Advancing International Pediatric Clinical Research

PART THREE

ASSENT AND CONSENT IN THE FIELD: Culture, Context, and Respect

29 June 2022
8:00-10:00 PM EDT

This series is supported by an FDA Scientific Conference Grant.
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.
Promoting Global Clinical Research in Children

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 life-cycle.
• **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/families/community members

• Diverse leadership (Academia, EMA, Industry, participant advocates)
• 80+ members from all stakeholder groups with geographic diversity
Funded in part through an FDA scientific conference grant award

5 virtual webinars; each session planned to be hosted twice, with similar content and different speakers and panelists, to allow for wide attendance and participation.

An offshoot of the MRCT Center’s *Promoting Global Clinical Research in Children* project
Advancing international pediatric clinical research—looking ahead

1. **Informing the future from COVID-19 lessons learned:**
   6 October 2021 & 7 October 2021

2. **Time to Listen—Hearing from young people in clinical research;** 2 February 2022

3. **28 June 2022: Assent and Consent in the Field: Culture, Context, and Respect**

4. **Fall 2022: Regulatory convergence to facilitate international cooperation**

5. **Early 2023: TBD**

Today:

Please see "Bio Book" for extended introductions to the speakers and panelists
ADVANCING INTERNATIONAL PEDIATRIC CLINICAL RESEARCH

PART THREE

ASSENT AND CONSENT IN THE FIELD: Culture, Context, and Respect

Keynote Speaker
Professor Phaik Yeong Cheah
University Of Oxford
MORU Tropical Health Network
Thailand

This series is supported by an FDA Scientific Conference Grant.
Consent and assent in paediatric research: challenges in global health research

Phaik Yeong Cheah, B.Pharm, MSc (Bioethics), PhD

Professor of Global Health, University of Oxford
Head, Bioethics & Engagement, Mahidol Oxford Tropical Medicine Research Unit
29/30 June 2022
• Part of University of Oxford, collaborate with Mahidol University

• Core funded by Wellcome Trust

• Bangkok hub, but conducting clinical research internationally

• Tropical medicine and infectious diseases: Malaria, antimicrobial resistance, maternal and child health, COVID-19

• Conduct research studies (clinical trials and non trials), many them include paediatric patients
Example of a MORU-led ongoing clinical trial with children

DeTACT project
Development of Triple Artemisinin Combination Therapies

- Clinical trial: Randomised, partially-blinded, placebo-controlled clinical trial with TACT vs. ACT+placebo (n=4494)

Africa
- Burkina Faso
- Democratic Republic of the Congo
- Guinea
- Niger
- Nigeria
- Tanzania
- The Gambia
- Rwanda

Asia
- Bangladesh
- Cambodia
- India (2 sites)
- Indonesia
- Myanmar

Triple artemisinin combination therapy (new treatment) vs artemisinin combination therapy (current treatment using two drugs)
“We should protect children through research not from research”

Informed Consent for Research

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial/research, after having been informed of all aspects of the trial/research that are relevant to the subject's decision to participate.

(ICH GCP 2016)

*clinical research’ covers an immensely wide range of activity
Assent

The US Code of Federal Regulations: “the IRB must determine that adequate provisions are made for soliciting the assent of the children”

When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative (Declaration of Helsinki 2013)
Why should assent be sought?

Ethical reasons
  o Respect for persons
  o Respect emerging autonomy of the child
  o Pedagogical reasons
  o “Capacity for preference”

• A child as a rights-holder and active agent in the assent (or informed consent) process
Instrumental reasons

- To obtain cooperation from the child
- Children have their own worries that are different from adults – related to missing school, teenage problems, get teased by other kids, stigma, looking cool, boys, girls
- Scared of needles etc
Many challenges!
# What does assent mean?

