



Operational Challenges in Pediatric Drug Development

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Clinical Development and Analytics

What are the goals of pediatric drug development programs?

- To facilitate the development and availability of innovative, quality medicines according to the highest ethical and scientific standards; to help extend and enhance the lives of infants, children and adolescents and fulfilling unmet medical need in pediatrics.
- Determine safety and efficacy of the product for the claimed indications in all relevant pediatric populations (same or different than adults)
- Provide information to support dosing and administration for each pediatric subpopulation for which the product is safe and effective
- Propose labeling
- Develop and make available age appropriate and acceptable formulation(s)
- Ensure involvement of child and parent in design and study feedback
- Ensure feasible protocols and programs are performed with greatest likelihood of study completion. (protocol and study feasibility) and **expediently!!**

Each Study is Effectively a Study in an “Orphan” Population

At least Five Pediatric Sub-Populations



Preterm Newborn Infants	Term Newborn Infants	Infants and Toddlers	Children	Adolescents
<i>Pre-term</i>	<i>0–28 days</i>	<i>29 days to 23 months</i>	<i>2 Years to 11 Years</i>	<i>12 Years to 18 Years</i>

- Incidence of most diseases requiring innovative medications in children is relatively low
- Eligibility criteria further narrow the pool eligible to be enrolled in a study as does off-label use for marketed drugs
- Separate clinical studies could be required for different sub-groups
- Studies in neonates are required unless reason for waiver well justified.
- Other types of categorization for pediatric population can be used if justified

LANDSCAPE - PEDIATRIC DRUG/DEVICE RESEARCH



Root Causes: Stakeholder misalignment, design issues, ad hoc infrastructure, slow start-up, ineffective recruitment, poor feasibility, multiple amendments, limited academic incentives, inadequate reimbursement, lack of sustainability of site 'network'

Pediatrics 2014;134 e512-e518

When to start considering operational aspects of a pediatric clinical trial?

- From conception
 - Begin pediatric considerations **early** in drug development
- Innovative trial designs and programs need to be part of operational plan
- Global pediatric clinical trials networks

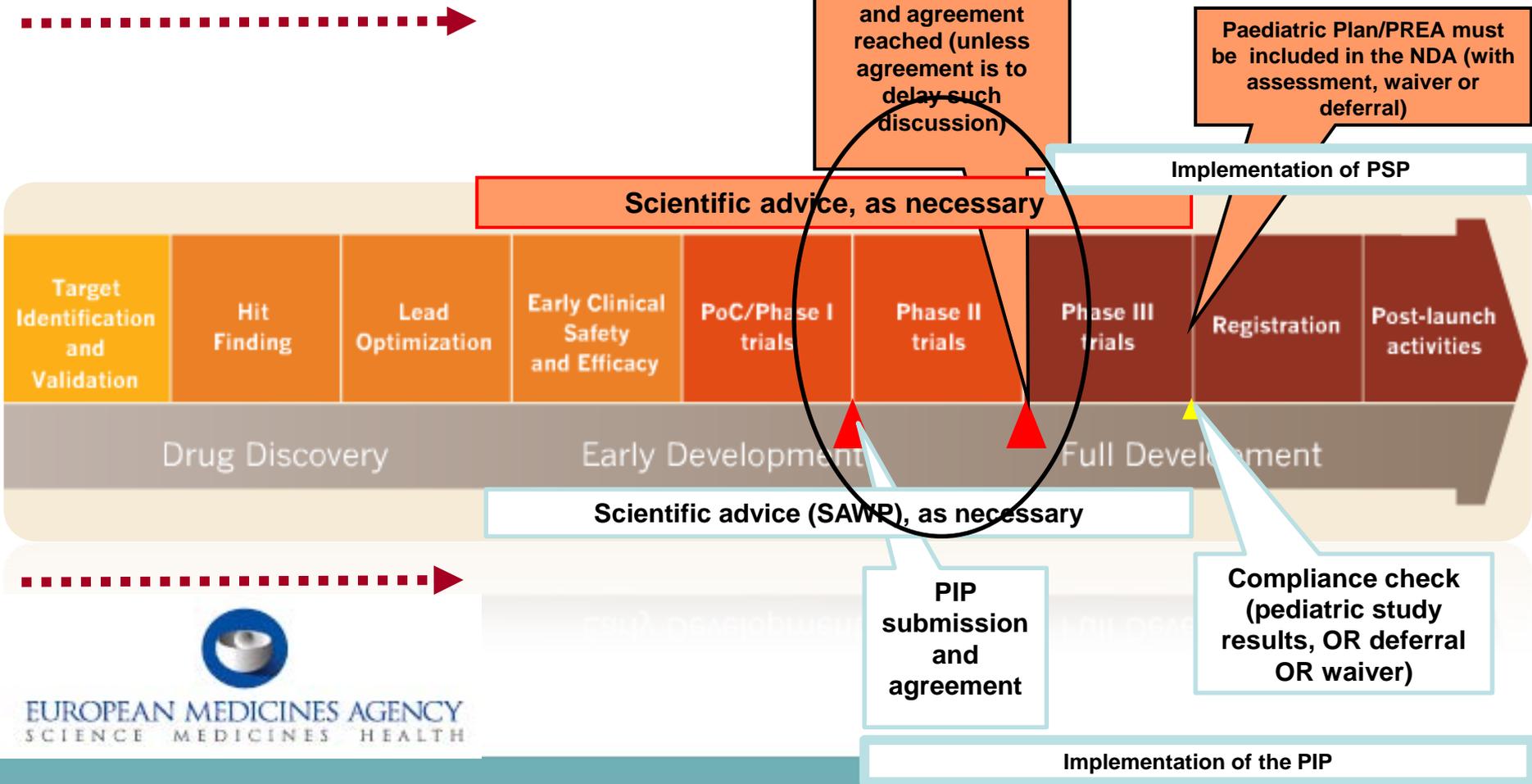
571 Steps to Operationize Pediatric Clinical Program

