

Pediatric Trial Design and Modeling: Moving into the Next Decade

Industry Approach to Innovative Pediatric Trial Design

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FDA Workshop

Great Room, US FDA White Oak



PEDIATRIC CENTER OF EXCELLENCE

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





OUR SCIENCE / Clinical Trials / Clinical Innovation

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.

- WHAT ARE CLINICAL TRIALS?
- HOW CLINICAL TRIALS ARE CONDUCTED
- CLINICAL INNOVATION**
- FIND A TRIAL
- TRIAL DATA & RESULTS +
- POST MARKETING COMMITMENTS +



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



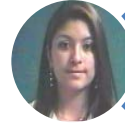
Pfizer Pediatric Center of Excellence (PedCoE)

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*



Edress Darsey, PharmD
• *Global Pediatric Medical Director*



Claudio Fracasso, MD
• *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.



Module 1:
Introduction to
Pediatric Research
at PFIZER

- Why Conduct Pediatric Trials
- Challenges of Pediatric Clinical Trials
- Pfizer Pediatric Research Resources
- Pediatric Development Strategy & Timeline



Module 2:
Current Legislation
and Regulatory
Environment for
Pediatric Research

- Prescribing Issues in Clinical Practice
- More Medicines for Children: Legal/Regulatory Landscape
- Why Is a Global Strategy Important?
- Global Pediatric Strategies



Module 3:
Drug Development
Considerations for
Pediatric Research

- When to Start?
- Getting the Drug In – Pediatric Formulations
- Getting the Dose Right
- Pharmacokinetics in Children



Module 4:
Designing a
Pediatric
Clinical Trial

- Pediatric Trial Considerations
- Design Considerations
- Designs for Pediatric Trials
- Protocol Development



Module 5:
Pediatric Clinical
Operations

- Plan for a Successful Trial
- Site Identification and Recruitment
- Operational Challenges of Limited Populations
- Monitoring in Pediatric Trials



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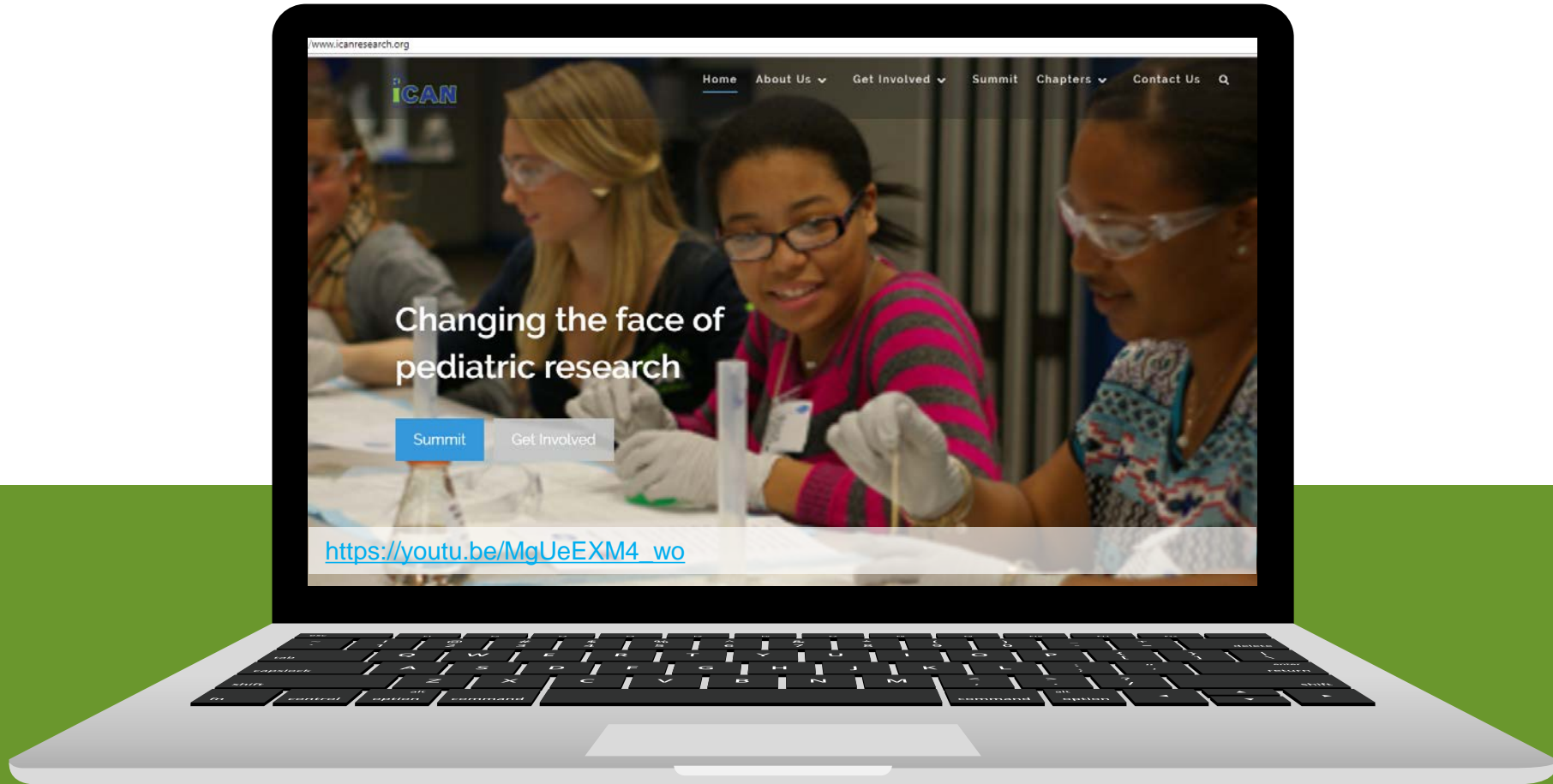
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Patient Engagement