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**Definition of assent in research guidelines**

<table>
<thead>
<tr>
<th>Research guideline</th>
<th>Text</th>
<th>Jurisdiction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Code of Federal Regulations(^a)</td>
<td>“Assent means a child’s affirmative agreement, to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as consent.”</td>
<td>USA</td>
</tr>
<tr>
<td>American Academy of Pediatrics(^a)</td>
<td>“… active agreement by a minor, not qualified to give consent, to participate in a research study. This generally applies to children who have reached an intellectual age of 7 years or greater.”</td>
<td>USA</td>
</tr>
<tr>
<td>Council for International Organizations of Medical Sciences(^a)</td>
<td>“Such knowing agreement, sometimes referred to as assent…”</td>
<td>International</td>
</tr>
<tr>
<td>Confederation of European Specialists in Paediatrics(^a)</td>
<td>“Informed assent means a child’s agreement for medical procedures in circumstances where he or she is not legally authorised or has insufficient understanding to be competent to give full consent.”</td>
<td>European</td>
</tr>
<tr>
<td>Royal College of Paediatrics and Child Health(^a)</td>
<td>“… ‘assent’ refers to acquiescence…”</td>
<td>UK</td>
</tr>
<tr>
<td>Medical Research Council(^a)</td>
<td>“… affirmative agreement to participate. Failure to object should not be construed as assent” but later on “Does the child actively object?” and if no, “research may proceed.”</td>
<td>UK</td>
</tr>
<tr>
<td>The Royal Australasian College of Physicians(^a)</td>
<td>“… the term assent for concurrence or agreement, without the formal and legal expectations of informed consent.”</td>
<td>Australia and New Zealand</td>
</tr>
</tbody>
</table>

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*Baines P: Assent for children’s participation in research is incoherent and wrong. Arch Dis Child 2011*
• If a child is deemed incompetent and therefore unable to consent to participate in a study.....

...how is it that he or she can provide “affirmative agreement” or “acquiescence?”
How much information and how to give it?

“...the agreement (assent) of the child or adolescent has been obtained in keeping with the child’s or adolescent’s capacity, after having been provided with adequate information about the research tailored to the child’s or adolescent’s level of maturity” (CIOMS 2016)

There is a spectrum of capacity to understand – difficult to determine, need child psychologists with a battery of tests
When should assent be sought?

- **Who is a child?** From baby to age of majority
- **Generally 7-18 years old, and written**
Who should provide proxy consent?

When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. (Declaration of Helsinki 2013)
Diverse terminology

- A wide range of terms are used
  - Earlier version of DOH – “responsible relative”
  - legally authorized representative’ (DOH 2013)
  - legally acceptable representative’ (ICH GCP 2016)
  - legally designated representative’ (EU)
  - legal guardian’, ‘parent’ and ‘representative’ etc
- with varying levels of legal authority - ‘permission’ (CIOMS 2016), ‘authorisation’ (Oviedo) and ‘informed consent’ (DOH 2013)
Who is this person??

- Deference given to application laws – challenging in LMICs, no specific laws on paediatric clinical research (e.g. Thailand, Zimbabwe)
- Usually means biological parent/guardian?
• Intergenerational households, grandparents caring the child
  o Many parents (eg in Thailand, Cambodia) work in the cities, their children are looked after by their grandparents
• Orphans
• Children of minor parents
• Children of parents without legal status (ethnic minority)
• Children living without parental care

Leads to presumptive exclusion from clinical research
More challenges in low-income settings challenges

- Local paediatric research guidelines not clear or non-existent
- Inexperienced personnel conducting paediatric research
- Resource starved hospitals need to cope with everyday clinical care
• Low level of formal education, literacy and health literacy – both parents & children
• Community not familiar with research and consent. Assent?
• Community not familiar with signing a document (children NEVER sign anything)
• Children do not formally assent for their own (non research) medical care
• More parental control (sometimes less)
• “Researcher may appear to insult the parent” – physician, Cambodia
• Children may be “cleverer” than their parents, more exposed
• Some (older) children take adult responsibilities and adult decisions day to day
• Some children can consent for themselves

• *Gillick competence – mainly for clinical care, not research
When should children consent in their own right?

