PART THREE

Advancing International Pediatric Clinical Research

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

28 June 2022
9:00-11:00 AM EDT

This series is supported by an FDA Scientific Conference Grant.

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

The MRCT Center

PART THREE

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

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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

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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

Webinar Series: *Advancing International Pediatric Clinical Research*

- 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

PART THREE

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

Prioritizing Young People's Voices in Clinical Research

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International Children's Advisory Network

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Advancing International Pediatric Clinical Research

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

Keynote Speakers

Dr. Dylan Graetz

Dr. Victor Santana

St. Jude Children's Research Hospital,
Department of Global Pediatric Medicine,
Department of Oncology Solid Tumor Division

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St. Jude Children's Research Hospital
Finding cures. Saving children.
ALSAC • DANNY THOMAS, FOUNDER

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MRCT Center Pediatrics Webinar Assent and Consent in the Field: Culture, Context & Respect

Lessons Learned Conducting Pediatric Clinical Research in Resource Limited Settings

Victor M. Santana

Dylan Graetz

St. Jude Children's Research Hospital

Assent and Consent in the field: Culture, Context & Respect

Guiding statement:
Research with children in resource-limited settings requires consideration of socioeconomic inequalities and cultural and linguistic differences.

Points to consider

Community and Leadership hierarchies

Influence of gender dynamics

Verbal consent in setting of low literacy

Social status of the researchers

Guarding against therapeutic misconception

Notion of assent

Finite resources to operationalize processes

Assent and Consent in the field: Culture, Context & Respect

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Family

“ A family's understanding of disease is not (only) biological but involves spiritual and social elements (more than medical factors), which alone will not determine decision making for participation in research”.

Assent and Consent in the field: Culture, Context & Respect

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- National Bioethics Advisory Commission. Ethical and policy issues in international research: clinical trials in developing countries
- Perspectives from US regulatory viewpoint
- How to operationalize? Practical details on how to implement?

Ethical and Policy Issues in Research Involving Human Participants

Volume I

Report and Recommendations of the National Bioethics Advisory Commission

Bethesda, Maryland August 2001

Assent and Consent in the field: Culture, Context & Respect

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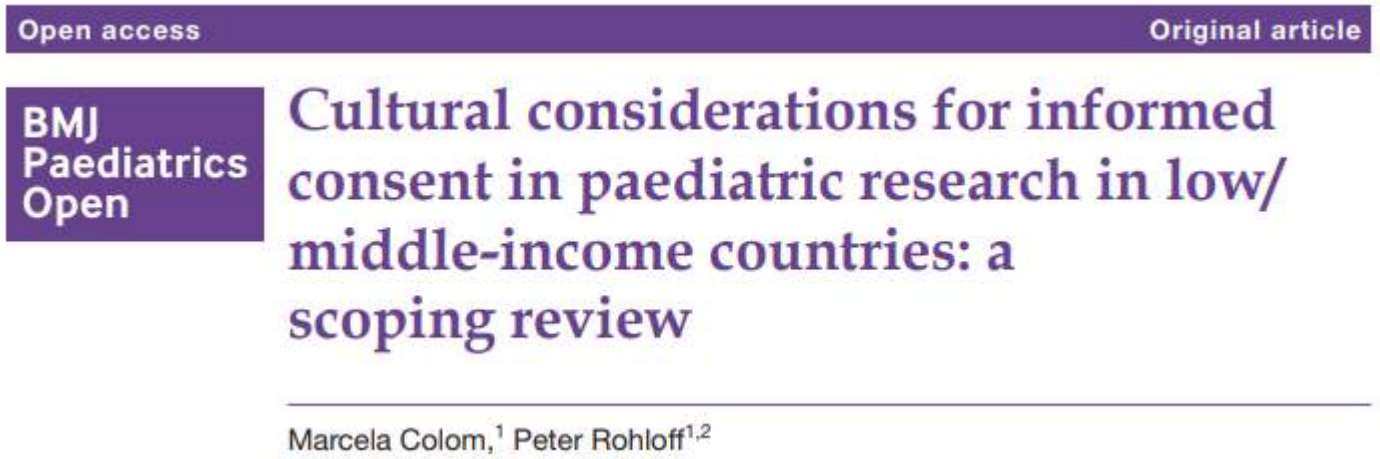

- Scoping review of the literature (50 articles)
- Summary of key recommendations
- Identified thematic areas where guidance is available
- Pointed to gaps in addressing individual-based consent, age related adaptations such as participation of adolescents and assent process and documentation