- Voice of child/caregiver (study design, simulation, feedback)



International Children's Advisory Network



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Collaboration

- Involvement with Collaborative groups (TransCelerate)
- Consortia
- Common protocol templates
- Study Design

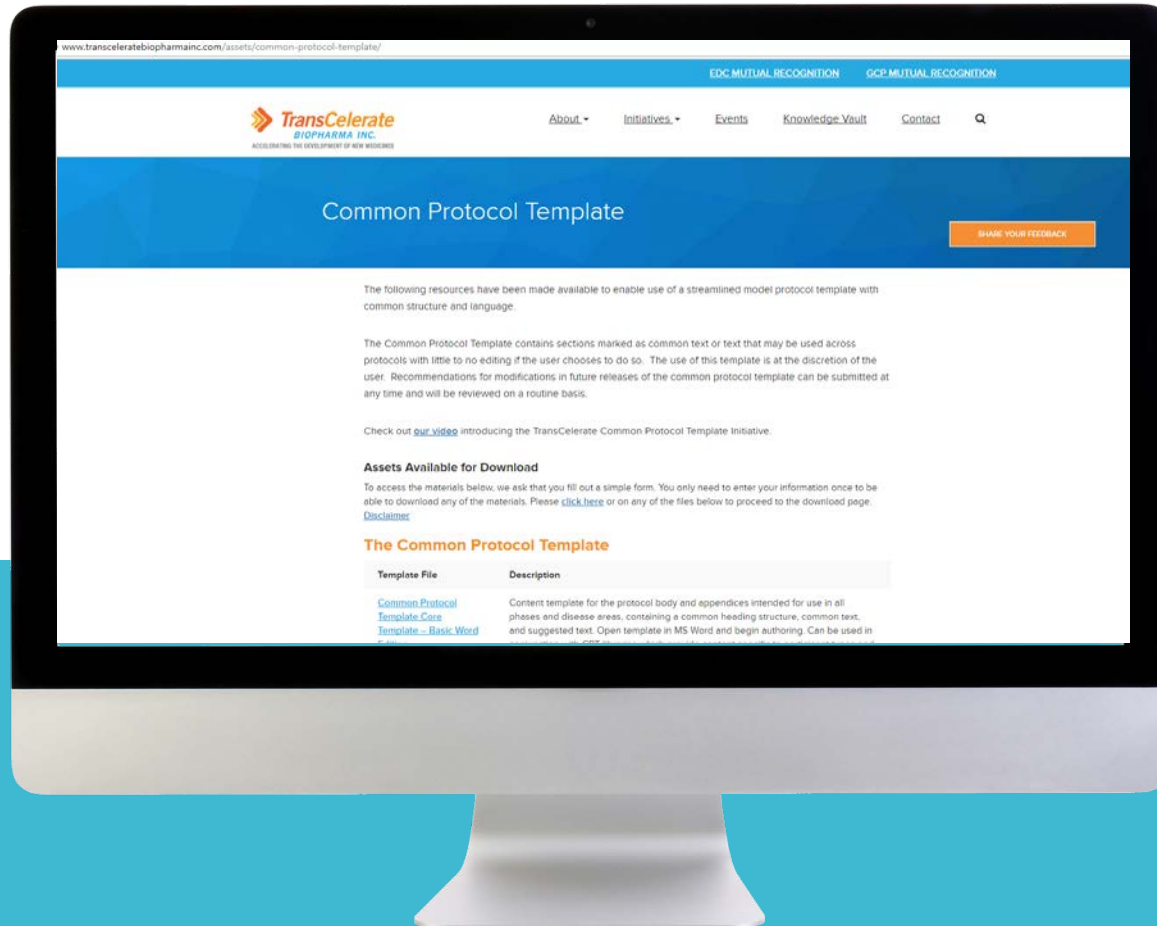


ABOUT TRANSCCELERATE BIOPHARMA