(not including formulation, toxicology, PK/PD, dose, endpoints, design discussion)

- Development Plan
- Regulatory strategy
- Feasibility assessment
- Protocol, Investigator brochure, parental permission, child assent
- Patient/parent engagement
- Educational materials
- Clinical study groups
- Project management
- Regulatory services
- eCRF and EDC
- Back end database
- CRO selection, internal, network
- Site identification and qualification
- Site and faculty and hospital **contracts**
- Site readiness
- Central laboratories/shipping
- Biostats and programming
- IRB
- Investigator meeting(s)
- DSMB
- Executive and adjudication committees
- Training and education
- Site initiation
- Site monitoring
- Patient recruitment and retention
- Long term extension studies
- Safety reporting strategy (AE, SAE)
- Data standards
- Pharmacy plan
- Extended distance considerations
- **Amendments**
- Site closure and study completion activities
- CSR completion
- Regulatory filing
- Publication

Early Considerations: Timing is everything....

 U.S. Food and Drug Administration




EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Early Considerations

- Toxicology in juvenile animals where appropriate (FIH, FIN)
- Formulations: ease of administration and flexibility in dosing
 - Takes up to 2 years to develop specific pediatric formulations
- Exposure response (E-R) assessment and modeling
 - FDA pharmacology guidance for pediatrics and shortly for neonates
 - Techniques such as extrapolation and Bayesian statistics cannot be used unless the adult E-R is sufficiently characterized – must be done in early phase adult program (Hampton LV et al Brit J Clin Pharm 2014;78:898)
- Natural history and disease assessment
 - Similar to adult disease or unique indication for pediatrics
- Innovative study designs: extrapolation, Bayesian statistics, adaptive designs, enrichment strategies, withdrawal designs, SMART designs, n of 1 designs
- Clinical Trial Simulations/modeling/Systems biology/PBPK

Proposed ICH E11 (R2) Comment on Pediatric Extrapolation

- Pediatric Extrapolation is an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that :
 - course of the disease**
 - expected response to a medicinal product**would be sufficiently similar in the pediatric and reference (adult or other pediatric) population.
- Pediatric extrapolation, when used appropriately, can improve the **feasibility** of pediatric product development.
- In using pediatric extrapolation, **early planning during adult development is necessary to generate the required data to extrapolate to the overall pediatric population or to pediatric subgroups.**
- There is also an **ethical imperative** to consider the appropriate application of pediatric extrapolation because children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults).