Assent and Consent in the field: Culture, Context & Respect

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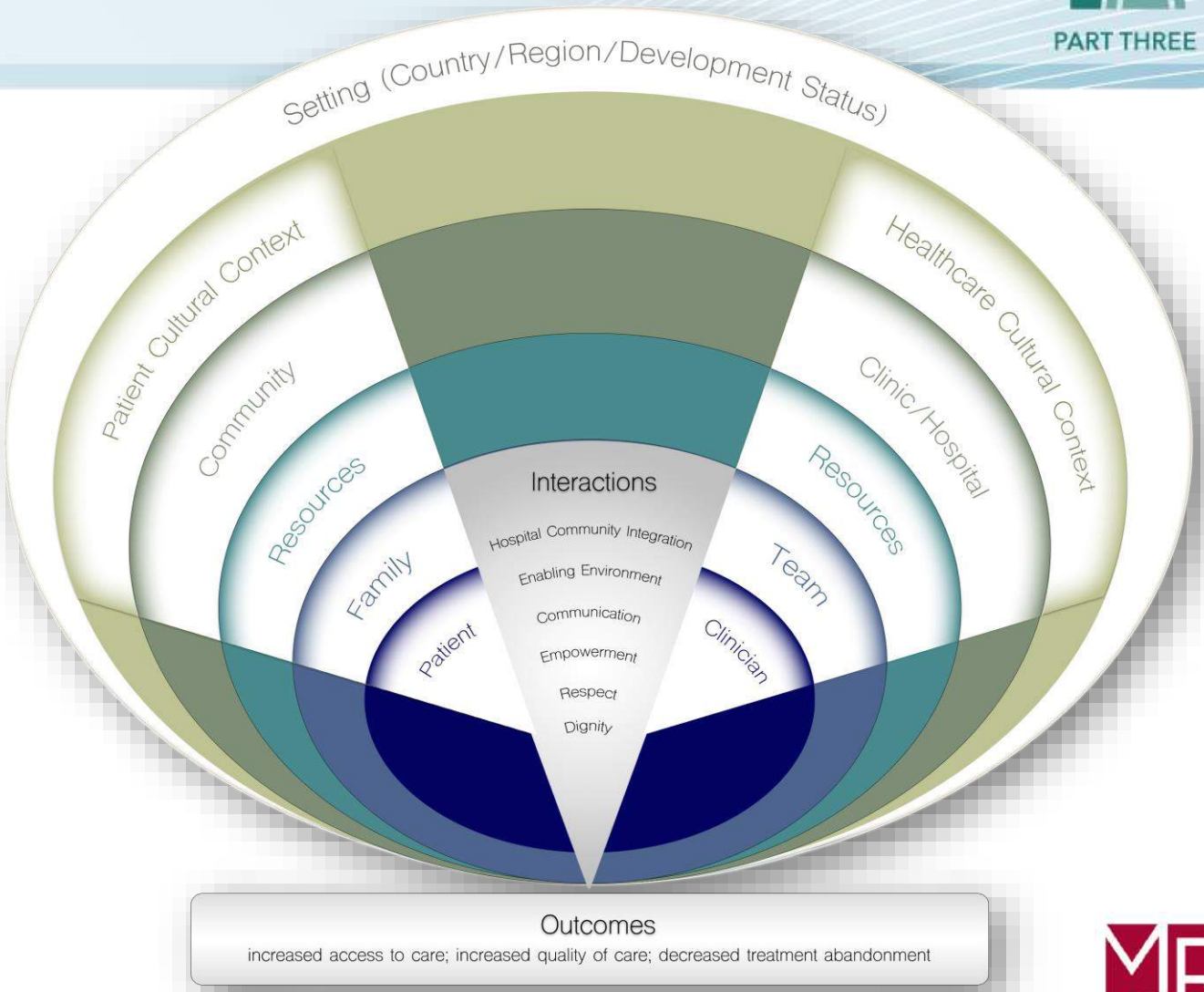
Commentary

A proposed global framework for pediatric cancer communication research

Dylan E. Graetz, MD, MPH [1,2]; Ana Caceres-Serrano, PhD[3]; Venkatraman Radhakrishnan, MD, DM, MSc[4]; Carmen E. Salaverria, MS[5]; Joyce B. Kambugu, MD[6]; and Bryan A. Sisk, MD, MSCI [7,8]



Assent and Consent in the field: Culture, Context & Respect

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- Child involvement
  - When and how to involve the child?
  - Should all children be involved?
  - Age of consent/assent?

- Clinician Time
  - How do you build trust without time?

Assent and Consent in the field: Culture, Context & Respect

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- Decision-maker
  - Preferred decision-making role
- Analysis of risks/benefits
  - Experience of a family
- Multidisciplinary team

Assent and Consent in the field: Culture, Context & Respect

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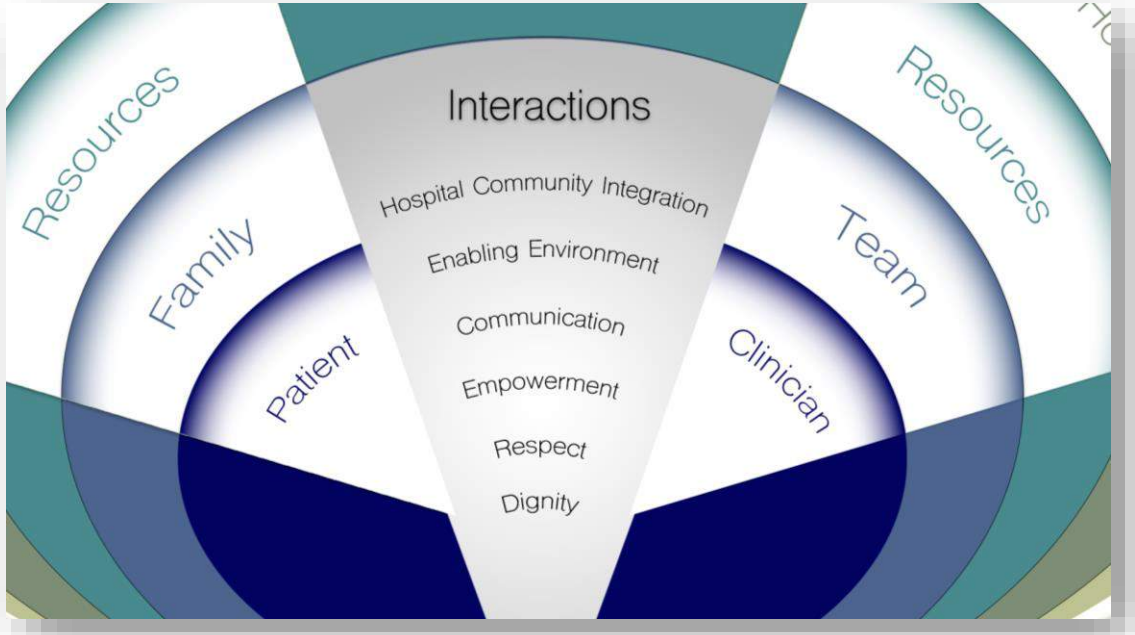
- Literacy/Education
  - Is written consent appropriate?
- Physical space
  - Private room? Bedside communication?



