Pediatric Trial Design and Modeling: Moving into the Next Decade

Industry Approach to Innovative Pediatric Trial Design

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Office of the Chief Medical Officer, Pfizer Inc.
Friday, September 8, 2017
FDA Workshop
Great Room, US FDA White Oak
Industry Approach to Innovative Pediatric Trial Design

Agenda

What is Industry Doing to Improve Pediatric Clinical Trial Innovation

- Infrastructure
- Patient Engagement
- Collaboration

Innovative study design and solutions

Moving forward – call to action
CLINICAL INNOVATION

Pfizer has taken an early leadership position in creating a discipline around Clinical Innovation, ensuring we are taking advantage of cutting-edge tools, approaches and partnerships to ensure our high-quality clinical trials are conducted with speed and agility. Pfizer's Clinical Innovation vision centers on making research participation easy for patients and healthcare providers. Our investments and initiatives are focused on three core domains:

1. Patient engagement
2. Making work easy for sites
3. Leveraging real world data

These initiatives are enhanced through our participation in key industry collaborations, such as TransCelerate BioPharma, and others seeking to improve the clinical trial process.

www.pfizer.com
What is Industry Doing to Improve Pediatric Clinical Trial Innovation

Infrastructure

- Development of Pediatric Centers
- Support for pediatric age-appropriate trial design, study sites, study support and regulation
- Enhance Pediatric Education
Pfizer Pediatric Center of Excellence (PedCoE)

Organization
Located in the Chief Medical Office of Dr. Freda Lewis-Hall

Mission Statement
To improve the health and well-being of children by applying science, driving operational excellence, aligning resources, and providing a unified voice for the needs of children

Sandra Parra
• Administrative Specialist

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• Global Pediatric Medical Director

Michael O’Connell, MD FAAAAI FCCP
• Global Pediatric Medical Director

Judy Skaggs, BS MSPM
• Director, Pediatric Strategy & Operations

Charlie Thompson, MD FAAP
• Global Lead, Pediatric Center of Excellence
5 30-minute eLearning Programs

The Pfizer Pediatric Education series is a 5-module eLearning curriculum intended to educate colleagues and partners about key topics related to Pfizer policies and national and international regulations pertaining to Pediatric Drug Development.

The approximately 2.5 hour series includes input from over 25 Subject Matter Experts, both Pfizer colleagues and recognized industry leaders. Each 30-minute module targets specific roles, so most learners will not be required to complete all 2.5 hours.
What is Industry Doing to Improve Pediatric Clinical Trial Innovation

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• Enhance Pediatric Education

Patient Engagement

• Voice of child/caregiver (study design, simulation, feedback)
International Children’s Advisory Network

Changing the face of pediatric research

https://youtu.be/MgUeEXM4_wo
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Patient Engagement
• Voice of child/caregiver (study design, simulation, feedback)

Collaboration
• Involvement with Collaborative groups (TransCelerate)
• Consortia
• Common protocol templates
• Study Design
ABOUT TRANSCELERATE BIOPHARMA

Pfizer is a founding member of TransCelerate BioPharma Inc., a non-profit organization focused on advancing innovation in research and development (R&D), identifying and solving common R&D challenges and further improving patient safety, with the goal of delivering higher quality medicines to patients. Joining us in the initiative are AbbVie, Astellas, AstraZeneca, Biogen Idec, Boehringer Ingelheim, Braeburn Pharmaceuticals, Bristol-Myers Squibb, Cubist Pharmaceuticals, Eli Lilly, EMD Serono, Forest Laboratories, GlaxoSmithKline, Johnson & Johnson, Onyx Pharmaceuticals, Roche, Sanofi and UCB.

This cross-industry initiative is dedicated to bringing innovative new medicines to the public more quickly. The five initial projects are: development of a shared user interface for investigator site portals; mutual recognition of study site qualification and training; development of risk-based site monitoring approach and standards; development of clinical data standards; and establishment of a comparator drug supply model. In November 2013, TransCelerate announced expansion of the comparator network and site qualification & training project, as well as three new global initiatives — creation of common clinical trial protocol templates, development of clinical trial networks for pediatric and minority populations, and establishment of a global investigator registry.
TransCelerate

Common Protocol Template

The following resources have been made available to enable use of a streamlined master protocol template with common structure and language.

The Common Protocol Template consists of sections marked as comment text or text that may be used across protocols with slight to no editing if the user chooses to do so. The use of this template is at the discretion of the user. Recommendations for modifications in future releases of the common protocol template can be submitted at any time and will be reviewed on a rolling basis.

Check out our video introducing the TransCelerate Common Protocol Template Initiative.

Assets Available for Download
To access the materials below, we ask that you fill out a simple form. You only need to enter your information once to be able to download any of the materials. Please click here or click on any of the files below to proceed to the download page.

Disclaimer:

The Common Protocol Template

<table>
<thead>
<tr>
<th>Template File</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Protocol</td>
<td>Common template for the protocol, study, and sponsor documentation.</td>
</tr>
<tr>
<td>Template Core</td>
<td>Contains common elements that are applicable to all studies.</td>
</tr>
<tr>
<td>Template - Basic</td>
<td>Basic template for creating a protocol.</td>
</tr>
</tbody>
</table>

Pfizer PEDIATRIC CENTER OF EXCELLENCE
TransCelerate Pediatric Protocol Template

The Common Protocol Template

<table>
<thead>
<tr>
<th>Template File</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Common Protocol Template Core Template - Basic Word Edition</td>
<td>Content template for the protocol body and appendices intended for use in all phases and disease areas, containing a common heading structure, common text, and suggested text. Open template in MS Word and begin authoring. Can be used in conjunction with CPT libraries which provide content specific to participant types and therapeutic areas.</td>
</tr>
<tr>
<td>Common Protocol Template - Technology Enabled Edition</td>
<td>MS Word enabled format and content template for the protocol body and appendices intended for use in all phases and disease areas, containing a common heading structure, common text, and suggested text. Includes features such as automated connection to the CPT libraries. Requires installation of template and add-ins on your workstation.</td>
</tr>
</tbody>
</table>

In order to allow for a single core template, content unique to specific populations has been organized into libraries, and can be inserted into the Core Template. If using the Basic Word Edition, you can download the libraries separately. Libraries are integrated within the Technology Enabled Edition.