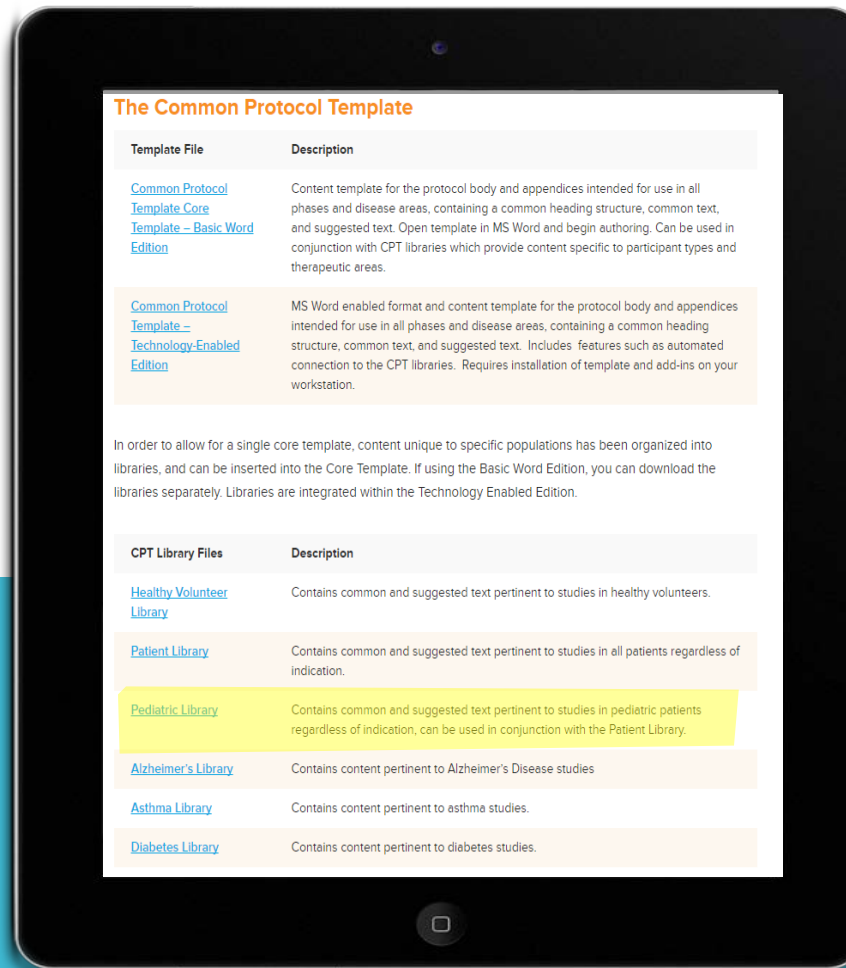
Pfizer is a founding member of TransCelerate BioPharma Inc., a non-profit organization focused on advancing innovation in research and development (R&D), identifying and solving common R&D challenges and further improving patient safety, with the goal of delivering higher quality medicines to patients. 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