• Competence - the ability to understand and retain relevant information, to weigh or judge the relative merits of the options and to make and communicate a decision

• Maturity a prerequisite for making decisions that are more significant in their consequences, involving perhaps substantial changes to a person's life prospects or where the decision may have irreversible effects.

• A great deal will depend on the nature of the study

Going forward
Case One: children who are not able at this time to contribute their own view as to whether they should take part in research, such as babies and very young children, or children who are temporarily unable to contribute because they are so unwell or are unconscious.

Case Two: children who are able at this time to form views and express wishes, but who are clearly not yet able to make their own independent decisions about research involvement

Case Three: children and young people who potentially have the intellectual capacity and maturity to make their own decisions about taking part in a particular research study, but who are still considered to be minors in their domestic legal system

"Know your audience": A hospital community engagement programme in a non-profit paediatric hospital in Cambodia

Sreyrom Pol, Shwani Fox-Lewis, Phaik Yeong Cheah, Claudia Turner

Published: August 3, 2017 • https://doi.org/10.1371/journal.pone.0183573
Young Persons Advisory Board – Siem Pang, Cambodia
PART THREE

Advancing International Pediatric Clinical Research

ASSENT AND CONSENT IN THE FIELD: Culture, Context, and Respect

PANEL DISCUSSION

Moderator
Dr. Steven Joffe
University of Pennsylvania
Perelman School of Medicine
USA

Guest Speaker
Dr. Jacinto “Jojo” Blas Mantaring
UP College of Medicine
Philippines

Guest Speaker
Dr. Erwin Khoo Jiayuan
School of Medicine
International Medical University
Malaysia

Guest Speaker
Dr. Seung-min Hahn
Yonsei University
College of Medicine
Korea

Guest Speaker
Dr. Wan-Ting Chou
PPD
Taiwan/Tokyo

This series is supported by an FDA Scientific Conference Grant.
Assent and Consent in the Field
Culture, Context, and Respect

Steven Joffe, MD, MPH
Art and Ilene Penn Professor of Medical Ethics and Health Policy
Professor of Pediatrics
Chair, Department of Medical Ethics and Health Policy

Perelman School of Medicine
University of Pennsylvania

Multi-Regional Clinical Trials Symposium
June 29, 2022
Assent: the U.S.A. view

- “the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent.”
“the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent.”

“"Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.”
INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

E11 (R1)

Final version
Adopted on 18 August 2017
ICH E11(R1) on assent

“As a rule, a pediatric subject is legally unable to provide informed consent. Therefore pediatric study participants are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations.”
ICH E11(R1) on assent

“All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.”
ICH E11(R1) on assent

“Where appropriate, participants should assent to enroll in a study (age of assent to be determined by IRB's/IEC's or be consistent with local legal requirements).”
“As a rule, a pediatric subject is legally unable to provide informed consent. Therefore pediatric study participants are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations.”
“Participants of appropriate intellectual maturity should personally sign and date either a separately designed, written assent form or the written informed consent.”
ICH E11(R1) on assent

“In all cases, participants should be made aware of their rights to decline to participate or to withdraw from the study at any time.”
Assent requirement is problematic in Western cultures

- When should kids be able to overrule their parents?
- How should age, maturity, the complexity of the study, the seriousness of the disease, and other factors affect the role that the kid plays in decisions?
Requirement to obtain assent may be Western-centered
  • May conflict with cultural and family norms
We know little about how requirement to obtain assent is followed in practice

- How are kids involved in decisions about research participation in the USA?
- How are kids involved in decisions about research participation in diverse cultures around the world?
Thank you!

