk

This was a review of the differences in approaches used by Ethics committees and the EMA / PDCO when they assess the benefits and risks of a paediatric trial. While Ethics committees conduct this assessment with particular focus on the individual trial participant, the EMA / PDCO does have a more general view, identifying significant therapeutic benefits of the medicine, or the unmet paediatric needs. The legislation in some Member states restricts the role of Ethics committees to reviewing risks only, but not potential benefits. Information and possible harmonisation between Member states would be useful. Pharmaceutical companies see themselves in the middle, conveying information back and forth between Ethics committees and the EMA / PDCO. It seems that trial protocols written by pharmaceutical companies are often better than those by investigators in respect of the ethical review.

Suggestions of the working group:

- The EMA / PDCO could set out requirements for paediatric developments and trials in other conditions with "standard or model PIPs" (cf. http://bit.ly/xW04mg).
- The EMA / PDCO Summary report should be clearer on the decision-making process, and on the agreed trials, including a more detailed rationale for the development programme.
- Stakeholders should be involved in the benefit / risk assessment of a paediatric trial. For example, clinical experts should be involved earlier, not to provide a personal clinical verdict on trial acceptability, but to help balancing risks / burdens and benefits.
- A checklist has been developed for paediatric trials by an Ethics committee in Denmark, and this could be shared with other Ethics committees.
- Sponsors could seek advice from Ethics committees before requesting the ethics opinion, when the trial is being designed. Such advice could then be included in PIP applications.

2.4. Trials with neonates - progressing clinical research

The working group discussed the importance and necessity of meaningful research with neonates. Some views were held that trials with neonates showed elements of overprotection, although this is the most vulnerable subset of the paediatric population. This may be due to the general lack of data necessary to perform safe trials with neonates, such as toxicology and juvenile studies, or excipient safety. The suggestions of the working group included:

- The Paediatric investigation plan (PIP) should provide a more extensive scientific analysis and the EMA / PDCO Summary report should be accessible to Ethics committees.
- Conceptual work should be carried out on how to link neonatal care with research. Methodological progress has recently been achieved (e.g., micro-methods). Some requirements and standards to use secondary data and stored samples have been set out. This progress should inform ethics discussions

3. Session 5: Actions and conclusions

The discussion led to joint follow-up activities that are preliminarily set out below. Additional follow-up activities will be pursued at the EMA to increase transparency and build on the suggestions made.

- **Sharing of expertise between Ethics committees and EMA / PDCO**: Members of Ethics committees should be able to attend the plenary meetings of the PDCO. Local participation of PDCO members in national / local paediatric Ethics committees is encouraged. Ethics committees could also visit each other, through organised exchange programmes (which are in place in some Member states for medical specialities).
- **Forum of exchange between Ethics committees and EMA / PDCO**: Participation of members of Ethics committees may be subject to resources and availability. Existing fora include the ethics working group of the EFGCP (http://www.efgcp.be/WorkingParties.asp?what=1&L1=5&L2=4), and the paediatric working group of EUCROF (http://eucrof.eu/workinggroups.php?id=6). The EMA could simply host an Ethics forum to help improve the quality of ethics opinions, participation of children in research, etc. A review of the "Ethical considerations for clinical trials on medicinal products conducted with the paediatric population" guideline could be discussed. The European network for paediatric research at the EMA allows interactions with different stakeholders (e.g. pharmaceutical companies on one day, network-only discussions on the second day).
- **Sharing of cases**: Ethics committees could exchange cases studies after anonymisation, or under a confidentiality agreement. Similarly, Ethics committees could share confidential information with the EMA. However, practicalities would need to be worked out (contact points, format of exchange, confidentiality arrangements).
- **Guidelines**: There is variable awareness of guidelines issued by the EMA. The latest guidelines, including those on paediatric diseases and therapeutics, may not be available. Information on open consultations could be disseminated to Ethics Committees. When sponsors discuss ethical aspects of research in a paediatric trial application, guidelines may be referenced but there is often a lack of specificity in respect of the case under discussion.
- **Transparency**: Members of Ethics committees highlighted the limited availability of their outcomes to the public. Currently, the Ethics committee opinion is only given to the applicant. The rationale for acceptance or rejection of a paediatric trial could be made public in a non-specific way. More work may be needed (a) to make sure that the negative opinion of an Ethics committee

is made available to the Competent authority and to make the Register more useful to Ethics committees with search and notification functions.