This can only be accomplished with planning early in drug development.

Natural History of Disease

Explanation of similarity of disease progression from older to young population

- Literature reviews
- Expert opinion – individual and group, questionnaires, reviews
- Results of other therapies for condition; similarity of response with source population
- Studies of similarity of disease/disease progression in adults and children
- Mechanism of action/pharmacogenomic information
- Assessment of same disease in different time frames of disease
- Biomarker and/or endpoint similarity
- Natural history studies (important role for disease advocacy groups, academia, NIH)
- Clinical Trial Simulations
- Historical data

Key Factors for Operational Success

After early considerations and study designs followed regulatory approval, operational aspects of pediatric studies are often limiting factors to successful completion of a pediatric drug development program

Pactical **P**rotocol(s) developed by a multi-stakeholder team

- Designed with experts to answer valid scientific questions with excellence and practicality
- Approved by regulatory agencies (global)
- Approved by IRB
- Developed in conjunction with operational network, academic experts, CRO

Recruitment

- Countries, sites, investigators, patient population

Enrollment and Retention

- Study team

Presentation

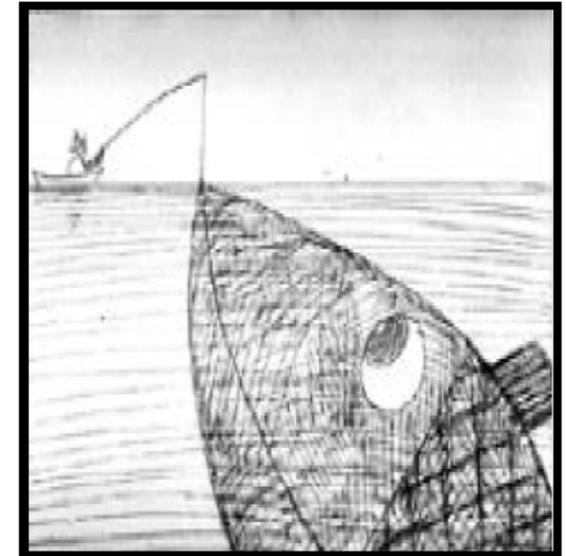
- Transparency: labeling, presentation, publication
- Investigators and Sponsor

Where and how do we best optimize recruitment and retention?

Fishing in the wrong place



Fishing with the wrong tool



Country Selection



- Prevalence of target condition for study
 - Treatment naïve pools of patients
 - Balance benefit of making drugs available to a population that needs them without exerting undue influence
- Appropriate clinical expertise/technology available for research
- Existence of networks/CROs in country
- Cultural considerations in research participation
- Ensure standards of care globally
 - Additional support, equipment, education, concomitant medications
- Ease or difficulty of study approvals
 - IRB: Brazil: >1 year for a Pediatric GERD program
 - Legal issues: prolonged therapy, onerous care requirements
 - Central coordination: Finland, UK
 - Customs: 18 months to allow equipment into country
 - Company's country footprint

Site Selection

- Networks vs ad hoc site selection
 - Ideal: network with common contracts, protocol approval and IRB process
- Patients with target condition; catchment area
- Appropriate units and clinics
- Pediatric clinical trials infrastructure, e.g., involvement in successful networks: PTN, COG, CTSA, PHN
- Ideal: separation of clinical care and clinical research
 - Dedicated research units and staff
 - Should patients be enrolled by their caregivers? Practical issues
- IRB – local or central
 - Reputation and processing time
- Track record of successful study participation: highly variable even within same institution
- Master contracts
- Virtual Sites

Investigator Selection(s)

- Academic Experts to Partner in Development Plan:
 - Well published, experienced, respected, productive, supportive of industry related research
 - Involved nationally and internationally in management of the considered condition
 - Prior regulatory experience an asset
- Participation in Study Committees
 - Steering committees
 - Data monitoring committees
 - Independent adjudication committees
- Investigators
 - Expertise and performance of PI
 - Training in clinical research: new fellowship structure
 - Motivation!!!!
 - Involvement with other similar studies, compounds, other companies
- Changing the Culture: Pediatric Faculty Scholar Program



Oh, the irony...