<table>
<thead>
<tr>
<th>CPT Library Files</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Volunteer Library</td>
<td>Contains common and suggested text pertinent to studies in healthy volunteers.</td>
</tr>
<tr>
<td>Patient Library</td>
<td>Contains common and suggested text pertinent to studies in all patients regardless of indication.</td>
</tr>
<tr>
<td>Pediatric Library</td>
<td>Contains common and suggested text pertinent to studies in pediatric patients regardless of indication.</td>
</tr>
<tr>
<td>Alzheimer's Library</td>
<td>Contains content pertinent to Alzheimer's Disease studies.</td>
</tr>
<tr>
<td>Asthma Library</td>
<td>Contains content pertinent to asthma studies.</td>
</tr>
<tr>
<td>Diabetes Library</td>
<td>Contains content pertinent to diabetes studies.</td>
</tr>
</tbody>
</table>

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Moving forward – call to action
Examples of Innovative Methods to Inform Treatment of Children

- Extrapolation (including Modeling and Simulation)
- Adaptive design
- Real World Data/3rd party (published) data
- Protocol Simulation
- Sparse and scavenge sampling for PK
- Opportunistic studies

Leveraging Existing and Emerging Data... rather than Interventional Trials
Examples of Innovative Design/Solution

• Background (anticoagulant):
  • 2 years ago – acquired from business deal peds study ongoing 8 yrs
  • Rare condition; strict eligibility criteria; 5 cohorts of age groups (newborn, infant, pre-school, school age, teen);
  • Over first 8 years – 5 amendments
  • After first 6 yrs of enrollment – 23/50 patients enrolled (all but 2 in school age and up; no newborns or infants)
  • CSR due Dec 2018
Examples of Innovative Design/Solution

• Innovative Solution:
  • After transfer of study – type C meeting to broaden subject criteria; simplify protocol; add innovative design
    – Continue to enroll patients as agreed with FDA
    – Request use of individual subject data on neonates and infants from published studies (retrospective analysis; prospective IIR multicenter dose-finding study; prospective open label)
    – Totality of data projected available on FDA timeline
Examples of Innovative Design: Endpoint for Sickle Cell Disease Study

• Drug for prophylactic treatment of Vaso-occlusive pain crises (VOCs)

• Traditional endpoint - based on the number of in-patient hospitalizations (requires large sample size and lengthy trial)
  
  AND many patients avoid the hospital when possible for VOC treatment
Examples of Innovative Design: Endpoint for Sickle Cell Disease Study

• Study team decided to describe the patient journey, identify the concepts, and define a clinically meaningful endpoint model that reflects the painful crisis experience from the perspective of the patient to allow for the development of a validated endpoint for use in the clinical development program for the sickle cell disease treatment portfolio.
Examples of Innovative Design: Endpoint for Sickle Cell Disease Study

• End result – development different endpoint of the “VOC day” which allowed patients to record VOCs managed outside a hospital stay either at home or via out-patient treatment on an electronic patient report device (ePRO) similar to a cell phone.
Domagrozumab (PF-06252616):
Phase II Development in Duchenne Muscular Dystrophy (#NCT02310763)

Period 1 (48W) → Period 2 (48W)

Sequence 1
- Low dose
- Medium dose
- High dose

Sequence 2
- Low dose
- Medium dose
- High dose

Sequence 3
- Placebo
- Placebo
- Placebo

4 Stair Climb time

Primary Analysis: NSTAR, 6MWT, Strength MRI and DXA imaging Safety biomarkers
Secondary Analysis

External Data Monitoring Committee

- 6-<16 year old boys with DMD
  - Ambulant on steroid
- Monthly 2hr IV infusion
- Dose escalation
- N=35 Randomized per sequence (Total 105)
- Enrollment completed

Rare Disease
A Pfizer Research Unit
Examples of Innovative Design/Solution

Background (Fosphenyntion)

1996 (21 years ago) - Post Marketing Commitment for pediatric study requested
1998  Pediatric supplement was submitted
1999  Non-approval issued to supplement (identify dose that can produce levels of free phenytoin that are safe and effective in children
2001  FDA Written Request for 2 studies (PK and safety)
2010  FDA asked for IV phenytoin PK study in children
2011  Pfizer proposed a modeling and simulation (M&S) approach alternative + use of 3rd party data
2014  Received comments from FDA on M&S; focus on Cmax
2017  Completion
Take Home Message

Don’t hesitate to try a different approach …in a collaborative manner with stakeholders …and with appropriate scientific rigor

Don’t let PMCs linger for a long time

Persistence is often rewarded
Leverage well conducted studies from 3rd parties

"This is taking too long — we'll have to induce hatching."
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Industry Pediatric Study Design Challenges Call to Action

• Innovative study design vs traditional placebo controlled, interventional studies
• Inconsistencies within the FDA divisions
• Old studies with long timelines
• Expertise in peds for all pediatric studies
• Are the studies feasible?
• Coordination between EMA and FDA