MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

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Promoting Global Clinical Research in Children:
Aligning Ethical, Pragmatic, and Regulatory Approaches

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The Multi-Regional Clinical Trials Center (MRCT Center)

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.

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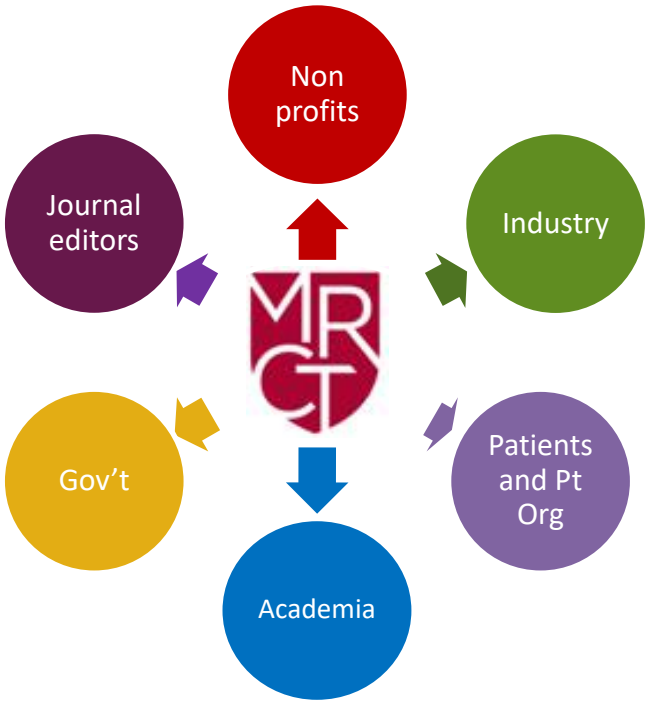
The MRCT Center

Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.



Transparency

Ethics, Conduct, Oversight

Global Regulatory Engagement

Capacity Building

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Promoting Global Clinical Research in Children

Why is this important?

- Children historically excluded from research; practitioners often prescribe based on extrapolation from adult data
- Children deserve access to safe and effective medicines, a goal that is contingent upon conduct of pediatric-specific clinical trials
- Pediatric market is small but important; some diseases specific to neonates, infants and children
- Persistent ethical issues
- Differing or nonexistent pediatric regulations in different jurisdictions
- Significant challenges in initiation and conduct of multi-site, multi-national pediatric trials

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Project phases

PHASE 1

Small Team Assembly & Project Scoping

- Host information-gathering calls with experts
- Assemble project leadership
- Develop and refine preliminary project plan
- Host kick-off meeting
- Outline essential questions

PHASE 2

Workgroup Expansion & Deliverable Development

- Assemble larger work group
- Identify areas of regulatory disharmony
- Identify common ethical principles
- Landscape analysis including international legal aspects
- Develop framework and deliverables

PHASE 3

Refinement and Dissemination of Deliverables

- Refine deliverables as needed
- Compile final guidance document
- Develop web tools
- Oversee implementation and dissemination of deliverables

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Individuals/organizations involved to date & Leadership

- *HRAs* : 8 health authorities encompassing wide geographic representation
- *Academic Medical Centers*: >2 dozen academic/academic medical centers with deep global and US presence
- *Industry*: 10 companies with broad international reach
- *Trade and Professional Associations*: 5 associations with broad collaborative networks
- *Research Institutes & Not-for-Profits*: 5 well connected organizations
- *Patient Advocacy:* 5 groups with US and international network access

Leadership:

- Barbara Bierer, MD
- Sharareh Hosseinzadeh, MSc
- Steven Joffe, MD MPh
- Dominik Karres, MD, CPM
- Gigi McMillan, DBe
- Robert Nelson, MD PhD