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Advancing International Pediatric Clinical Research

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ASSENT AND CONSENT IN THE FIELD: Culture, Context, and Respect

Guest Speaker
Dr. Jacinto "Jojo" Blas Mantaring
UP College of Medicine
Philippines

This series is supported by an FDA Scientific Conference Grant.
Assent Issues in the Philippine Setting

Jacinto Blas V. Mantaring III, MD, MSc
Chair, University of the Philippines Research Ethics Board

This series is supported by an FDA Scientific Conference Grant.
• Archipelago - 7100 islands
• Under Spanish rule for 300 years
• Predominantly Catholic
• Traditionally agricultural and fishing
• Strong sense of family and religion
Demographics

- Total population - 109,035,343
- Household population - 99.7%
- 17 regions
- 40% of the population is in Luzon and
• Predominantly young
• Median age - 23.4 years
• Dependency ratio - 61 dependents per 100 persons in the working-age group
• School age - 4 in 10,000

Figure 1. Age-Sex Pyramid of Household Population: Philippines
Family values

- Family Oriented
- Respect for elders
- God-fearing
- Fellowship
- Hospitality
- Debt of Gratitude
- “Bayanihan”
- Love and Happiness
Factors affecting assent in Philippines

- Maturity and neurodevelopment
- Family factors
- “Independence” and perceptions on “self” factors
- Respect
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ASSENT AND CONSENT IN THE FIELD: Culture, Context, and Respect

Guest Speaker
Dr. Erwin J. Khoo
School of Medicine
International Medical University
Malaysia

This series is supported by an FDA Scientific Conference Grant.
ADVANCING INTERNATIONAL PEDIATRIC CLINICAL RESEARCH
Part three: Assent and consent in the field: Culture, context, and respect

Associate Professor Dr Erwin Jiayuan Khoo, MBBS, FRCPCH, AM

Head of Paediatrics Department, International Medical University, Malaysia
2022-23 Fellow, Center for Bioethics, Harvard Medical School
1. Process of seeking assent should be modified to different cultural contexts
   • Whether children’s assent or parent’s permission is sought first depends on cultural norms
   • The family may take priority over an individual’s self-autonomy
   • Family-facilitated and collective decision making becomes a neutral consequence of this social structure

2. Cultural humility, proper assent practices, and independent review boards
   • Awareness of the minor’s best interest and of any risk of maleficence

1. Assent is not just a form
   • It is a dialogue between the researchers and the potential participants
   • Additional time to address cultural and economic differences can augment research’s professional self-awareness and promote children’s participation
   • This is a process and not an end in itself

2. The key lies in the practice of listening
   • Feedback of the child-parent unit
   • Embrace the feelings and thoughts of their decision-making process
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ASSENT AND CONSENT IN THE FIELD: Culture, Context, and Respect

Guest Speaker
Dr. Seung-min Hahn
Yonsei University
College of Medicine
Korea

This series is supported by an FDA Scientific Conference Grant.
“Korean Perspective”

Seung-min Hahn

Pediatric Hematologist-Oncology Department
Yonsei University College of Medicine, Severance hospital, Seoul, Korea
**Background Information : ‘Consent’**

- **Laws in Korea**
  - Under ‘Rules regarding the Safety of Medicines’
    - ‘Informed consent’ is mandatory for approval, running of clinical trials in Korea
    - Content of the ‘Consent form’ is stipulated by law
  
  - Under ‘Regulations on education for investigators and designation of educational institutions for clinical trials’
    - Education about ‘Subject consent and understanding of recruitment process’
    - The education must be provided for investigators
Background Information ‘Assent’

- Under ‘Rules regarding the Safety of Medicines’ Law
  - Assent is allowed for subjects ‘who are lack of understanding/expressing’ their willness
  - Deputy: Legal representative → Spouse → lineal ascendant (parent/child) → other relatives

- Guidelines/Recommendations for Clinical trials in children by ‘Ministry of Food and Drug Safety (based on ICH guidelines)
  - Children are ‘vulnerable subjects’
  - Age under 19 years old (18 years 364 days old are considered legally children in Korea)
    - Term newborn infants (~28 days after birth)
    - Infants and toddlers (under 24 months old)
    - Children (24 months ~ 12 years old)
    - Adolescent (12 years old~ under 19 years old)
  - Assent of parents + Consent is also recommended from 7 years old
Ministry of Food and Drug Safety ‘Recommendation’