Assent and Consent in the field: Culture, Context & Respect

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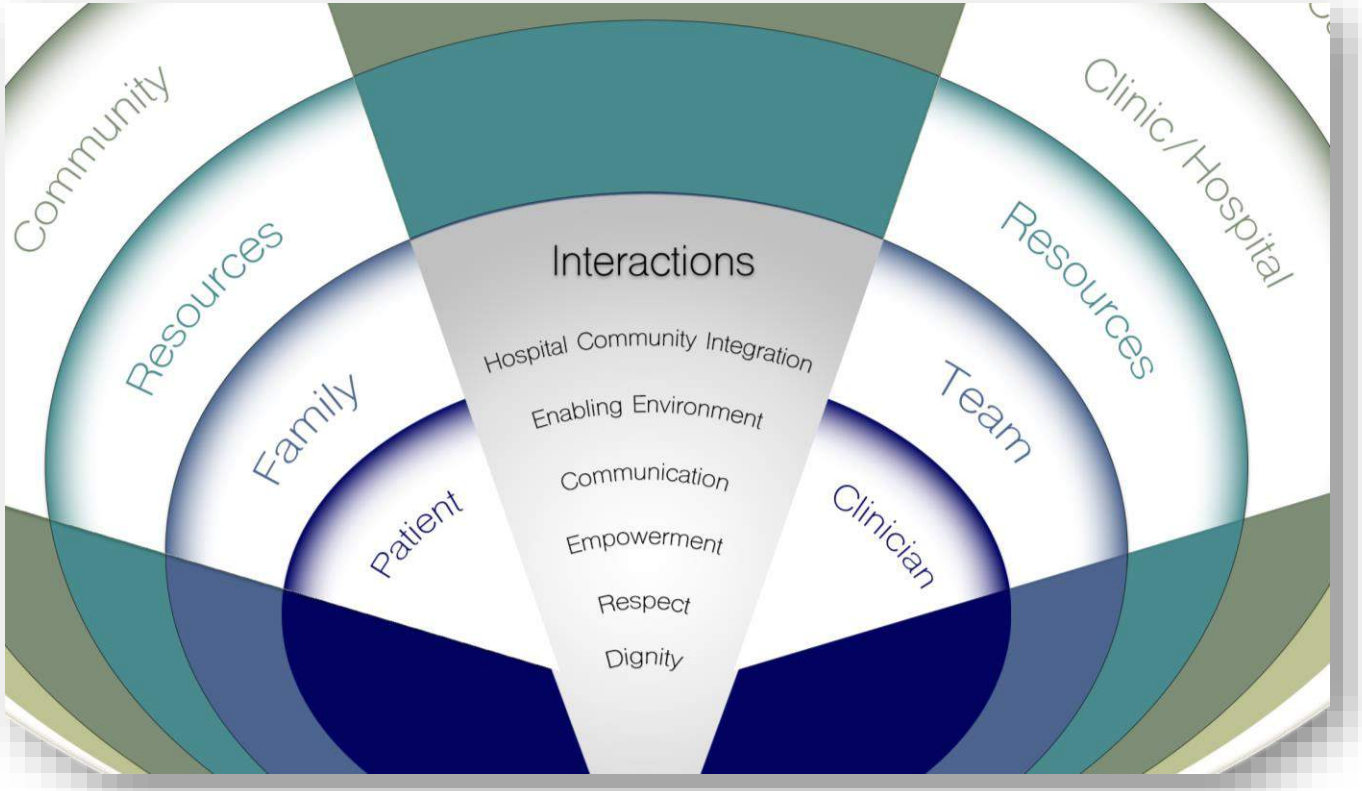
- Community
  - Spiritual community
  - Stigma
- Referral network
  - Traditional healers