Patient Recruitment

- Patient/family trust with care giver
- Care givers attitude and skill in approaching patient
- Educational tools for patients and parents
- Therapeutic options
- Education of patients and families
 - Local and national
- Involvement in parent/groups: UK YPAG, iCAN. Disease specific parent advocacy groups
- Risk/benefit
- Convenience for visits, procedures
- ‘Incentives’ but not ‘coercives’
- Consent/permission/assent that makes sense to patient/family (iCAN review)



What is a network?



- Dictionary definition: an association of individuals having a common interest, formed to provide mutual assistance, helpful information, or the like
- For clinical trials, no standard definition – 100's of pediatric networks of all sorts and sizes and objectives
- Most loose affiliation of individual experts and institutions for the study of specific conditions or groups of conditions
- Lack structure: NO legal underpinning, common contracting or budgeting, common IRB, administrative core, research or dedicated personnel, tenuous financial structure
- Often organized for specific study and then dissipate
- Can be very successful but often not sustainable
- Successful networks must have involvement of all stakeholders

What kind of Pediatric Networks Exist Today?

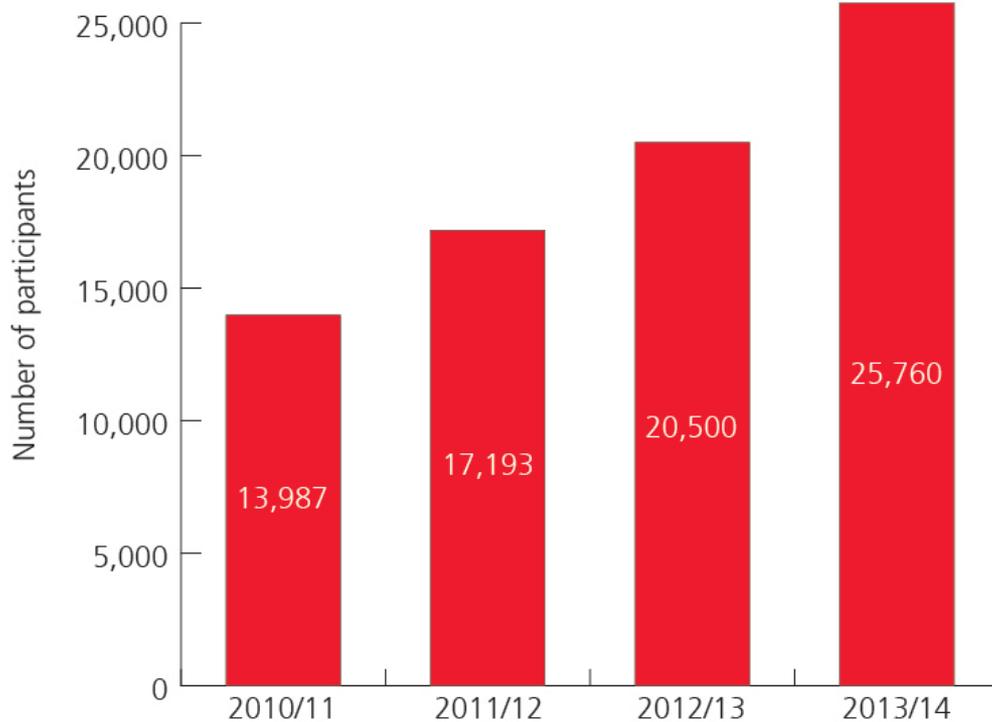
- State (e.g. Ohio), national (UK CRN), regional networks
- Disease/subspecialty-specific networks: COG, ITCC, PRINTO, PRCSG, NAPRTCS
- NIH networks: PHN, Rare Disease, >80 more, PTN, CTSA
- Foundation networks (CFF, JDF)
- Office-based networks: PROS
- Children's hospital networks: PHIS, PedsNet
- Patient advocacy networks: iCAN, YPAG
- New initiatives: Public Private Partnerships
 - ❖ Institute for Advanced Clinical Trials for Children
 - ❖ (IACT for Children)
 - ❖ International Neonatal Consortium (Critical Path Institute)
 - ❖ European Pediatric Clinical Trials Network (IMI2 process)