- Special measures are needed ‘to protect the rights and interests of pediatric research participants and to protect them from serious risk’
- Except in special circumstances discussed in ICH E6, such as non-therapeutic trials, it should be possible to benefit from clinical trials

The problem is

- In the clinical trial setting, often, we don’t know for sure what is a real benefit to children
- Different ‘adverse event’ in pediatric population (growth, development, long term safety issues..)

→ Often investigator’s (doctor’s) decision is critical
In Korea, parent’s trust and loyalty to medical staff is very high (esp. in severe, chronic diseases) – relates to parent’s passion and devotion to their children, most parents seek best doctors and treatments nationwide

- Doctors, parents together can, do discuss ‘what is the best option’
- However, usually the final decision usually rests with the doctor
- And, often children/adolescent’s own opinion is would not be considered

→ Again, often investigator’s (doctor’s) decision is critical
→ Doctors’ opinion > parents’ opinion >> children’s own opinion or decision
Investigators’ Role in Pediatric Clinical Trial

- Should try to exclude prejudices
  - Affect the study design and trial performance or the presentation of results and conclusions
  - In real, investigators cannot be free from prejudice

- Should have balanced view of risks and benefits of performing the study

- Expertise of the investigator & personal ethics are important

- In real,
  - Still lack of education, programs focusing on ethical issues in pediatric clinical trials
  - Investigators (doctors) are very busy – snowed under with work, multiple roles as a clinician, researcher, and investigator of clinical trial
Informed consent/assent is required in pediatric clinical trials

We all know the importance

More meticulous guidelines, education programs (esp. for investigators) are “Unmet need”
Advancing International Pediatric Clinical Research

PART THREE

ASSENT AND CONSENT IN THE FIELD: Culture, Context, and Respect

Guest Speaker
Dr. Wan-Ting Chou
PPD
Taiwan/Tokyo

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Local Network Support

1. How New Medicine is Made

A lot of researchers spend a lot of time studying a new medicine before people are able to use it.

Sick people (patients) help test new medicines to see how they work in a "clinical trial." All the researchers make sure nothing bad happens to the sick people in a trial. The new medicine that's being tested is called an "investigational product (IP)."

Like at other hospitals, the doctors at this hospital plan and do clinical trials after discussion.

After a clinical trial proves that a new medicine is safe and works well, it can be used to help many patients.

6) Our request to young people growing up

- For girls
  
  Body and mind, you are on your way to becoming a grown-up. If you are a girl, you may start having your period, which happens at different times to different girls and is a normal part of becoming an adult.
  
  We cannot say how the IP will affect the part of your body where babies grow.
  
  If you have already begun having your period, please make sure not to get pregnant during the clinical trial. If you become pregnant, please tell your family or the researchers right away so that we can make sure that you and your baby are OK.

- For boys
  
  Body and mind, you are on your way to becoming a grown-up. If you are mature enough, you may already have sperm. When your body starts growing sperm is different for different boys and is a normal part of becoming an adult.
  
  We cannot say if the investigational product will affect the part of your body where your sperm is made. If you are physically mature enough to have sperm, please make sure that you don't get your girlfriend pregnant.

Pediatric Clinical Trials Network (Japan)

Many thanks!

- Webinar recording and slides will be posted in approximately one week
- Youth video will be also be available on YouTube
- We look forward to hearing from you
- Sign up for future webinar(s)
Special Acknowledgements

Thank you to our speakers, participants, and particularly the young people who shared their stories and taught us so much.

**International Children’s Advisory Network (iCAN),** producer of “Prioritizing Young People’s Voices in Clinical Research” video

All the youth who shared their time, expertise and stories with us from iCAN and Kids Barcelona
Please follow the MRCT Center

Thank you!