- Elisa Koppelman, MSW, MPH
- Walker Morrell, BA

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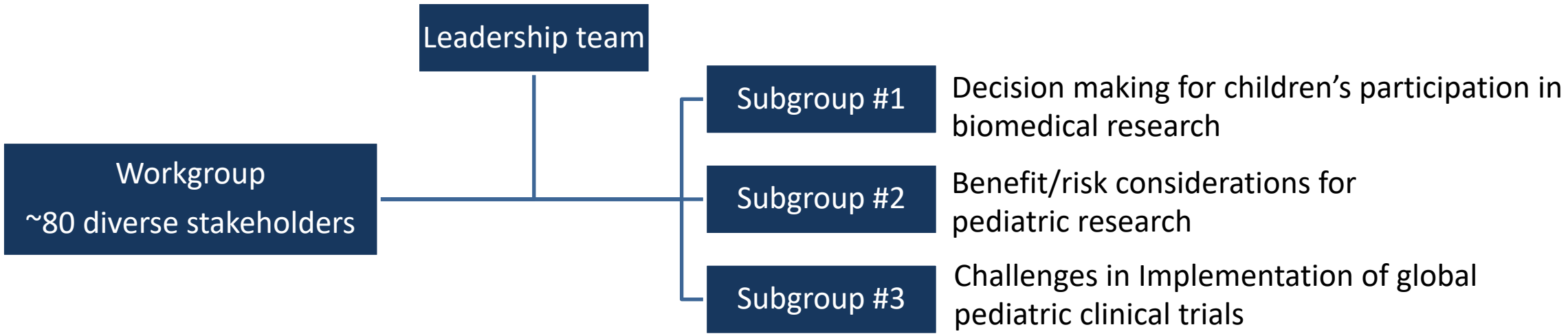
Project Structure



Workgroup: Meet by conference call once/month for 60-90 min

Each subgroup: Meet by conference call once/month for 60-90 min

Leadership team: Meet weekly

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Preliminary Project Objectives

- 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
- Identify meaningful ways to engage patients/families/community members
- Address benefit and risk considerations that create barriers and inefficiencies in transnational research with children.
- Identify and propose solutions to regulatory, ethical, and operational challenges

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#1: Decision making for children's participation in biomedical research

1. Parental decision making (newborn→young children prior to age of assent)
2. Child's role and voice
3. Adolescents
4. Interaction between parent & child
5. Resolving conflicts within families
6. Cultural considerations
7. Guardianship/children without parents
8. Compensation
9. Other issues- e.g., *1 vs. 2 parents*

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#2: Benefit/risk considerations for pediatric research

1. Limits on risk and burden absent clinical benefit
   - Minimal risk and minimal burden
   - Does this vary with the research population?
2. Characterizing the benefits of research participation
   - Language of direct and indirect; clinical; knowledge; altruism, etc.
3. Assessment of the acceptable risks given the potential benefits
4. Concepts involved in risk/potential benefit analysis:
   - Equipoise (and its multiple meanings)
   - Component analysis / net benefits
5. Evaluation of the Scientific and Social Value of the Research
   - Use of Extrapolation to minimize risks/optimize scientific value
6. Choice of Control Group/Comparator
7. Impact of Culture/Age/Developmental Capacity/ disease specific considerations

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#3: Challenges in Implementation of global pediatric clinical trials

1. Preparation and Design
   - Inception: designing the pediatric development plan
   - Data required to start pediatric clinical trial: pre-clinical data; proof of relevance; animal vs adult data
   - Regulatory involvement—agreement on the global development plan
2. Trial Set Up
   - Placement of trial; sites chosen; intent to file; other (IRB/REC)
   - Local regulatory authority review
3. Trial Conduct
   - Challenges of conducting the trial once it has started
4. Trial Close Down
   - In-country regulations—e.g., post-trial access—some countries require access for the life of the child
5. Post-Marketing
   - Market approval and market access
   - Expanded access
   - Accelerated approval
   - Post approval clinical trials that are conducted

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Challenges of multi-national trials

- Pediatric clinical trials must be conducted in multiple jurisdictions and countries since targeted pediatric population widely dispersed
  - Pediatric clinical trials involve more study sites in more countries than a comparable adult trial
  - Variations in local and national ethical and regulatory requirements lead to delays in data availability to inform safe and effective use of medicines for children
- Though governing ethical principles may be generally agreed on, differences in interpretation and application of principles exist
  - Variation leads to delays in ability to conduct clinical trials at local/national level
  - Differences can result in different assessments of ethical acceptability of a trial
  - Enrollment difficulties include small number of eligible subjects per site
  - Major contributor to high cost of pediatric trials is time it takes to complete based on enrollment

→ Conceptualizing a better model of cooperation and transparency

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Deliverable Planning

- All deliverables are created with relevant stakeholders at the table, including involving and respect the centrality of the participants who participate and clinical research.
  - By involving patients, families, patient advocates, and patient advisory groups in the development and refinement of project deliverables, we hope to generate **relevant** resources with a **positive global impact.**
- Will track with the workgroup foci, and subject to change in discussion with the workgroup and work subgroups.