Assent and Consent in the field: Culture, Context & Respect

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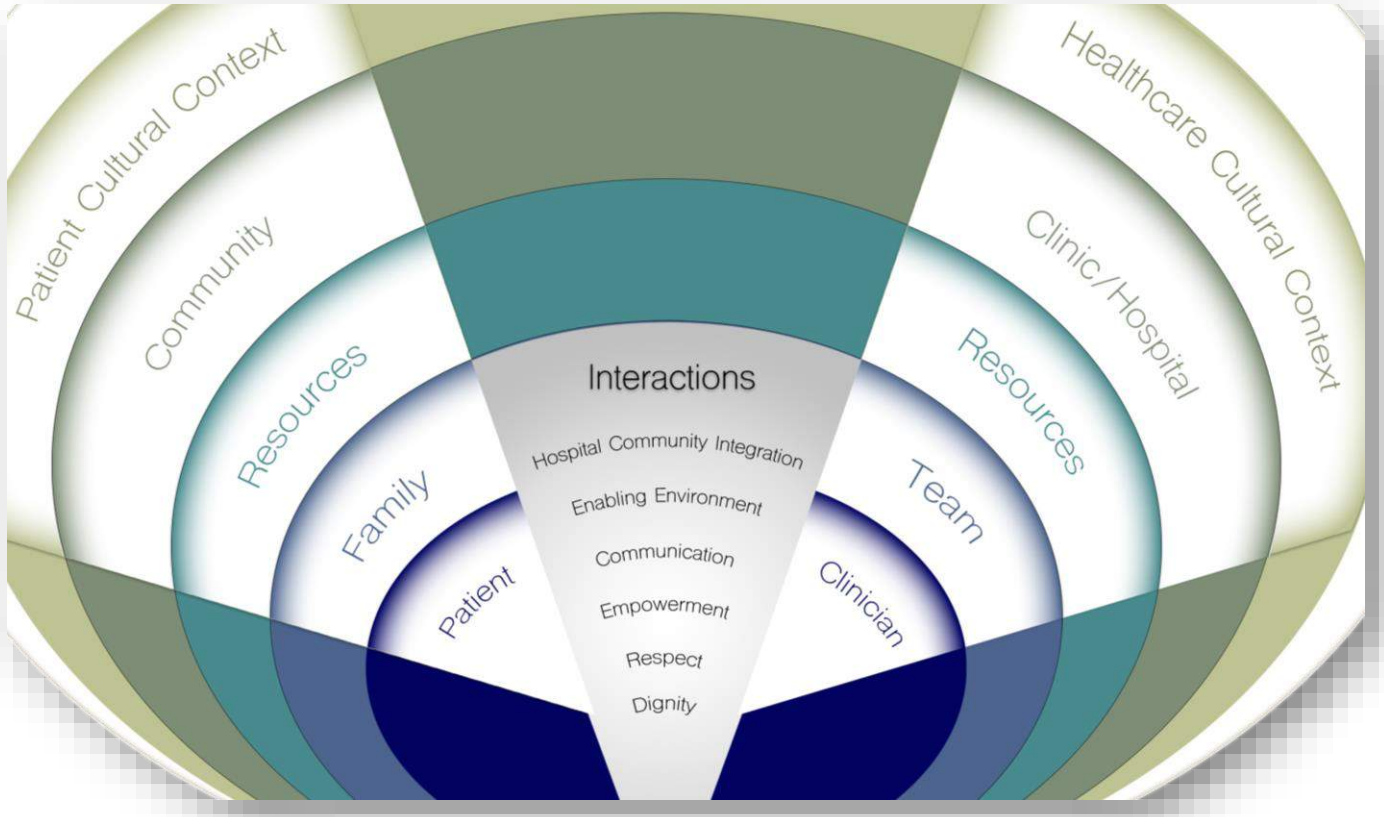
- Role of medical providers
  - Deference
- Autonomy
  - Relational autonomy