TransCelerate Pediatric Protocol Template



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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.



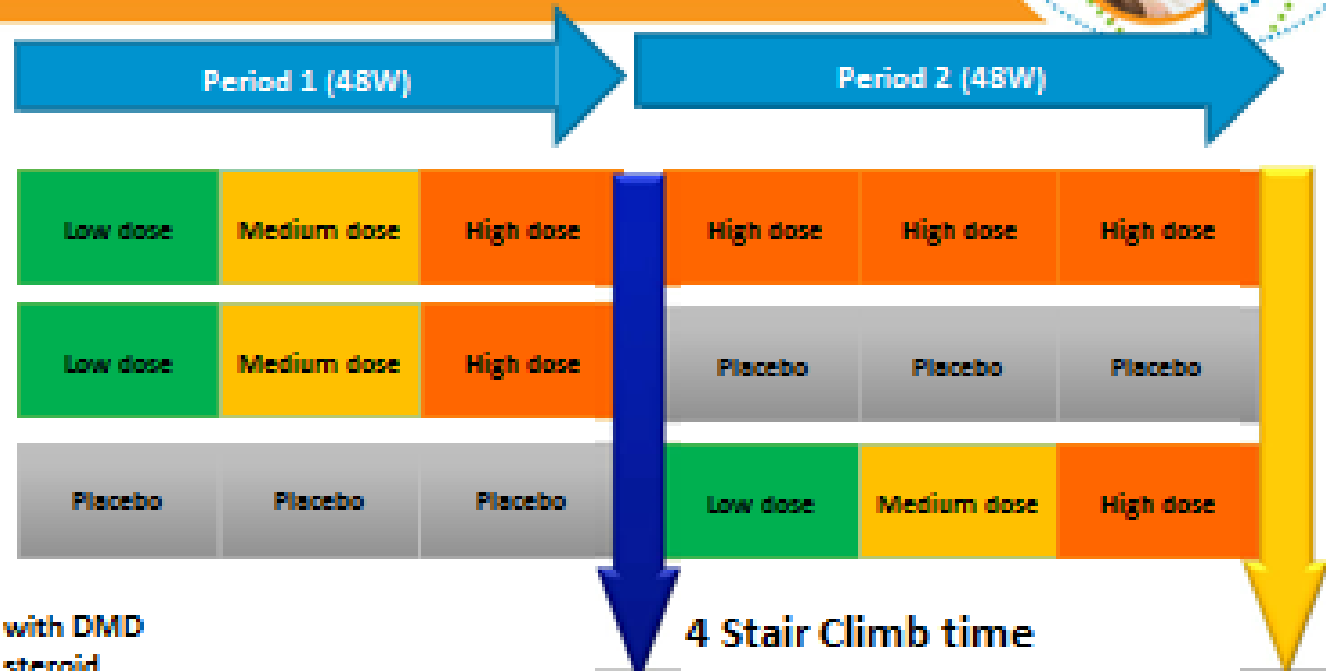
Examples of Innovative Design: Endpoint for Sickle Cell Disease Study

- 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)



- 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

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

Secondary Analysis

External Data Monitoring Committee

Examples of Innovative Design/Solution

Background (Fosphenytoin)

- 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



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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



