Ethical Considerations of Pediatric Clinical Trials

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The views expressed in the following slides are those of Pirkko Lepola and should not be attributed directly to Enpr-EMA (European Network of Paediatric Research at the European Medicines Agency)

Slides and the main information of the Enpr-EMA have been provided by courtesy of:

Irmgard EICHLER, MD, Co-chair Enpr-EMASenior Scientific Officer, Paediatric Medicines, Product Development Scientific Support Department, EMA
Outline

- Background information
- Actions done & to be done
  - Enpr–EMA & Working Group 4: Ethics
  - Enpr–EMA Collaboration with EUREC
  - Young Persons Advisory Groups
  - New EU–Initiatives for pediatric trials
  - NordicPedMed
  - FinPedMed Ethics guidance
- Contact information

NTA Ethics
Pharma industry represents the majority of paediatric clinical trials

This Regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations. These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations.
The following 5 years: > 1000 PIP*s -> **500 000 children** need to be recruited to these trials

*PIP=Pediatric Investigation Plan*
Enpr-EMA
European Network of Paediatric Research at the European Medicines Agency (2011)

Legal basis: Article 44 – Paediatric Regulation (EC) 1901/2006

www.ema.europa.eu / Partners & Networks / Networks / Enpr-EMA
Introduction

• Enpr-EMA will facilitate studies in order to increase availability of medicinal products authorised for use in the paediatric population

• Enpr-EMA is a network of research networks, investigators and centres; i.e. Members* performing research with children (newborns to adolescents), in multiple therapeutic areas, and ranging from pharmacokinetics to pharmacovigilance

*39 networks; 21 category- I;
1 academic institution, 8 national-, 12 disease/age/therapeutic area –specific
Key operational goals

- To link together existing networks
- To provide expertise and access to infrastructure for industry to conduct studies in children
- To define consistent and transparent quality standards
- To harmonise clinical trial procedures
- To define strategies for resolving major challenges
- To communicate with external stakeholders
Main Stakeholders

- Pharmaceutical Industry
- Patients, parents and patient organisations
- National Competent Authorities
- Ethics Committees
- Medical devices industry
- CRO’s
- Hospital pharmacists
EnprEMA
Working Group 4 - WG Ethics;

Dialogue and Interaction
with Ethics Committees
Structure 2016

- Pirkko Lepola, Chair (Finnish Investigators Network for Pediatric Medicines, Finland)
- Diane Hoffman, co-Chair (Janssen Research & Development, Philadelphia, U.S.A.)
- Martine Dehlinger-Kremer (SynteractHCR Deutschland GmbH, Germany)
- Jo Mendum (PRA HealthSciences, Reading, UK)
- Peter Sallabank (RegulinX, Surbiton, UK)
- David Neubauer (University Children’s Hospital, Ljubljana, Slovenia)
- Adriana Ceci (CVBF-Consorzio per Valutazioni Biologiche e Farmacologiche, Italy)
- Viviana Giannuzzi (Fondazione per la Ricerca Farmacologica Gianni Benzi, Italy)
- Heidi Glosli (Oslo University Hospital, NorPedMed, Norway)
Specific tasks for WG 4 Ethics by Enpr-EMA:

- To address the most important identified needs
- To develop pragmatic responses that can be implemented within six months
- Gather examples of good practice when Ethics Committees (ECs) consider trials relating to children and young people
- Develop proposals to disseminate examples of good practice to ECs
WG 4 Deliverables

• First Plan Report: 2013 - 12 Recommendations for Enpr-EMA

• 1. Deliverable: “Tool Kit” - Informed Consent and Assent for Paediatric Clinical Trials in Europe
  – Published on Enpr-EMA web-site on 18 December 2015
  – Will be updated by the Enpr-EMA from now on


Path to documents:
EMA Home -> Partners & Networks -> Networks -> Enpr-EMA -> Enpr-EMA Activities
1. Deliverable: The Tool Kit (example page)