Assent and Consent in the field: Culture, Context & Respect

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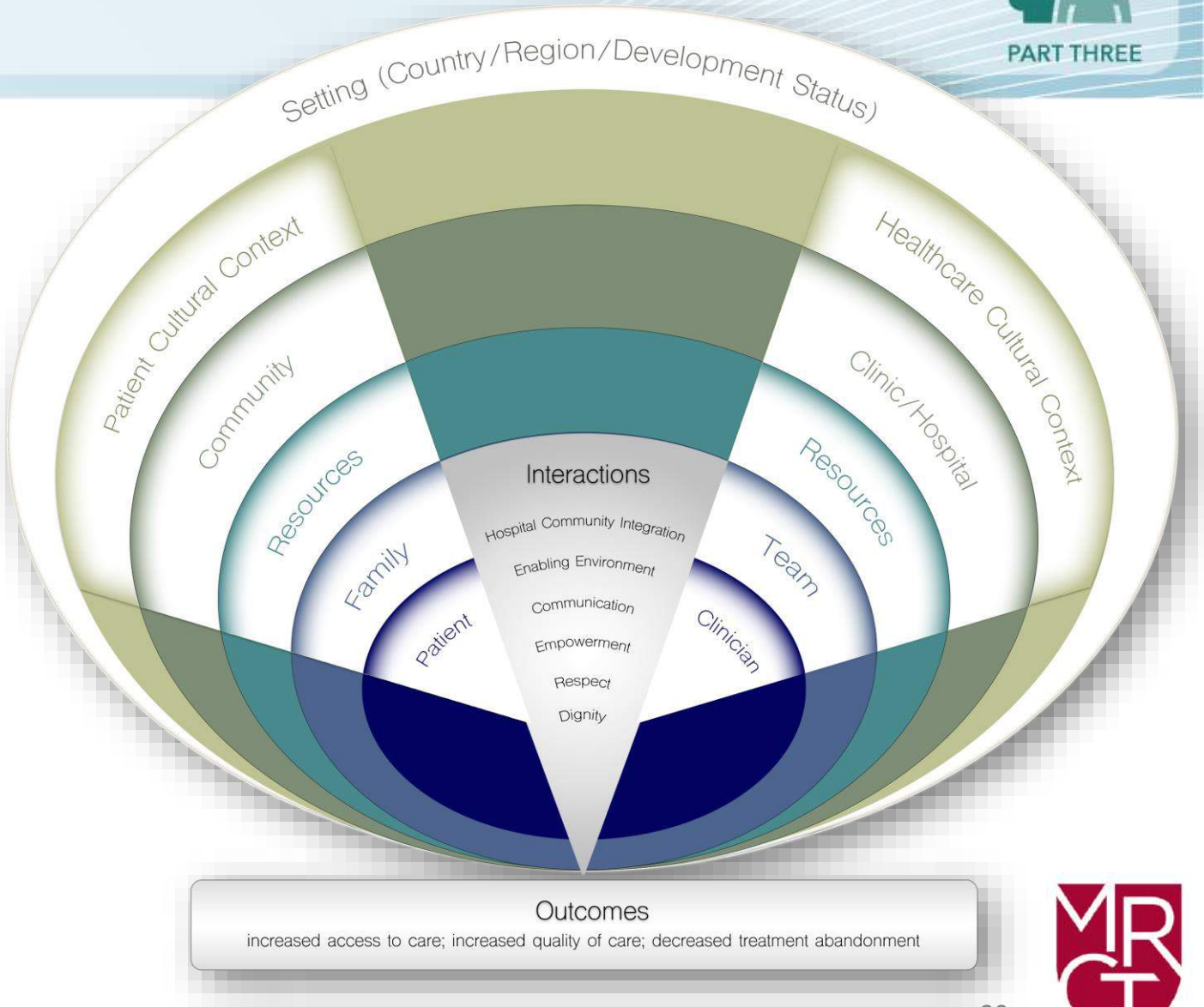
- A model for communication, including consent, with a foundation of cultural context and respect



Finding cures. Saving children.

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Advancing International Pediatric Clinical Research

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

PANEL DISCUSSION

Moderator
Dr. Martine Dehlinger- Kremer
Vice President of Scientific Affairs,
Pediatric Subject Matter Expert
Drug Development Solutions,
ICON PLC

Guest Speaker
Dr. Ruben Cuttica
Hospitals General De Niño's Pedro de Elizalde
Argentina

Guest Speaker
Dr. Haleema Saeed
Shaukat Khanum Memorial Cancer Hospital & Research Centre
Pakistan

Guest Speaker
Dr. Muhammed Afolabi
London School of Hygiene & Tropical Medicine
England

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Advancing International Pediatric Clinical Research

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

Moderator

Dr. Martine Dehlinger- Kremer
Vice President of Scientific Affairs,
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Advancing International Pediatric Clinical Research

Assent and Consent in the Field: Culture, Context, and Respect

MRCT Webinar
June 28, 2022

Dr Martine Dehlinger-Kremer
VP Scientific Affairs, Paediatric SME
Center for Paediatric Clinical Development
Drug Development Solutions

Clinical Trials on Minors and Consent

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Consent

- Process by which volunteer/patient voluntarily confirm willingness to participate in a trial, after having been informed of aspects of the trial that are relevant to its decision to participate

Clinical Trials on Minors

- Parenteral/Legal Guardian consent is required
  - Frequently from the 2 parents unless the local jurisdiction requires only one parent
- Child to be involved in process of informed consent
  - Age-appropriate assent / consent
  - Re-consent required if minor reaches age of legal competence

The Process of Informed Consent - Informed Consent from the Legally Designated Representative

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- Informed Consent must be sought from the parents/legally designated representative on the child's behalf
- Specific, written informed consent must be obtained prior to enrolling a child in a trial
- The person providing the information should be experienced in providing tailored research information, competent in communicating and working with children and young people, and providing them and their legal representatives with the time and space to reach a decision without pressure
- The information should be given to each parent, or legally designated representative, both in oral and written form
- The information be provided in a "comprehensive, concise, clear, relevant, and understandable" manner
- Parents/legally designated representative should be explicitly informed of their right to refuse to the child's participation, and to withdraw the child from the clinical trial at any time without any resulting detriment for the child and without having to provide any justification

Informed Consent of Families with Different Cultural Background

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- Information to be adapted to the language skills and understanding of the child and the parents/legal representative
- Cultural differences may lead to misunderstandings
- Where appropriate, the investigator should arrange for translations: a translator and/or a cultural mediator to be available in the planning of the study and during the process of informed consent and assent / agreement
- This person should be familiar with medical terminology, experienced in the language, social habits, culture, traditions, religion and particular ethnic differences