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Deliverables

- **Short publication** to establish the expectation that children be invited to play a role in some way in decision making regarding research participation in addition to the local jurisdiction's guidance
- **Formal annotation** of the ICH-E11 principles to strengthen, clarify and improve
- **Educational materials/brochures:** develop educational materials & resources that fill identified gap(s); e.g., specific to academic trials, applicable in resource limited spaces; more broadly applicable (many existing resources are trial specific)

https://catalyst.harvard.edu/pdf/regulatory/SophieScienceProject_English_LowResolution.pdf

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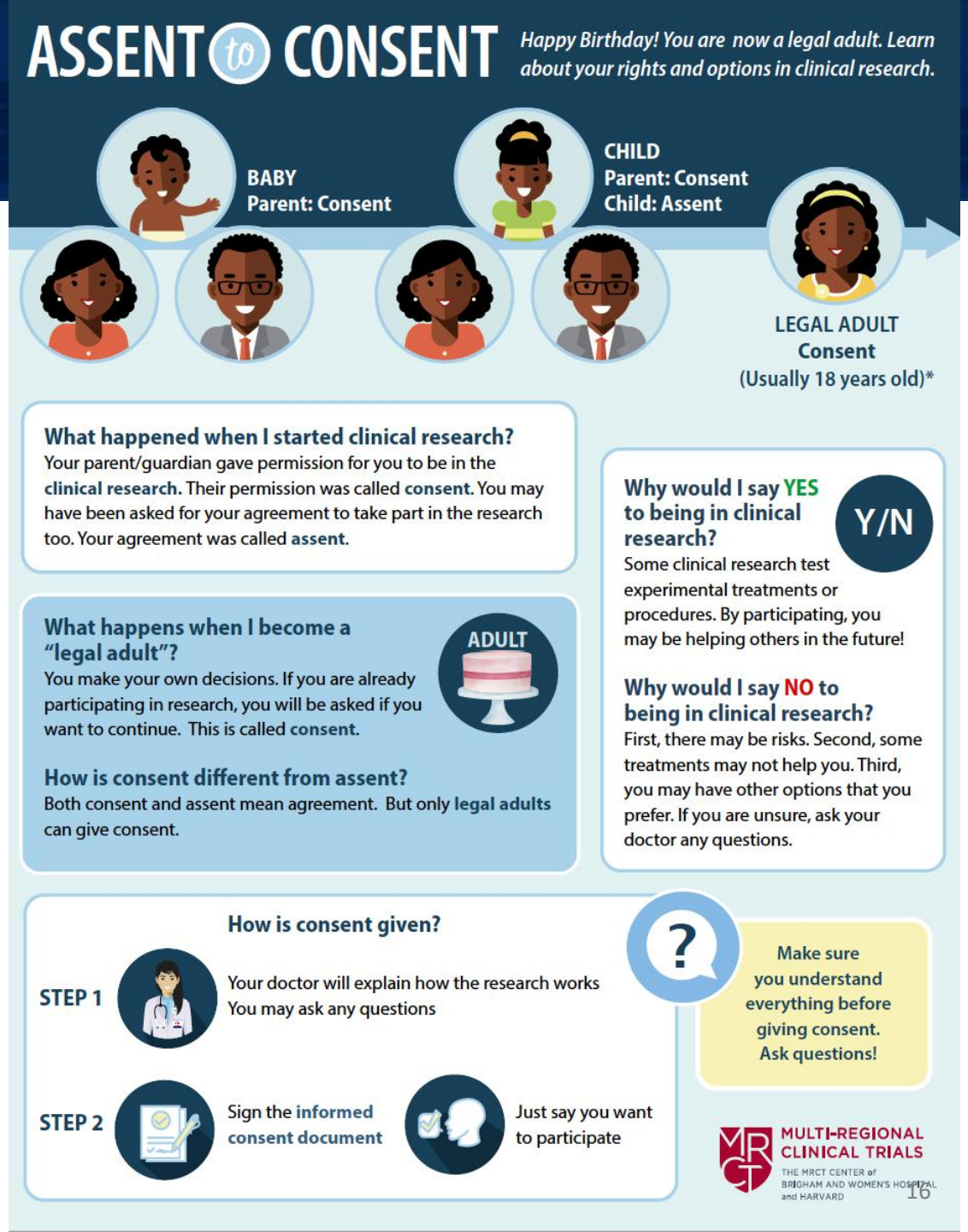
Educational Materials

- Assent to Consent (for 17-18 years)
- Additional materials in development (12-17 year-old target audience):
  - ❑ What is assent?
  - ❑ Research and your data
  - ❑ What is clinical research
  - ❑ Your opinion matters
  - ❑ Is there privacy anymore?