Children's Oncology Group (COG) (2008-2010)

- Took 50 years to develop from multiple smaller study groups.
- >90 % of pediatric oncology trials in US done through COG
- Open studies - 130 (86 Rx)
- Total enrollments – 25,726; Active F/U - 69,773 Survivor F/U - 270,000
- Funding primarily from NIH/NCI and private sources; close relationship with FDA
- 220 Sites in US, Canada, Australia, NZ, Switzerland, Ireland, others
- Performance Metrics
- Site structure costs are included in base funding
- Academic advancement for members: Motivated Investigators!!!
- Key role in care of pediatric cancer patients
- BUT: Selective of studies they will do; processes time consuming and decision making ponderous

UK Children's Research Network Industry Performance: Improved Delivery; Increased Recruitment 'THE MODEL'

Number of participants into Commercial NIHR CRN Portfolio studies



- **96,000** patients recruited to industry studies over the last 6 years
- **25,000+** patients recruited to commercial contract studies in 13/14
- **35 first global patients** in 2013/2014
- **80% of industry studies delivered to time and target**

info@mcrn.org.uk

<http://www.mcrn.org.uk/>

Pediatric Trials Network (www.pediatrictrials.org)

NIH funded network primarily for study of off-patent, off label drugs for children and neonates with expanding role. Opportunistic sampling strategy.



International Neonatal Consortium

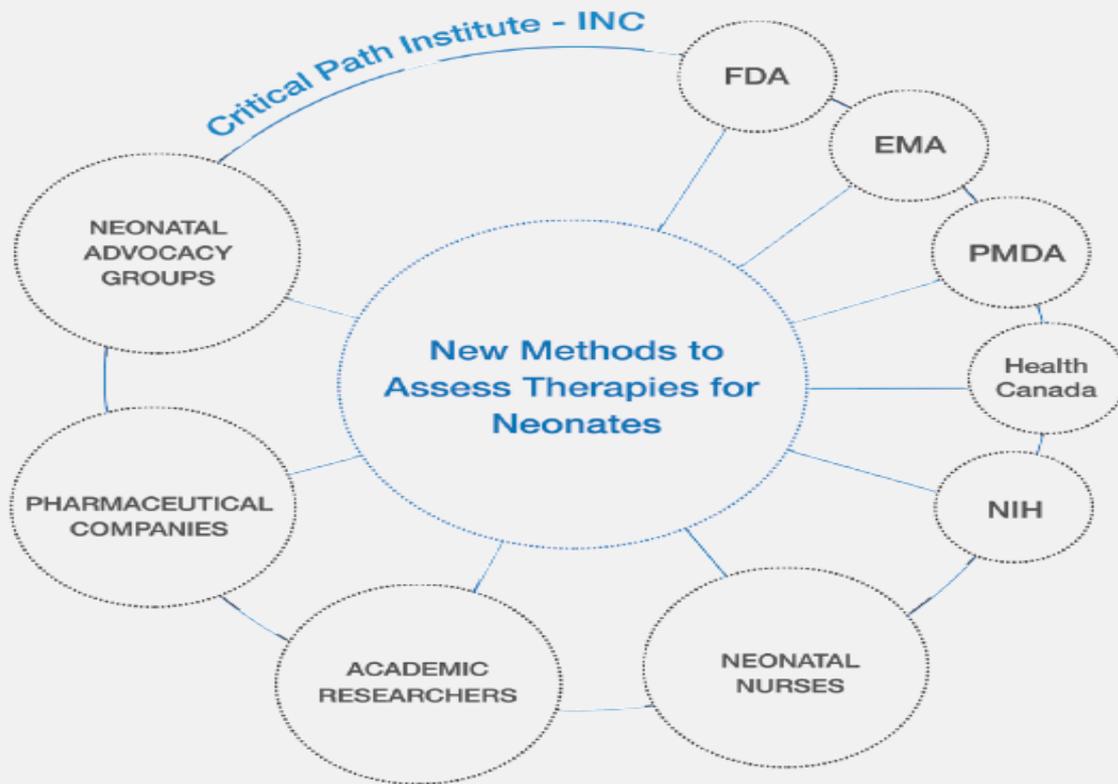
One of the Critical Path Institute Consortia

