Advancing International Pediatric Clinical Research

Promoting Global Clinical Research in Children: Informing the Future

21 March 2023, 9-11 am ET

This series is supported by an FDA Scientific Conference Grant.
Disclaimer

• The opinions expressed today are those of the speakers and are not intended to represent the position of Brigham and Women's Hospital, Harvard University, or any other organization, government, or entity.

• The MRCT Center is supported by voluntary contributions from foundations, corporations, international organizations, academic institutions and government entities (see www.MRCTCenter.org) and well as by grants.

• We are committed to autonomy in our research and to transparency in our relationships. The MRCT Center—and its directors—retain responsibility and final control of the content of any products, results and deliverables.

• I have no personal financial conflicts of interests to disclose.
• This webinar will be recorded and will be posted publicly on our YouTube channel.
We would like to offer a brief remembrance to our valued colleague and close collaborator, Dr. Vasantha Muthuswamy, who passed away in Mumbai in February 2023.
Our Vision
Improve the integrity, safety, and rigor of global clinical trials.

Our Mission
Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.
Where we started & why this is important:

- Children **deserve access** to safe and effective medicines
- Children **historically excluded** from or underrepresented in research
- **Pediatric population widely dispersed** so clinical trials must be conducted in multiple jurisdictions
- **Persistent ethical issues**: while governing ethical principles may be generally agreed upon, differences in interpretation and application of principles exist
- Differing or nonexistent pediatric **regulations**
- Challenges in **trial initiation and conduct**
- The **pediatric patient and family voice** is not routinely solicited nor included in research lifecycle.
- **Children are not routinely offered a seat at the table.**
Project Objectives

Broadly, sought to identify and propose solutions to regulatory, ethical, and operational challenges

• Current global landscape of pediatric research governance, focusing on legislative, regulatory, and guidance gaps and inconsistencies
• Identify current initiatives to improve pediatric research globally
• Identify challenges related to decision-making by and on behalf of children
• Address benefit and risk considerations that create barriers and inefficiencies in transnational research with children.
• Identify meaningful ways to engage patients, their families, and community members
• Diverse leadership and membership, broad geographic diversity
Webinar Series:
Advancing International Pediatric Clinical Research

- An offshoot of the MRCT Center’s *Promoting Global Clinical Research in Children* project
- Funded in part through an FDA scientific conference grant award
- 5 virtual webinars

1. Informing the future from COVID-19 lessons learned: October 2021
2. Time to Listen—Hearing from young people in clinical research: February 2022
3. Assent and Consent in the Field: Culture, Context, and Respect: June 2022
5. **Today - Promoting Global Clinical Research in Children: Informing the Future**

*Please see “Bio Book” for extended introductions to the speakers and panelists*
## Today’s Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker(s)</th>
</tr>
</thead>
</table>
| 9:20 – 9:40 AM | Including Children in Decisions About Research: Towards Consistent Global Standards | Steve Joffe  
University of Pennsylvania |
| 9:40 – 10:00 AM | Involving Young People in Research: The Pediatrics Toolbox | Lisa Koppelman  
MRCT Center  
Gigi McMillan  
Loyola Marymount University |
| 10:00 – 10:15 AM | Establishing a Model to Integrate Children’s Voices into the Clinical Research Process | Thierry Lacaze  
Maternal Infant Child & Youth Research Network (MICYRN) |
| 10:15 – 10:45 AM | Innovations in the Pediatric Regulatory Space: Fireside Chat | Dominik Karres  
European Medicines Agency  
Skip Nelson  
Johnson & Johnson |
| 10:45 – 10:55 AM | Closing | Barbara Bierer  
MRCT Center |
Including Children in Decisions About Research: Towards Consistent Global Standards

Dr. Steven Joffe
University of Pennsylvania
Perelman School of Medicine
SPECIAL ARTICLE

Establishing a global regulatory floor for children’s decisions about participation in clinical research

Steven Joffe1,2, Albert J. Allen3, Jonathan M. Davis4, Elisa Koppelman5, Susan Z. Kornetsky6, Grace Marie V. Ku7, Victoria A. Miller8, Jennifer Preston9, Lesha D. Shah10 and Barbara E. Bierer5,11
Process

- Working group including 13 members, subset of larger 80+ person workgroup
- 12 monthly 90-minute Zoom meetings
- Working group identified International Council for Harmonisation (ICH) recommendations as best approximation of global standard for pediatric research
  - Analysis of ICH standards (and recommendations for improvement) in light of working group’s insights
1. Sharing information with participants & parents

- Key ICH points
  - Fully inform parents as legal decision makers in language they can understand
  - When seeking child assent, provide information appropriate to child’s capabilities
1. Sharing information with participants & parents

