Implementing Paediatric Trials Based On Your Approved PIP

March 2012
Discussion Points

- Verifying feasibility of the PIP approved studies

- Confirmed feasibility:
  - Implications on timelines
  - Implications on regulatory actions

- Choosing the appropriate countries and working with paediatric site networks

- Paediatric case study
Verifying Feasibility of the PIP Approved Studies
PIP Development Timelines

- Preclinical
- Clinical Trial Application
- Phase 1
- CTA
- Phase 2
- CTA acc. PIP
- Phase 3
- Marketing Authorisation Application
- Marketing Authorisation
- Paediatric studies defined in deferral
- Post Approval
- Paediatric Committee
- Compliance or Deferral or Waiver
- Opinion
- PIP Amendments
- Paediatric Invest. Plan
Feasibility of Paediatric Commitments - Prospective

- Remember you are not alone...there will be (more and more) competitive studies
- Try to avoid agreeing to do something until you know you can!

“We must not promise what we ought not, lest we be called on to perform what we cannot”  *Abraham Lincoln*
Feasibility of Paediatric Commitments - Prospective

- Make sure the data on the prevalence and incidence of the paediatric condition in the literature is reliable.

- Check the feasibility of finding paediatric patients who will fit the protocol(s) and use the results of these feasibility studies to justify the paediatric development plan.

- Consider whether the studies are ethically viable (e.g. blood sampling, placebo groups, pharmacokinetic studies, contraceptive requirements).
Paediatric Study Design Considerations

- Scientifically rigorous
- Feasible for the child/parent
Study Design

Why up to 50% of paediatric studies fail

- Ethical constraints in protocol development
- Small sample size, low enrolment
- Endpoints that are not well defined or paediatric relevant
- PK-PD correlations not established
- Incorrectly identified dosages for efficacy studies
- Feasibility issues
Confirmed Feasibility

Timelines and Regulatory actions
Adapting to reality...

- Modifications to a PIP are possible if the original plan is either unworkable or is no longer appropriate
- Multiple modifications are possible
- New waivers/deferrals can also be requested
- New opinion supersedes original
- 60-day procedure - same EMA coordinator / Rapporteur / Peer Reviewer in most cases

Changes have to be justified and should not be perceived to gradually erode the original PIP requirements
**PIP Modification Submission Timelines**

- **Day -60**: Letter of Intent
- **Day 0**: PIP Application
- **Day 30**: Draft Summary Report
- **Meeting/TC if requested by PDCO**
- **Day 60**: Final Opinion

**PIP Preparation**

**Start**

**Assessment**

4 Months
Choosing the Appropriate Countries and Paediatric Site Networks
Ongoing Paediatric Clinical Trials

Map of Currently Enrolling Studies with Children

Colors indicate number of studies with locations in that region

Least

Labels give exact count

Most

Source: clinicaltrials.gov
Therapeutic Areas of Ongoing Studies

- Bacterial and Fungal Diseases
- Behaviors and Mental Disorders
- Blood and Lymph Conditions
- Cancers and Other Neoplasms
- Digestive System Diseases
- Diseases and Abnormalities at or before Birth
- Ear, Nose, and Throat Diseases
- Eye Diseases
- Gland and Hormone Related Diseases
- Heart and Blood Diseases
- Immune System Diseases
- Mouth and Tooth Diseases
- Muscle, Bone, and Cartilage Diseases
- Nervous System Diseases
- Nutritional and Metabolic Diseases
- Occupational Diseases
- Parasitic Diseases
- Respiratory Tract (Lung and Bronchial) Diseases
- Skin and Connective Tissue Diseases
- Substance Related Disorders
- Symptoms and General Pathology
- Urinary Tract, Sexual Organs, and Pregnancy Conditions
- Viral Diseases
- Wounds and Injuries

Source: clinicaltrials.gov
## Approved PIPs in Europe

### By Indication

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Number of PIPs</th>
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<tbody>
<tr>
<td>Anaesthesiology</td>
<td>1</td>
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<tr>
<td>Cardiovascular diseases</td>
<td>36</td>
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<tr>
<td>Dermatology</td>
<td>22</td>
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<tr>
<td>Diagnostic</td>
<td>4</td>
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<tr>
<td>Endocrinology, -gynecology-fertility-metabolism</td>
<td>59</td>
</tr>
<tr>
<td>Gastroenterology-Hepatology</td>
<td>20</td>
</tr>
<tr>
<td>Haematology-Hemostaseology</td>
<td>32</td>
</tr>
<tr>
<td>Immunology-Rheumatology-Transplantation</td>
<td>42</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>50</td>
</tr>
<tr>
<td>Neonatology-Paediatric Intensive care</td>
<td>6</td>
</tr>
<tr>
<td>Neurology</td>
<td>19</td>
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<tr>
<td>Nutrition</td>
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<tr>
<td>Oncology</td>
<td>48</td>
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<tr>
<td>Ophthalmology</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
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<tr>
<td>Oto-rhino-laryngology</td>
<td>9</td>
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<tr>
<td>Pain</td>
<td>13</td>
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<tr>
<td>Pneumology-allergology</td>
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<td>Psychiatry</td>
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<tr>
<td>Uro-nephrology</td>
<td>8</td>
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<tr>
<td>Vaccines</td>
<td>31</td>
</tr>
</tbody>
</table>
Operational Considerations for Paediatric Investigative Site Selection

- In general, use same principles as selecting sites for adult trials:
  - Expertise and experience
    - Therapeutic area
    - Clinical research
    - Paediatric studies
  - Adequate number of appropriate patients
    - PI/SC/nurse known to the family and have their trust
  - Degree of interest expressed by the site
- Facilities need appropriate equipment and activities and that can accommodate children/families
- Consider using a Paediatric Research Network
Medical Considerations for Paediatric Investigative Site Selection

- Absolutely MUST have person experienced in paediatric lab draws

- Depending on protocol, may also need personnel with expertise in catheterising small children, paediatric IV starts, placing paediatric NG tubes, etc.