Accelerating the development of safe and effective therapies for neonates.

The consortium will address the need for measurement and assessment of clinical outcomes in neonates through teams that share data, knowledge, and expertise to advance medical innovation and regulatory science.



International Neonatal Consortium



<http://c-path.org/programs/inc/>

MEMBERS

Neonatal Nurses

- NANN
- COINN

Companies

- AstraZeneca
- Bristol-Myers Squibb
- Chiesi Pharmaceuticals
- Eli Lilly and Company
- Janssen Research & Development
- Novartis Pharmaceuticals
- Pfizer Inc
- Sanofi Pharmaceuticals
- Shire
- TriNetX

Families/Advocacy

- Graham's Foundation
- March of Dimes

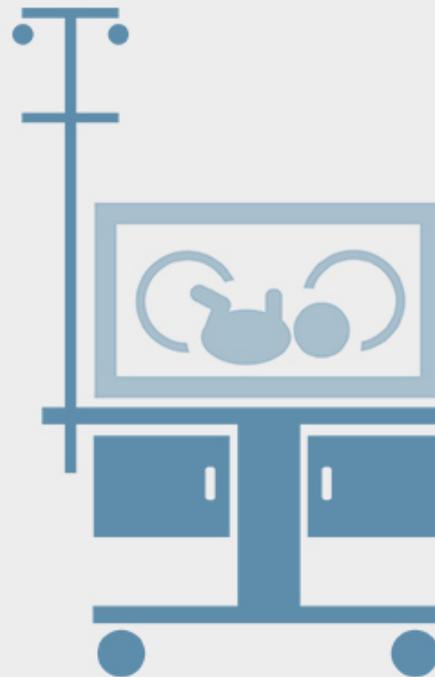
Developing Priorities

INC AND THE NICU

The International Neonatal Consortium will concentrate its efforts on those conditions most commonly encountered in Neonatal Intensive Care Units (NICUs), and on the prevention of pre-term birth.



International Neonatal Consortium



NEONATAL LUNG INJURY AND CIRCULATORY FAILURE

PERINATAL/NEONATAL INFECTIONS

NEONATAL ABSTINENCE SYNDROME (NAS)

RETINOPATHY OF PREMATURITY (ROP)

NEONATAL GASTROINTESTINAL INJURY

NEONATAL BRAIN INJURY

DRUGS TO PREVENT PRETERM LABOR

Concept of a Global Pediatric Clinical Trials Network

- Initial funding from a public-private partnership (industry, public/private research institutions, patient groups)
- Disease-agnostic; phase I-IV; neonatal-adolescence
- Global: US, Canada, EU and beyond
- >100 of the best children's medical centers in the world
- Heterogeneous study sponsors including industry, NIH (government research), European Commission, private foundations, patient advocacy groups, investigator initiated
- Cooperate and partner with existing networks, patient groups, medical societies, foundations
- Global resource for advancing science of pediatric drug development and advocating for sound regulatory policy
- Provide benefits for all involved: patients, parents, faculty regulators, foundations, industry



AAP Forum

2014

Clinical Trials Stakeholder's Meeting...

Diverse global experts resolved that a clinical trials network should be created and sustained....



Bogue et al. on behalf of The Pediatric Clinical Trials Stakeholder Forum Planning Committee. *Pediatr Res* doi:10.1038/pr.2015.255

C-Path and PTC

2015-2016

Critical Path Institute established the *Pediatric Trials Consortium* in 2015 to provide advice and recommendations regarding establishment of a new independent non-profit organization dedicated to advancing pediatric medicines and devices research.