- Recommendations—guidance should...
  - Specify what information is material
  - Distinguish research-specific elements from ordinary care
  - Ensure opportunity for questions & clarifications
  - Address the readability of documents
  - Highlight need to assess understanding (and correct misunderstandings)
2. Children’s roles in authorizing participation

- Key ICH points
  - Where appropriate, children should give assent
  - May be necessary to reconfirm assent (or obtain consent) over course of a trial
2. Children’s roles in authorizing participation

- Recommendations—guidance should...
  - Define assent
  - Clarify “when appropriate”
  - Address whether & how to engage children when assent is not required
3. Children’s signatures on “assent forms”

- Key ICH points
  - Participants of appropriate intellectual maturity should sign an assent or consent form
3. Children’s signatures indicating agreement

- Recommendations—guidance should...
  - Define “appropriate intellectual maturity”
  - Clarify the function of a signature (as opposed to other means of seeking & documenting agreement)
4. Right to withdraw or decline

- Key ICH points
  - In all cases, participants should be made aware of right to withdraw or decline
  - Refusal to assent or withdrawal of assent should be respected
4. Right to withdraw or decline

- Recommendations—guidance should...
  - Acknowledge possibility that, depending on child’s capacity and other factors, meaningful dissent may not be possible
  - Recognize that, in some cases, continuing in trial may be in child’s best interests despite dissent
  - Distinguish between objection to research-specific element and objection to element of ordinary care
5. Overriding request to withdraw

- Key ICH points
  - Although wish to withdraw must be respected, there may be circumstances in which parents/guardians & judge that leaving study would threaten child’s welfare
  - In such circumstances, child’s objection may be overridden
5. Overriding request to withdraw

- Recommendations—guidance should...
  - Reconcile contradiction between “request to withdraw must be respected” and ability to override that request
  - Clarify role of IRB/REC in decisions to override objection
Summary

- Harmonizing practices for including children in decisions about research will facilitate global pediatric clinical trials
- ICH recommendations provide a strong global ethical framework for authorizing children’s participation in research
- But they include several contradictions and areas of ambiguity that future revisions should aim to address
Involving Young People in Research: The Pediatrics Toolbox

Ms. Lisa Koppelman
MRCT Center

Dr. Gianna “Gigi” McMillan
Loyola Marymount University
Project Objectives

Broadly, sought to identify and propose solutions to regulatory, ethical, and operational challenges

• Current global landscape of pediatric research governance, focusing on legislative, regulatory, and guidance gaps and inconsistencies

• Identify current initiatives to improve pediatric research globally

• Identify challenges related to decision making by and on behalf of children

• Address benefit and risk considerations that create barriers and inefficiencies in transnational research with children.

• Identify meaningful ways to engage patients/families/community members
18 Guiding Principles

Children should only be enrolled in research that has scientific and social value related to the health of children or diseases that originate in childhood.

Children and their health needs are an important research priority.

Pediatric research often requires multi-site and multinational trials. Regulations across jurisdictions should be aligned.
Children are entitled to have a voice in making decisions to the extent their capacity allows throughout the research process.
INCLUDING YOUNG PEOPLE IN RESEARCH:

A “How-To” Guide
<table>
<thead>
<tr>
<th>Country</th>
<th>Primary Applicable Laws and Guidance</th>
<th>Adapated ICH?</th>
<th>What is the age of majority?</th>
<th>Is consent (or expression of will) to participate in a study?</th>
<th>For parents, is permission by one or both required?</th>
<th>Are all parts of the study required? (not implied)</th>
<th>ICH Harmonized Guideline Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population E11R1, August 18, 2011 (&quot;ICH E11&quot;)</th>
<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediatric Research Center</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pediatric Research Comparison Chart: Risk Benefit Analysis**