➢ Translation



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Tools for kids

https://mrctcenter.org/blog/resources/covid-19-clinical-research-flyers/

DESCARGAR EN ESPAÑOL

I AM A CHILD WITH COVID-19: Should I Join a COVID-19 Research Stud

Kids who have COVID-19, or might have COVID-19, may be able to join a COVID-19 research study.

A research study:

- collects new information about health and disease.
- tries to answer new questions that researchers have.
- needs volunteers to sign up.

Being in a COVID-19 research study is your choice.

COVID-19:

- is a new coronavi
- may caus cough, fe and brea
- can be m very sick.

Why should I be more careful around people?

- This virus spreads from a sick person to a healthy person very quickly.
- Being too close to your friends can pass the virus around.
- You sit and stand close to your friends when you are at school and when you play.

Why are th COVID-19

COVID-19 is a r important to u about:

- How the
- Why son get sick very sick
- Which tr
- How to s

There are more because adults than children.

It is ver childre metho

Being i

What else should I know about being in a COVID-19 research study?

- You can talk to your doctor, your parent, or any adult you trust to help you decide if you want to be in the research study.
- You can change your mind at any time.

More can be learned about COVID-19 if you join a research study.

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Thank you for thinking about joining a COVID-19 study. Please ask the research team ANY questi have. We hope you feel better soon.

SOY MENOR DE EDAD Y TENGO COVID-19: ¿Debería participar en un estudio de investigación de COVID-19?

Los menores que tienen COVID-19, o que podrían tener COVID-19, podrían participar en un estudio de COVID-19.

Un estudio de investigación:

- Obtiene nueva información sobre salud y enfermedad.
- Trata de responder nuevas preguntas que los investigadores tienen.
- Necesita voluntarios para que sean participantes.

Unirse a un estudio de investigación sobre COVID-19 es su decision.

COVID-19:

- es una enfermedad nueva causada por un tipo de virus llamado coronavirus.
- Puede hacer que algunas personas presenten síntomas como tos, fiebre, debilidad, dolor muscular y de otro tipo, y problemas para respirar.
- Puede ser leve, pero también puede enfermar muy gravemente a algunas personas.

¿Por qué debo ser cuidadoso cuando estoy cerca de personas?

- Este virus se trasmite de una persona enferma a una persona sana muy rápidamente.
- Acercarte mucho a tus amigos puede trasmitir el virus.
- Cuando estás en el colegio o cuando estás jugando, te sientas cerca o te paras cerca a tus amigos.

¿Por qué hay estudios de investigación sobre COVID-19 ahora?

COVID-19 es una enfermedad nueva, así que es importante entender más sobre:

Los virus no tienen patas, así que ¿Cómo viajan?

- Como se trasmite el virus que la causa.
- Por qué algunas personas se enferman en forma muy leve y otras se ponen graves.
- Que tratamientos funcionan mejor.
- Como detener la trasmisión.

Actualmente hay más estudios de investigación con adultos porque parece que los adultos se enfermas más gravemente de COVID-19 que los niños.

Es muy importante realizar estudios con niños para encontrar tratamientos y formas de prevenir que funcionen en niños.

Participar en un estudio puede ayudar a otras personas.

¿Qué más debo saber sobre participar en un estudio sobre COVID-19?

- Puedes hablar con tu médico, con tus padres, o cualquier adulto de tu confianza para que te ayude a decidir si quieres participar en el estudio.
- Puedes cambiar de opinión cuando lo desees.

Se puede aprender mas sobre la COVID-19 si su hijo participa en un estudio de investigación.

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Gracias por pensar en participar en un estudio de investigación de COVID-19. Por favor, haga TODAS las preguntas que tenga. Esperamos que se mejore pronto.

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Harvard Clinical & Translational Science Center

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Additional Deliverables

- Develop a **structured recommendation** to regulatory agencies, IRBs, etc. describing the importance of input from parents/patients and ensuring that all stages of product development reflect that voice
- 3 Pillar Structure:
  - **Why:** Get decision makers (industry sponsors, IRBs/ethics committees, regulatory agencies, patient community) to buy in to the concept
  - **Who:** Focus on how to explicitly and systemically build representativeness into the process; how to generate what is sufficient evidence to implement; structure around the FDA guidance that indicates whether patient experience data was submitted with the application
  - **How:** Offer practical considerations for patient/parent or guardian & sponsor interaction
- Models of international regulatory and ethical collaboration, cooperativity, and reliance

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Thank you

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