<table>
<thead>
<tr>
<th>Country</th>
<th>Legal age of consent</th>
<th>Mandatory / suggested age ranges defined for assent (or consent if assent not used)</th>
<th>Number of required signatories</th>
<th>Official language requirements</th>
<th>IC template(s) / guidelines / information sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>18 years</td>
<td>4-11 years (some sites do not use under 12 years) 12-14 years 14-17 years</td>
<td>One parent at recruitment, but both parents at some point for signatures</td>
<td>Dutch, French German at site request</td>
<td><a href="http://www.fagg-afmps.be/en/human_use/medicines/medicines/research_development/ethic_committee/templates_informed_consent/">Link</a> Do not have paediatric templates</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>18 years</td>
<td>6-11 years 12-14 years 14-17 years – use own consent + parental signature also required</td>
<td>Both parents</td>
<td>Bulgarian</td>
<td>No national EC websites available in English Bulgarian Drug Agency -&gt; clinical trials <a href="http://en.bda.bg/index.php?option=com_content&amp;view=category&amp;layout=blog&amp;id=14&amp;Itemid=34">Link</a></td>
</tr>
<tr>
<td>Croatia</td>
<td>Nothing specified</td>
<td>Nothing specified</td>
<td>Nothing specified</td>
<td>Croatian</td>
<td><a href="http://www.almp.hr/?ln=en&amp;w=o_SEPu">Agency for Medicinal Products and Medical Devices of Croatia -&gt; Central Ethics Committee -&gt;</a> Information on clinical trials not available in English.</td>
</tr>
</tbody>
</table>
1. Publication; Tool Kit related article

Informed consent for paediatric clinical trials in Europe

Pirkko Lepola, Allison Needham, Jo Mendum, Peter Sallabank, David Neubauer, Saskia de Wildt

Results  Consent and assent requirements are heterogeneous across these countries. We compiled our findings in ‘The Informed Consent and Assent Tool Kit’, a table including 27 national consent and assent requirements listed by individual country.
Results

- Terms “consent” and “assent” are interpreted differently in legal texts between EEA countries.
- In EEA countries, 18 years generally the legal age for independent consent - exceptions; 14 Austria, 15 Finland and Denmark, 16 UK.
- 32 different age groupings (0-18).
- 3 countries (Croatia, Lithuania and Slovakia) without specific age groups for consent / assent.
- Different definitions for legal consent and the requirement of legal signatures; criteria are not uniformly defined in European guidelines or recommendations (unknown reasons).
Conclusions

• Wide variation in paediatric consents and assents presents challenges for multinational paediatric trials in Europe.

• The toolkit is available for all those involved in paediatric clinical trials and ethics committees, providing a new platform for proactive feedback on informed consent requirements, and may finally lead to a needed harmonisation process, including uniform standards accepted across Europe.
WG4 – Other activities in 2016

• Contribution to PROPOSED CHANGES TO THE U.S. COMMON RULE Implications for Pediatric Research (Federal Policy for the Protection of Human Subjects)
  
  – Included comments on two points relating to paediatric research:

  1. The value of taking an international perspective when revising the Common Rule

  2. Informed Consent

  - Comments submitted on January 2016 on behalf of Enpr-EMA
2. Task: Public Consultation of the “Ethical considerations for clinical trials on medicinal products conducted with the paediatric population” (2008) – a response of Enpr-EMA and Partners

- In collaboration with the EFGCP CMWP (European Forum for Good Clinical Practice, Children’s Medicines Working Party)
- In collaborating with a small group of PDCO members, lead by the Ralf Herold, EMA
- With the consideration of risk benefit issues and risk assessment
- Submitted in 30 August 2016
Consultation on the revision of "Ethical Considerations for Clinical Trials on Medicinal products Conducted with Minors": a response from Enpr-EMA and partners

Introduction

The EU Clinical Trials Regulation 2014 (CTRs) offers a great opportunity to improve research involving children. The supporting document "Ethical Considerations for Clinical Trials on Medicinal products conducted with Minors" is crucial to its implementation and achieving the Regulations’ aims to facilitate research and promote the health of our children and young people (minors).

This document represents the response from Enpr-EMA, its working groups (including representatives of networks, National Competent Authorities and pharmaceutical industry), and partners. It was led and drawn up by Hugh Davies (European Forum for Good Clinical Practice), Pirkko Lepola (Finnish Investigators Network for Pediatric Medicines, chair Enpr-EMA working group on Ethics) and Martine Dehlinger-Kremer (chair paediatric working group of EUCROF and member of EFGCP Children Working Party); then circulated to Enpr-EMA members and partners for their comments.
Part 1: General comment on content and layout

General comment
We feel this document is very complicated and lengthy with repetition on some issues. All these will cause difficulties for readers of different audiences (this must include families and participants). We are sorry to be making such criticism and are keen to help and would be happy to be contacted for further collaboration.
Part 2: Specific comments on the text*

*We found the guidance rather difficult to follow in places; therefore, have shaped our response around key principles we have identified that underpin this research and the specific groups referred to in the text:

**Principles underpinning ethical conduct of CTIMPS involving minors**

1. Children have vulnerabilities both as research participants and as recipients of unresearched care so fair balance must be struck between the two.