- ✓ PTC Advisory Report
- ✓ A Delaware Not for Profit Organization

I-ACT for Children

2016+

Critical Path Institute establishes the *Institute for Advanced Clinical Trials for Children* as a new independent non-profit organization and prepared for launch of I-ACT.



A sustainable infrastructure to enable global and timely execution of high-quality clinical trials that adhere to regulatory standards.

I-ACT for Children

Strategy and Planning

Getting it right the first time...



Non-Proprietary Work

- Focus on impact on child health
- Neutral, independent forum
- Alignment of stakeholder interests
- Innovation in trial design
- Up-front data-driven feasibility
- Quality and efficiency by design
- Interface with global infrastructure

Product-Specific Work

- Independent assessment of sponsors' programs/strategy, including PIPs, PSPs, protocols, etc. through Clinical Study Groups
- Independent assessment of modeling/simulation, extrapolation, master protocols, etc.
- Independent assessment of feasibility and efficiency

Network of Trial Ready Sites

Home for Regulatory Quality Pediatric Trials



On site research staff: Site Champions, Network Trial Associates

Impact of European Paediatric Regulation

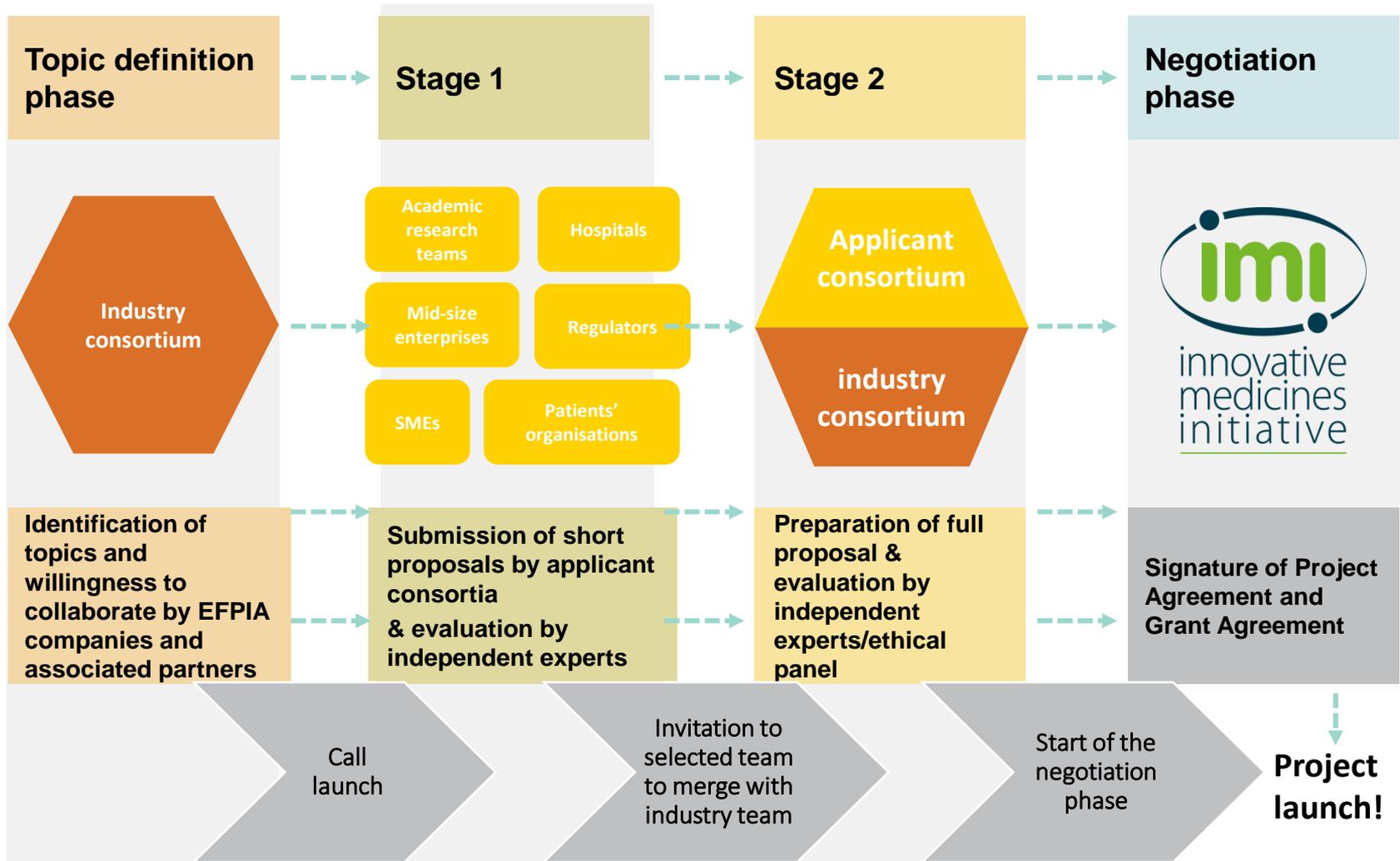
Number of children to be involved in Clinical trials is constantly growing