<table>
<thead>
<tr>
<th>Country</th>
<th>Primary Applicable Laws and Guidance</th>
<th>Adapated ICH?</th>
<th>How is &quot;risk&quot; defined?</th>
<th>How is &quot;benefit&quot; defined (including for which populations it is measured)?</th>
<th>What risk level is acceptable for research studies that may offer the prospect of benefit to the individual participant? (&quot;Direct benefit&quot;)</th>
<th>What risk level is acceptable for research studies that only may offer the prospect of benefit to the group of children in which the participant falls?</th>
<th>Are placebo controls permitted and why?</th>
<th>Are healthy volunteers permitted and why?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICH E11</strong></td>
<td>ICH Harmonized Guideline Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population E11R1, August 18, 2011 (&quot;ICH E11&quot;)</td>
<td>N/A</td>
<td>Not defined, but risks and benefits are evaluated in relation to the use in connection with toxicity and adverse events. &quot;Distress&quot; includes procedures that may cause pain or discomfort.</td>
<td>Comparable to those encountered in routine clinical care</td>
<td>Greater than low risk; clinical benefit is required. Anticipated clinical benefit must be at least comparable to the available alternative treatment</td>
<td>Low compared to those encountered in routine clinical care</td>
<td>Not specified, but possible if risk is low</td>
<td>Not generally, unless criteria must be justified</td>
</tr>
<tr>
<td><strong>ICH E11</strong></td>
<td>ICH Harmonized Guideline Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population E11R1, August 18, 2011 (&quot;ICH E11&quot;)</td>
<td>N/A</td>
<td>Any age determined by ICH E11 or consistent with local legal requirements</td>
<td>For studies comparing populations</td>
<td>For studies comparing populations</td>
<td>For studies comparing populations</td>
<td>For studies comparing populations</td>
<td>For studies comparing populations</td>
</tr>
<tr>
<td><strong>ICH E11</strong></td>
<td>ICH Harmonized Guideline Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population E11R1, August 18, 2011 (&quot;ICH E11&quot;)</td>
<td>N/A</td>
<td>Yes, age determined by ICH E11 or consistent with local legal requirements</td>
<td>For studies comparing populations</td>
<td>For studies comparing populations</td>
<td>For studies comparing populations</td>
<td>For studies comparing populations</td>
<td>For studies comparing populations</td>
</tr>
<tr>
<td><strong>ICH E11</strong></td>
<td>ICH Harmonized Guideline Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population E11R1, August 18, 2011 (&quot;ICH E11&quot;)</td>
<td>N/A</td>
<td>Yes, age determined by ICH E11 or consistent with local legal requirements</td>
<td>For studies comparing populations</td>
<td>For studies comparing populations</td>
<td>For studies comparing populations</td>
<td>For studies comparing populations</td>
<td>For studies comparing populations</td>
</tr>
</tbody>
</table>

**Other Materials**

©MRCT Center
Video Series: Prioritizing Young People’s Voices
If the doctor does not speak to me directly – but only to my parents – I wonder what information is being withheld.
Monitoring the Pediatric Clinical Trials Enterprise

Robert M. Calif, MD, Deborah A. Zarin, MD

Common Commentary on Paediatric Oncology Drug Development
Published: Another Step in Optimising Global Regulatory Coordination of Paediatric Development Plans

Dominik Karres, Gregory Reaman, Franca Ligas, Giovanni Lesa, Susan McCune, Suzanne Malli, Ralph Bax, Jean Temeck

The Parent’s Dilemma: Pediatric Assent in Research

Ganna McMillan, DBioethics

SPECIAL ARTICLE
Establishing a global regulatory floor for children’s decisions about participation in clinical research

Steven Joffe, Albert J. Allen, Jonathan M. Davis, Elsa Koppelman, Susan Z. Kornetsky, Grace Marie V. Ku, Victoria A. Miller, Jennifer Preston, Lesha D. Shah, and Barbara E. Blier
A reminder of why this is so important
Establishing a Model to Integrate Children’s Voices into the Clinical Research Process

Dr. Thierry Lacaze
Maternal Infant Child & Youth Research Network (MICYRN)
Space: Children and YP must be given safe, inclusive opportunities to form and express their views

Voice: Children and YP must be facilitated to express their views

Audience: The views must be listened to

Influence: The views must be acted upon as appropriate

• Several existing Pediatric research networks in different jurisdictions are developing capacities to integrate the voices of children and young people in the development of clinical trials

• Following the MRCT webinar #2 and building on the expertise at these existing networks, a small group of individuals who work with young people has gathered and met several times

• Can we build upon those existing networks to create a cooperative and sustainable global structure that sponsors and investigators can access?
Innovations in the Pediatric Regulatory Space

Dr. Dominik Karres
European Medicines Agency

Dr. Robert “Skip” Nelson
Johnson & Johnson
Disclaimer

• The views and opinions expressed in the following PowerPoint slides are those of the individual presenters and should not be understood or quoted as being made on behalf of the European Medicines Agency or its scientific Committees (DK) or Johnson & Johnson (RN).
• Pediatric medicines development is a global enterprise taking place in a highly complex ecosystem.

• Existing pediatric development policies have enriched the innovative medicines development research space.

• However, for certain molecules, authorization of pediatric uses continues to lag well behind adult authorization.¹

• Globally relevant and efficient pediatric medicines development requires global cooperation
  • In pediatric cluster calls, EMA and FDA have a high rate of convergence (~70%).²

• Reliance models can be used for any regulatory function.³

• Models discussed each serve a useful purpose, are complementary and not mutually exclusive.
  ✓ Pediatric Cluster; Parallel Scientific Advice; Multi-stakeholder Forums (ACCELERATE); Reliance.