- Sites that are not paediatric based must have access to resources needed for the paediatric population
### Site Networks with Enpr-EMA Membership

<table>
<thead>
<tr>
<th>Network</th>
<th>Membership</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Cystic Fibrosis Society – Clinical Trials Network (ECFS-CTN)</td>
<td>Newcastle CCLG Pharmacology Studies Group</td>
</tr>
<tr>
<td>European Network for Hyperkinetic Disorders (EUNETHYDIS)</td>
<td>Paediatric European Network for the Treatment of AIDS (PENTA)</td>
</tr>
<tr>
<td>European Paediatric Oncology Off-patent Medicines Consortium (EPOC)</td>
<td>Pediatric Rheumatology International Trials Organization (PRINTO)</td>
</tr>
<tr>
<td>Finnish Investigators Network for Pediatric Medicine (FINPEDMED)</td>
<td>Scottish Medicines for Children Network (Scotmcn)</td>
</tr>
<tr>
<td>German Neonatal Network (GNN)</td>
<td>United Kingdom Paediatric Vaccines Group (UKPVG)</td>
</tr>
<tr>
<td>Innovative Therapies for Children with Cancer (ITCC)</td>
<td>European Group for Blood and Marrow Transplantation (EBMT)</td>
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<tr>
<td>International BFM Study Group (I-BFM-SG)</td>
<td>Paediatric Network of Clinical Investigation Centers (CICPed)</td>
</tr>
<tr>
<td>Italian Paediatric Federation – Medicines for Children Research Network (FIMP-MCRN)</td>
<td>Networks undergoing clarification for membership</td>
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<tr>
<td>Medicines for Children Research Network, The Netherlands (MCRN)</td>
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<tr>
<td>Mother Infant Child Youth Research Network, Canada (MICYRN)</td>
<td>Children Leukemia Group (CLG) (EORTC)</td>
</tr>
<tr>
<td>National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) (UK)</td>
<td>Network of Excellence for Research in Paediatric Clinical Care</td>
</tr>
</tbody>
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Site Networks Working to Become Enpr-EMA Members

<table>
<thead>
<tr>
<th>Network Name</th>
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<tbody>
<tr>
<td>Belgian Pediatric Drug Network (BPDN)</td>
<td>Neocirculation</td>
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<tr>
<td>EuroNeoNet</td>
<td>Paediatric European Network for the Treatment of Infection (PENTI)</td>
</tr>
<tr>
<td>European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)</td>
<td>Reseau d'Investigations Pediatriques des Produits de Sante (RIPPS)</td>
</tr>
<tr>
<td>Futurenest Clinical Research</td>
<td>Swedish Pediatric Society (BLF)</td>
</tr>
<tr>
<td>International Pediatric Transplant Association (IPTA)</td>
<td>Paediatric Trial Network (AMIKI)</td>
</tr>
<tr>
<td>Irish Paediatric Clinical Research Network (IPCRN)</td>
<td>Italian Neonatal Network (INN)</td>
</tr>
<tr>
<td>Juvenile Scleroerma Working Group – Paediatric Rheumatology European Society</td>
<td></td>
</tr>
<tr>
<td>National Center for Child Health and Development (NCCHD) Japan</td>
<td></td>
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US Sites

- Similar network system is not in place in the US
- However, some specific networks are in place working directly with government sponsored research, though industry research can be included, including:
  - Children’s Oncology Group (COG)
  - Pediatric Pharmacology Research Unit (PPRU)
  - Pediatric Emergency Care Applied Research Network (PECARN)
  - Collaborative Pediatric Critical Care Research Network (CPCCRN)
- Therapeutically aligned consortia continue to be developed (e.g. Analgesia, Allergy) to work with industry
- Rather, individual institutions and physicians are selected for US trials
Paediatric Case Study
Case study:

A large pharmaceutical company made the following commitment to FDA:

- Perform a paediatric study in a very rare indication in 31 patients
- Single treatment study
- Based on calculations of disease incidence over 24 months, only 1 patient expected to be recruited per country
- Study therefore required initiation of one site with one patient in 31 different countries
Keeping Your Paediatric Commitments Feasible

Implications of the commitment were:

▪ Difficult logistics

▪ High costs due to regulatory submission fees for numerous countries, multiple site initiation costs, far ranging project management, drug importation hurdles, etc.

▪ No guarantee of finding the patients within the 24 month timeframe
Key Points for Successful Paediatric Studies

- Plan your PIP strategy early in development
- Conduct adequate feasibility on proposed studies to ensure these are practicable
- Monitor amendments to protocols and check for impact on key binding elements of the PDCO opinion
- Justify all modifications and submit in a timely manner
- Chose a CRO partner experienced in paediatric trials
Choosing Your CRO Partner

Experience confirms:

“The difference between theory and practice tends to be very small in theory, but in practice it is very large indeed”

Anon
Thank you for your attention