Continued Consent Process during the Clinical Trial

Consent, assent and agreement, is a dynamic, continual process

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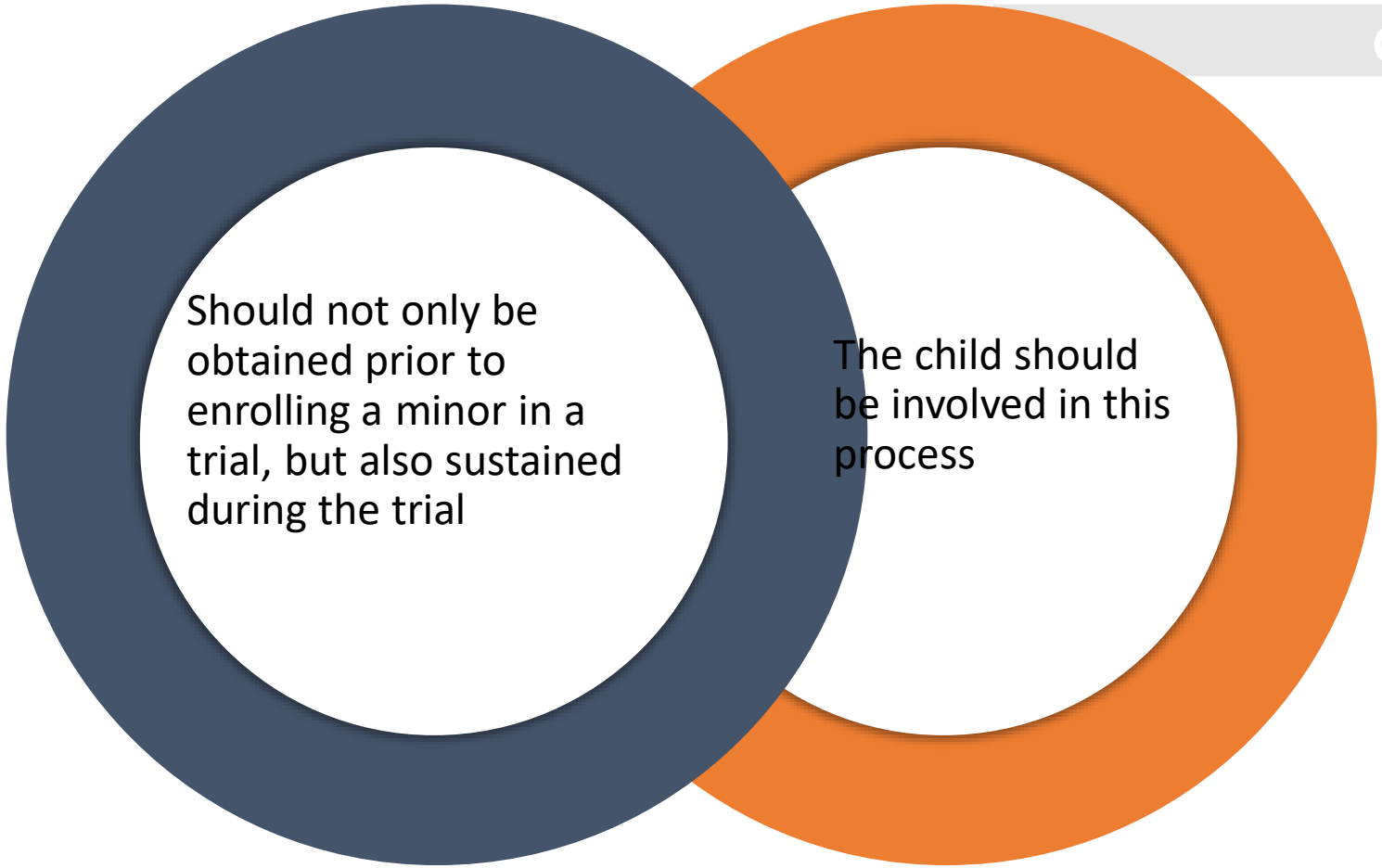

Could be achieved by

- Brief discussion during trial visits and documented
- The discussion is part of the ongoing dialogue between minors, parents and investigators and should focus on new information that arises from the trial and may affect the willingness of the parents and minor to continue
- Especially in long-term trials, the investigator should follow up on a regular basis and document the evolving maturity of the child, his or her ability to assent or agree, and act accordingly

Minor's Participation in the Informed Consent Process

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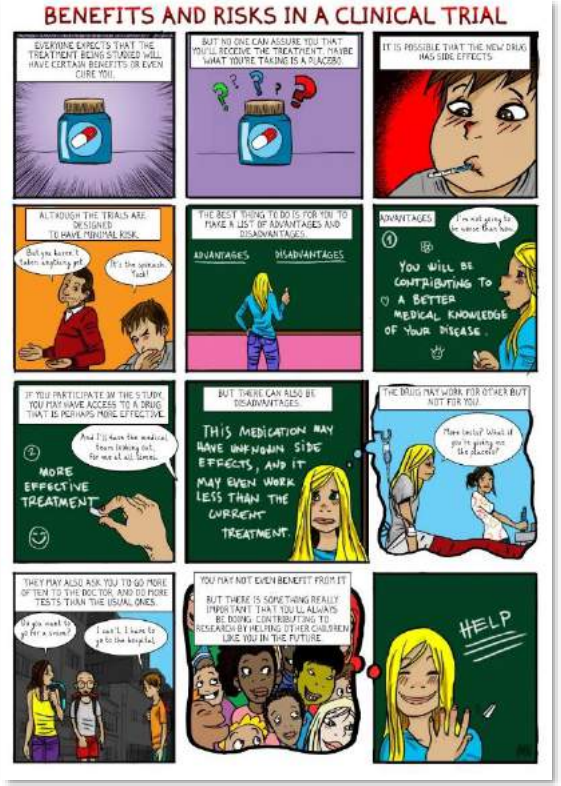