¹Gilles Vassal, Gustave Roussy. Presentation on R13.4 Day One.;
²Donna Snyder, FDA. Presentation on R13.4 Day One.;
³Marie Valentin, WHO. Presentation on R13.4 Day One.
Enhancing global cooperation in pediatric medicines development planning

Pediatric Medicines Development Ecosystem

- Regional and National Health Authorities
- Regional and National Policies
- Iterative Process
- Coordinate & Timing

Reliance pathways

Regulatory Decision Making

Patient Voice/ Multi-stakeholder Forums

©MRCT Center
Enhancing global cooperation in pediatric medicines development planning

**Multistakeholder Forums**

- Enhance linkage to regulatory guidance (esp. when co-authored by regulators)
- Expand to other therapeutic areas and/or competitive development spheres
- If expanded into early-stage development, some structural modification needed
- Role for professional societies
Enhancing global cooperation in pediatric medicines development planning

**Pediatric Cluster**
- Expand to all regions where pediatric policies are implemented (e.g., MHRA and SwissMedic)
- If Pediatric Cluster leads to Common Commentary, agencies should review prior Scientific Advice Meeting Minutes to reduce risk for contradictory regulatory guidance.

**Parallel Scientific Advice**
- A dedicated global pediatric scientific advice pathway is warranted for the 1/3 of pediatric plans where convergence on design elements cannot be achieved in Cluster.

**Reliance**
- Given the “high rate of convergence” of Cluster conversations, 2/3 of pediatric plans may be suitable to a reliance procedure (i.e., to agree a pediatric plan).
- **Model 1** (existing): Switzerland - Reliance on US a/o EU decision on an agreed pediatric plans (at submission of marketing authorization).
- **Model 2**: Submission of a PIP or PSP through usual regional procedure. Cluster held to coincide within a region’s procedure or agencies invited to listen as per pediatric memorandum of understanding (or other). At completion of the procedure, other agencies have the option to adopt the reviewing agency’s opinion for the plan.
Meeting the Regulatory Challenges

• Growing pipelines of innovative products, how to identify and support completion of development efforts in children for products able to address existing unmet medical needs?
  • This includes avoiding premature exclusion of paediatric developments of potentially effective products, whilst acknowledging failure of a product at (early/late) development stage being reality.

• Acknowledgment that regulatory decision making on mandated paediatric developments cannot take place in isolation

• Mindful of regulatory guidance and standards

• Whilst appreciating the need to be innovative, fostering a R&D environment that allows for evolution of scientific knowledge and takes changing evidence and unmet needs into consideration
Actions to support the development of medicines for children

- Strengthened focus on unmet medical needs
- **Adapting regulatory processes to better support innovation**
- Increased alignment of data requirements between decision-makers

Adapting regulatory processes to better support innovation

- Paediatric Investigation Plan (PIP) as a tool to fostering an environment of evolving evidence and needs

Focus on unmet medical need - the final target population

- Early Phase study a starting point only, based on robust biological rational to generate PK, safety and (preliminary) activity
  - To increase knowledge and allow for evidence generation to further inform final target population and subsequent (pivotal) design considerations
  - Go/no-go decisions to be incorporated early in the development to identify lack of activity/unexpectable toxicity

- An intermediate step in a PIP towards pivotal development in a target population where the need and consequential benefit of new innovative drugs is expected to be highest

Moving from early clinical trial to ‘pivotal’ development

• Inclusion of ‘placeholder’ studies/key elements in the PIP - outlined at a high level - with (inter)-dependencies included, allowing for and awaiting supportive evidence to inform subsequent regulatory decision making related to the development towards the ‘final’ target population

➢ Requires multi-stakeholder collaboration, coordination and discussions including early academia/ (multi)-company engagement followed by early involvement of regulators

PIP – a living document – allowing for decision-making based on emerging evidence while advancing science*

• Bringing competing development efforts (within same condition/same in class) together into one arena allows for **timely evidence-based** and **focused discussions on priorities** structured around **multi stakeholder meetings**.

• The agreed **content of a PIP**, which can/should be modified as evidence emerges, will need to be **fit for purpose**, allowing for evidence generation and a **focus on scientific dialogue** when interacting with the regulators.

• This will allow us to provide continuous support through the PIP development to **achieve the goal of timely authorizations** of novel agents (and subsequent access).

Compétition

Collaboration
References:

• European regulatory strategy for supporting childhood cancer therapy developments: https://doi.org/10.1016/j.ejca.2022.09.025


Fireside Chat
• Find all these resources (and more!) on our [website](#) and on [YouTube](#)

• Direct links to all resources will be shared with the slides following the webinar
Thank You!

Please follow the MRCT Center:

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

©MRCT Center