2. Minors (children, young people and their families) should be involved in research from inception, in its design and the material to be used.

3. Research involving minors must be preceded by careful risk assessment (benefits and harms) and then management.

4. The arrangements for consent, assent and recognising dissent require specific consideration in clinical trials involving minors.

5. Extrapolation of adult data is possible but this must be done with due care.

6. Those conducting research involving minors should have appropriate expertise.

7. Those reviewing research involving minors should have appropriate expertise.

8. Openness and transparency are important parts of ethical research.

AND

**Research involving particular groups**

1. Neonatal research
2. Research involving healthy minors
3. Research recruiting female adolescents
4. Emergency research
WG4 – Other activities in 2016

3. Task: Define uniform Consent / Assent template elements

Background facts:

1. New EU CT Reg. (impl.approx.10/2018) will harmonise clinical trial application (CTA) process, but IC/Assent issues remain with each Member State

2. There are noticeable differences between national IC and assent requirements in Europe due to national laws and regulations (Ref.: Tool Kit data)

   - These discrepancies present challenges for multicentre paediatric CTs

3. Deliverable: Comparison of Assents from WHO, MCRN and Finland - Guidance template provided January 2017*
Enpr-EMA Collaboration with EUREC

- 08Sep2016, EUREC meeting Helsinki, Finland
- 01-02/2017, teleconferences with Enpr-EMA
  - Brainstorming ways to collaborate more
  - Ideas of distribute & change information
  - Ideas for EC training for pediatric trials
- 05/2017, EUREC meeting with YPAG Barcelona, Spain
Minors (children, young people and their families) should be involved in research from inception, in its design and the material to be used.

The best way of preventing vulnerability is through researchers working in partnership with children, young people and parents. One way of doing this is for researchers to involve children, young people and parents in the design of their research from the beginning.
Young People of senior school age (11-18yrs) to act as representatives of and advocates for children under 16yrs, participating in research and clinical trials.

Specific tasks were to:

- Comment on the language, terminology, design and content of information sheets, questionnaires and other research tools.
- Raise awareness of clinical research in children young people and their parents aimed at increase availability and efficacy of medicines and health care in children.
- Provide opinions on research methods, on ethics, on methods of contacting or approaching young people and provide a pool of young people for focus groups.
- Determine the appropriateness and effectiveness of research tools.
- Influence content and design of proposed research.
- Ensure that all clinical trial documentation however complex, communicates the required information effectively to participants and their parents or carers.
YPAGs worldwide
New EU Initiatives


2. **PedCRIN³(=ECRIN⁴+EPCTRI⁵) 2017-2020** – Funding: EU Commission. PedCRIN applies to ESFRI⁶ Road Map.

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Stage-1; 2014-2015 – Feasibility
Stage-2; 2016-2017 – Governance and Implementation
Official establishment: 26.1.2016 Oslo
Objectives

Nordic network collaboration can increase pediatric research opportunities by:

- Increasing competitiveness of Nordic Area and Developing stronger position within the European Network of Paediatric Research at European Medicines Agency (Enpr-EMA)
- Raising the recruitment potential by larger child population (5.2 million < 18 yrs. old)
- Fostering high-quality, ethical research, to find out safety and efficacy of pediatric medicines
- Enhancing collaboration between the networks and various stakeholders
- Avoiding unnecessary trials in children
- Creating scientific and administrative competence at a Nordic level

Most importantly, the Nordic network provides benefits to sick children by offering opportunities for early access to new promising medicines in a safe and controlled way in clinical trials.
FinPedMed Picture Cards
Materials

FINPEDMED has created various materials to help support and serve pediatric clinical trials:

- Guidelines and a Table of important facts for investigators and sponsors to be used in Informed Consent process design (available only in Finnish)
- Document templates for Informed Consent and Patient Information for all pediatric age groups; Informed Consent template for minors contains integrated patient information
- Patient Information template (index) for 15 to 17-year-old adolescents
- Notification of Participation template to guardians of 15 to 17-year-old children
- Picture Cards for pediatric clinical trials and clinical practice; support material

All materials (other than guidelines) are available in English, Swedish, and Finnish:

Document templates and Picture Cards
Thank You!

Finland  Sweden  Iceland  Norway  Denmark  NTA Ethics
30 Jan 2017 / PL
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