- Each minor should participate in the informed consent process together with the parents/legally designated representative, in a way that is appropriate to his or her age and maturity
- Minors are to be treated as persons who have the potential from an early age to express altruism and play an active role on decisions for their own lives, within their familial and social environment
- The central role of parents in the protection of their child should be recognized
- To provide age-appropriate information and assent/agreement forms, separate material should be used for children, using language and communication tools (visuals, cartoons, videos etc.) appropriate to the participants' age and maturity. It is strongly recommended to check the information material for sufficient understanding in the relevant population

Adolescent Who is no Longer a Minor

- Once an adolescent is no longer a minor, or when he or she is an “emancipated minor”*, he or she should be asked to provide written informed consent as soon as practically reasonable, as for any adult capable of giving consent
- Informed consent is no longer required from the parents/legally designated representative
- The withdrawal of informed consent by the adolescent shall not affect the activities already carried out and the use of data obtained based on informed consent before its withdrawal
- The legal age to give informed consent varies, i.e., follows the specific jurisdiction requirements

*This is a legal term and applies under exceptional conditions: Minors can become emancipated through certain actions, such as marriage

Guidance for Informed Consent and Assents for Paediatric Trials in Europe

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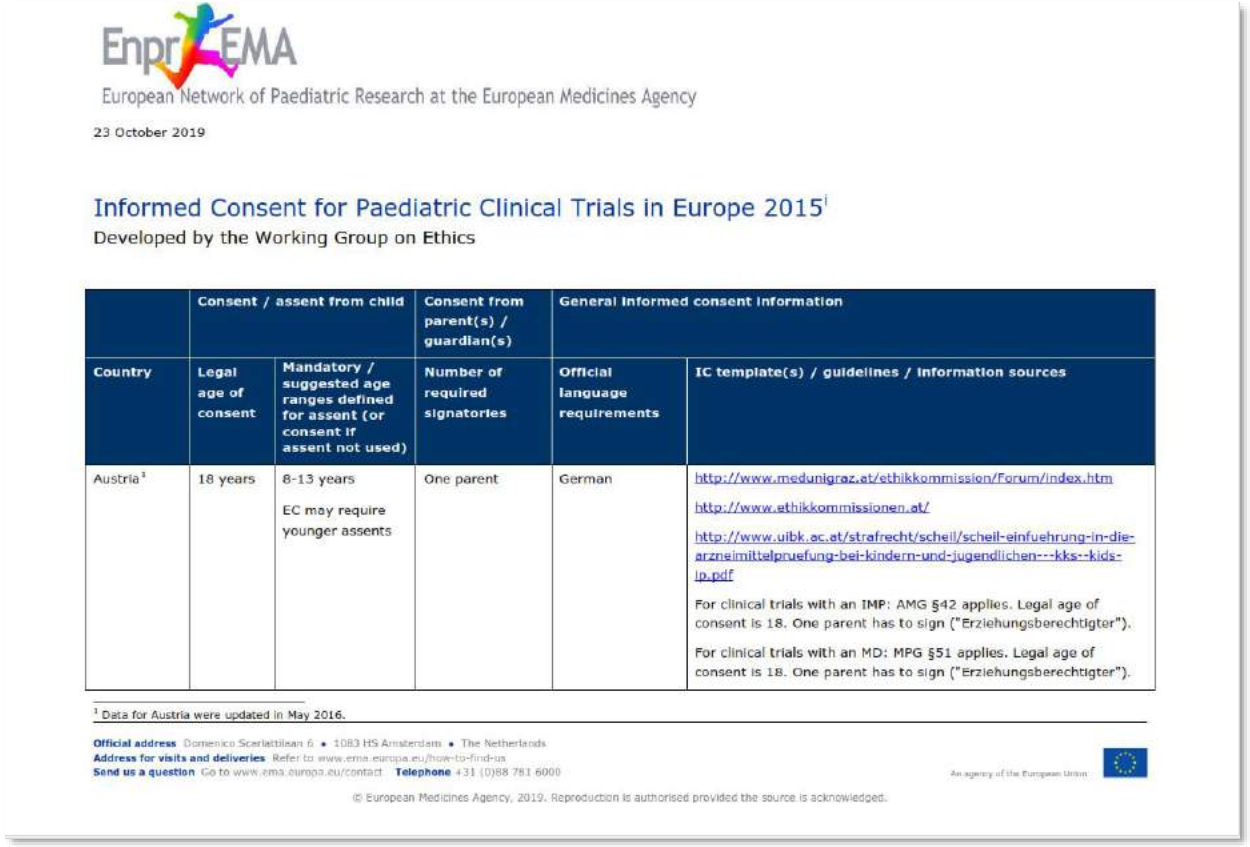
– Country specificities in terms of one or two parent signatures

– Country specificities in terms of age of assent and consent



EnprEMA

European Network of Paediatric Research at the European Medicines Agency

23 October 2019

Informed Consent for Paediatric Clinical Trials in Europe 2015[i]