- **Confidentiality**: This protects the sponsor, who however has to be transparent on previous or parallel discussions with Ethics committees. There may be an overriding public health interest to disclose commercially confidential information to avoid unsafe or unnecessary paediatric trials for example.
- **Applications for an Ethics committee opinion on a paediatric trial**: Applications should be more harmonised, using a specific template (addressing the information needed for paediatric trials). This would cover the presentation of clinical data (such as suggested in the literature [ASR2010]) and also the risks and thresholds of risks / burdens. All ongoing clinical trials should be listed.
- **Education in bioethics and development of competencies**: Ethics committees suggested developing strategies for formal training in ethics for students, academic secretaries, and young investigators. This would be an interdisciplinary teaching of medicine, philosophy and law. In this respect, the project "Training upcoming leaders in paediatric science" (Tulips) in the Netherlands was mentioned (http://www.nvk.nl/Onderzoek/TULIPS.aspx).
- **Involvement / participation of children and young people in study design, review and conduct**: This it is one of the criteria for networks to be recognised in the European network of paediatric research at EMA (Enpr-EMA). The involvement and participation of needs further encouragement and preparatory work, both theoretical and practical. Language issues can be taken care by international organisations. Panels of children could be convened on general or specific questions.
- **The EMA / PDCO** will work on improving the PIP evaluation guidance by addressing more explicitly uncertainties at the time of the PIP evaluation (e.g., proof of concept, outcomes of other developments, relation of response to intervention, treatment effect size, results of first PIP study(ies) safety in younger children) and how these can be managed and / or may impact the study program.

Project	What / objective(s)	What exactly	What is available already now	From / by whom to whom	Further needs and possible solution
1	Active communication from EMA on paediatric matters. Increasing awareness. Encouraging Ethics committee involvement.	Information on new guidelines relevant to paediatrics Information on newly adopted PIPs or modifications Information on new guidelines and public consultations	Interested parties can subscribe to information on EMA website (http://bit.ly/NaQPYh), including PDCO opinions, consultations, individual medicines. European Database on suspected adverse drug reaction reports, http://www.adrreports.eu/	EMA Paediatric medicines to ECs	EMA email distribution lists have been replaced by RSS feeds that allow users to select their topics and medicines. RSS feeds need to be loaded by a user. To be more proactive, it could be considered that the EMA Paediatric medicines section sends an email (monthly or less often) to registered Ethics committees.
2	Case-triggered communication on a paediatric	Details on ethical problems, e.g. uncertainties of risks	EU Clinical Trials Register captures and	EC(s) to EMA	Ethics Committees could approach the EMA / PDCO. For contact, send email to

	trial	and benefits, ethical issues, rationale for rejection because of an ethical reason (even if application is withdrawn). This applies particularly to studies in a PIP. When PIP applicants report to the PDCO that paediatric trials are no more appropriate for ethical reasons, or flag problems with acceptability as assessed by Ethics committees	makes public the reasons for non-favourable Ethics committees' opinions.	EC(s) to NCA PDCO to EC	paediatrics@ema.europa.eu. Then establish confidentiality declaration, if not yet in place. Clarify with Paediatric Co-ordinator how to manage discussion, which data are needed, how to involve the PDCO. PDCO / EMA would seek contact point for Ethics committees.
2	Standardised paediatric trial description for submissions to Ethics committees	Structured / standardised fact sheet could be developed to summarise a planned paediatric trial, including details on how risks will be monitored, frequency and volumes of blood sampling and other burdens on the participants, on the validity of endpoints assessed and on how assent will be sought throughout the trial.	Suggestions for structured presentations of protocol-related trial information (e.g., [ASR2010])		Content based on suggestion by working group 1 (section 2.1 above). Joint development of a template of Ethics committees and PDCO, including PDCO non-clinical and formulation working group. If possible, ensure that template can be re-used for other purposes such as clinical trial application and PIP application. Pilot phase. Roll out.
3	Increase usefulness of EMA information for Ethics committees	Improve EMA / PDCO Summary report to better capture rationale and dialectic discussions of paediatric trial features and medicine development programmes	EMA / PDCO Summary report with confidential information is available only upon establishing confidentiality or through submission by sponsors.	EMA Paediatric medicines to ECs	See details below (section 4.2). Comments on a draft improved EMA / PDCO summary report could be asked from selected EC members.
4	Create opportunities for exchange. Facilitate ethical evaluation. Improve scientific and ethical review outcomes. Increase paediatric trials. Possibilities for continuous dialogue. Improve relationship. Training in paediatric trial review.	Participation of Ethics committee members at PDCO meetings Visit of PDCO members to meetings of local / regional / national Ethics committees Creation of an Ethics forum dedicated primarily to paediatric trials	Members of Ethics committees can be welcomed as experts to PDCO meetings after declaration and checking of conflicts and interests		Please see section 5 (below) for how to participate in a PDCO meeting individually. A co-ordinated approach between Ethics committees and possibilities to share this experience with other Ethics committees is desirable. A European-wide organisation of Ethics committees for the purpose of establishing contact and for effective communication is desirable. An Ethics forum could be hosted by the EMA (no costs can be taken over) or attached to external working groups.

Post-meeting activities

The EMA undertook the following activities after the meeting:

- Members of Ethics committees who are interested to participate in PDCO meetings are welcome; please note that EMA cannot pay for any costs. Participation requires signing a confidentiality undertaking and submitting a declaration of interests. Please contact EMA at paediatrics@ema.europa.eu and follow the instructions (http://bit.ly/MhEeD8).

4. References

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