Paediatric networks for clinical trial in children - regulatory authorities perspectives

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• Context
  – The clinical trials regulatory system in EU

• Investigators networks
  – Expectations
  – Perspectives
Regulatory provisions for CTs on children

- The clinical trials directive and guidelines (Volume 10)
- ICH E6
- Regulation N° 1901/2006
- ICH E11
- Draft implementing strategy for the network of paediatric networks at EMA
- European Network of paediatric research (EnprEMA), recognition of criteria for self assessment.
The clinical trials directive (CTD)

Interventional clinical trial

Medicinal products

Same general principles in the 27 MS

Protection of CT subjects

Procedures, time lines, documents

Quality:
- clinical trials (GCP)
- investigational MP (GMP)

Exchange of information between Member states (2 data bases).

EudraCT

EV-CTM
Procedure for starting a clinical trial in EU

1. In each MS concerned
2. Sponsor
   - 1. EudraCT Number
   - 2. CTA dossier
3. Ethics committee
4. Single positive opinion
5. Start of CT
6. Clinical trial Authorisation
7. National Competent Authority
8. CTFG, network of NCAs
## Ethics Committees and National Competent Authorities

**ECs**

1. **Subjects protection:**
   - Written information/informed consent (content and modalities)
   - Indemnity/compensation
   - Insurance
   - Arrangement for recruitment

2. **The trial**
   - Relevance of the CT, CT design
   - Evaluation B/R is satisfactory

3. **Facilities**
   - Suitability of investigators/staff
   - Quality of facilities

**NCA**

1. **Benefit/risks of the CT is satisfactory**

2. **Quality** of IMP and of CT is ensured

3. **Safety of subjects** is monitored and acceptable, taking into account all data in IMP Dossier

5. ± methodology (MS depending)

→ IMP Q, E, S

CT subject’s safety

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If multinational CT, possible coordination of assessment by NCAs (VHP)
Procedure for the conduct of the CT

In each MS concerned

Sponsor

Substantial amendments

SUSARs

New events likely to Impact/security

Annual safety report/DSUR

End of trial, results

Ethics committee

National Competent Authority

Eudra-Vigilance CT module (EMA)

Suspension, Prohibition, modification of the CT: NCA

SUSARs
NCAs are also responsible for

- Assessment of safety data
  - NCA may suspend, prohibit or require modification of the CT

- Inspections
  - GMP
  - GCP
  - Information in EudraCT
  - Decision on the trial
  - Sites of the trial (investigators), sponsor’s or CRO’s facilities and other actors of the CT.
## CTs in children in EU

**source EudraCT**

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<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
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<tbody>
<tr>
<td><strong>Adults</strong></td>
<td>4273</td>
<td>4156</td>
<td>3886</td>
</tr>
<tr>
<td><strong>Children (%-total)</strong></td>
<td>328 (7.1%)</td>
<td>423 (9.2%)</td>
<td>405 (9.4%)</td>
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<tr>
<th></th>
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<th>2010</th>
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<tr>
<td><strong>Commercial</strong></td>
<td>45 %</td>
<td>45 %</td>
<td>60 %</td>
</tr>
<tr>
<td><strong>Non commercial</strong></td>
<td>55 %</td>
<td>55 %</td>
<td>40 %</td>
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<tr>
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<th>2010</th>
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<tbody>
<tr>
<td><strong>Phase 1 CTs in children</strong></td>
<td>29 (8.8 %)</td>
<td>28 (6.6 %)</td>
<td>50 (12 %)</td>
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Networks of investigators

Context

• Foster clinical research
• But need to ensure quality of clinical research and similar quality
• Reminders:
  – Suitability of each investigator is assessed, per CT, by Ethics Committees
  – GCP compliance is controlled by NCAs’ inspectors
  – No legal EU accreditation of networks
Expectations from authorities (1)

• Rules to be understood by all stakeholders
  – Rules on clinical trials (GCP)
  – Rules on specificities of clinical trials conducted on paediatric population
  – Rules on networks
Expectations from authorities (2)

• Rules on networks
  • Definition of a Network
    – Predefined set of clinical research sites/investigators, technical wards and resources
    – With a common quality system (procedures, means, tools, communication)
    – With a coordination body.
  • Requirements for a Network
    – Quality management system
    – Training and educational capacity
    – Communication
    – Coordination
Expectations from authorities (3)

- **Networks of investigators in paediatrics**
  - Capacities/competencies for clinical research + children
  - Appropriate research teams (investigators, nurses, facilities…)
  - Appropriate experts
  - Appropriate ethical standards

- **Transparency on the practices**
  - Existing networks and their experience and ability to conduct trials
  - Existing trainings for trial participants
  - Rules for project public fundings: assessment of candidates
Qualification of an investigator?

- **CTD: Appropriate experience**
- **Experience in GCP**
  - Knowledge of ICH E6
  - Qualified by training and experience
  - Adequate resources to properly conduct the trial
  - Compliance to the protocol, procedures, reporting…
  - Knowledge of the IMP
- **Experience in paediatrics**:
  - Knowledge of ICH dedicated guidelines
  - Development of MP in children
  - Ethical specificities
  - Implication of child + family
  - Information/consent modalities
  - Blood samples/investigation modalities
  - Management of pain…
Examples: Perspective in France

- Working group implemented by Afssaps in 2008
  - Participants: Inserm, investigators, networks, ECs, industry, CROs, parents associations…
  - Topics
    1. Public Information/communication on actors in paediatrics research
    2. Public information on existing trainings on clinical trials in paediatrics
    3. Trainings for trainers/ amend the existing content and implement
    4. Guidance on the QMS requirements for a network of investigators and resources
    5. Guidance on information and consent in CTs on paediatrics population in France
Trainings for trainers of investigators in France

• Current content
  – Afssaps, LEEM, CROs
  – Published on January 2009
  – Afssaps website
  – General principles on medicines development, main principles on clinical trials, communication in clinical trials, recommended workshops content (informed consent, organisation of sites, monitoring and auditing, adverse effects notification).

• Chart to use the document
Where to get information on CTs in EU

European Commission website
http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/

CTFG website:
http://www.hma-eu/78.html

Afssaps website
http://www.afssaps.fr

Thank you!
Abbreviations

- B/R : benefit/risk
- CRO : clinical research organisation
- CT : clinical trial
- CTA : clinical trial authorisation
- CTD : clinical trial directive
- CTFG : clinical trial facilitation group
- DSUR : development safety update report
- EC : Ethics committee
- EMA : European Medicines Agency
- EV CTM : Eudravigilance CT module
- GCP : good clinical practice
- GMP : good manufacturing practice
- IMP : investigational medical product
- MS : member state
- MNCT : multinational clinical trial
- NCA : national competent authority
- QMS: quality management system
- VHP : voluntary harmonised procedure