Number of children planned to be enrolled in clinical trials, by age by year of authorization (or, if not available, by year of protocol upload into EudraCT).

Number of subjects	2006	2007	2008	2009	2010	2011	2012	2013	2014
Preterm newborns	0	0	0	327	82	2,522	1,552	3,724	4,331
Newborns	0	98	5	184	169	1,348	2,283	1,496	1,948
Infants and toddlers	530	119	20	54,715	2,212	13,313	62,224	13,414	39,615
Children	2,683	706	270	5,783	2,721	21,654	30,826	23,230	62,979
Adolescents	435	36,458	285	5,801	4,831	20,206	22,680	17,300	42,353
Sum of above	3,648	37,381	580	66,810	10,015	59,043	119,565	59,164	151,226

Research infrastructure lagging behind need

Typical IMI2 project life cycle



EUPCTN - Scope of the proposal

providing common infrastructure, processes and scientific advice
to all sponsors via a single point of contact

- EU initiative that promotes more rapid delivery of paediatric drug trials through dedicated linked network personnel, and **consistent administrative processes across all member states**
 - Arranged around “**national hub coordinating centers**”: a qualified paediatric institution/center with contracts/connections to multiple sites within each member state
 - One **single point of contact** for study sponsors
 - Investment in the infrastructure will spill over beyond the initial scope: **sustainable**
 - Innovative Medicines Initiative 2 – Funds Public-Private Consortia
- ❑ **Standardized procedures and practices within each MS and across Europe:**
- CDAs, site contracts, budget templates
 - Advisory Clinical Study groups
 - Feasibility assessments (with regards to study design and enrollment)
 - Patient and public involvement in study assessment
 - Data coordination center (common data dictionary, common data coding procedures) *
 - GCP and clinical trials training
 - Site qualification criteria and performance metrics

IACT and IMI2 Collaboration: on to global!

Principle:

IACT and IMI2 will work together from inception to jointly recommend quality standards, performance expectations and key steps to achieve process efficiency. IACT established the Global Interoperability work stream to support this work.

Global Interoperability Deliverables:

IACT and IMI2 will work together to:

- Articulate the most important shared goals
- Describe key quality standards, performance metrics and processes
- Identify key stakeholder engagement practices to sustain alignment
- Set forth proposal to ensure long-term collaborative partnering



Conclusions



- Pediatric drug development is necessary to:
 - Provide the best care for children
 - Prevent inappropriate use of drugs by providing appropriate dosing/usage information
 - Have age appropriate formulations
 - Quantify safety information in pediatrics pts
- Operational factors are critical in successful completion of pediatric clinical trials including:
 - Protocol – Trial design and feasibility
 - Recruitment
 - Enrollment and retention
 - Presentation
- A highly functioning global pediatric clinical trial network should be developed and utilized in concert with existing highly functioning networks to facilitate and expedite providing safe and effective drugs to children in age appropriate formulations