Developed by the Working Group on Ethics

	Consent / assent from child		Consent from parent(s) / guardian(s)	General informed consent information	
Country	Legal age of consent	Mandatory / suggested age ranges defined for assent (or consent if assent not used)	Number of required signatories	Official language requirements	IC template(s) / guidelines / information sources
Austria[1]	18 years	8-13 years EC may require younger assents	One parent	German	http://www.medunigraz.at/ethikkommission/Forum/index.htm http://www.ethikkommissionen.at/ http://www.uibk.ac.at/strafrecht/scheil/scheil-einfuehrung-in-die-arzneimittelpruefung-bei-kindern-und-jugendlichen---kks--kids-ip.pdf For clinical trials with an IMP: AMG §42 applies. Legal age of consent is 18. One parent has to sign ("Erziehungsberechtigter"). For clinical trials with an MD: MPG §51 applies. Legal age of consent is 18. One parent has to sign ("Erziehungsberechtigter").

[1] Data for Austria were updated in May 2016.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact Telephone +31 (0)88 781 6000

An agency of the European Union

https://www.ema.europa.eu/en/documents/other/informed-consent-paediatric-clinical-trials-europe-2015_en.pdf

Guidance for Assent / Informed Consent Preparation

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25 January 2021

Assent / Informed Consent Guidance for Paediatric Clinical Trials with Medicinal Products in Europe

Developed by Enpr-EMA's Working Group on Ethics

This document is intended to be used as an overview tool of the contents for assent/informed consent forms for all stakeholders (such as patients, sponsors and investigators) to support the conduct of high quality paediatric clinical trials in Europe across all paediatric age groups, from birth to less than 18 years of age.

Age Groups

- 0<2 Years
- 2<6 Years
- 6<10 Years
- 10<18 Years

eConsent - Superior Comprehension with eConsent

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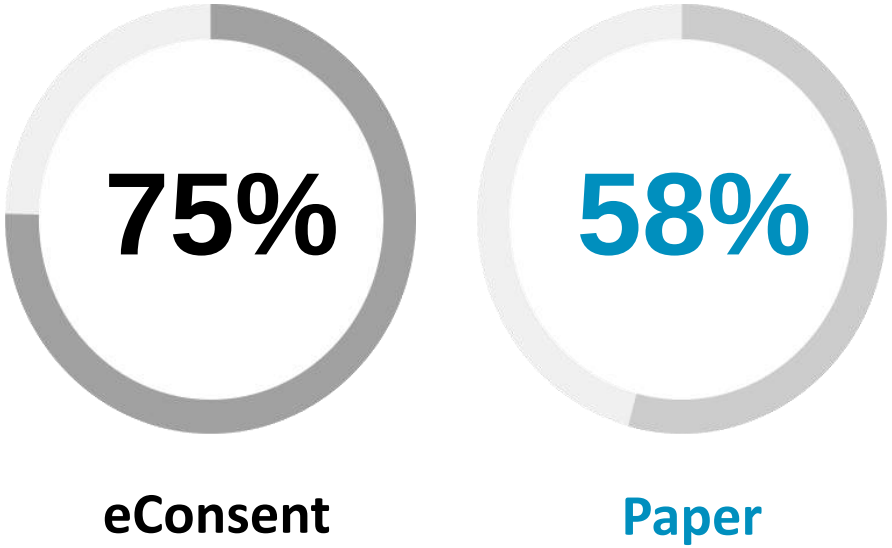

Patients that use eConsent have a better understanding of the study purpose, risks, benefits, schedules, and their rights and responsibilities than patients using paper

Reference - 2013 Independent validation study conducted by California Pacific Medical Center research Institute using Enroll®

Conclusion

Conclusion

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- Assent and consent follow local jurisdictions regulations
- No harmonization on legal age of consent nor on assent age groups
- Integrity, honesty, and clarity are paramount in physician-patient and investigator-trial participant relationships regardless of age
- Cultural differences are to be taken into account
- Will econsent be the future process?

Thank you

For questions, please contact us:

CenterPediatricClinDev@prahs.com

ICONplc.com

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Advancing International Pediatric Clinical Research

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

Guest Speaker

Dr. Haleema Saeed

Shaukat Khanum Memorial Cancer Hospital & Research Centre

Pakistan

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

Shaukat Khanum Memorial Trust
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Assent and Consent in the Field
Culture, Context and Respect

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Haleema Saeed
Pediatric Hematology/Oncology
Shaukat Khanum Memorial Cancer Hospital and Research Center
Lahore, Pakistan

Perspective from Pakistan

- Developing middle income country
- Population of 242 million, 35% are children
- Limited clinical trials and research in pediatric patients
- National bio ethics committee and Pakistan medical counsel oversee and regulate research
- Consent by legal guardian required for those under 18 years
- No requirement for assent under law

Challenges in the Field- Language

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- > 60 language
- No written form
- Lack of medical interpreters

Challenges in the Field- Family structure

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- Variation in decision maker
- Family involvement in decision making
- Patriarchal family structure

Challenges in the Field – Autonomy vs. Paternalism

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- Overall dependence on physician of make the decisions.
- Lack of education
- Trust in physicians

Kongsholm NCH, Lassen J, Sandøe P. "I didn't have anything to decide, I wanted to help my kids"- An interview-based study of consent procedures for sampling human biological material for genetic research in rural Pakistan. *AJOB Empir Bioeth*. 2018;9(3):113-127. doi:10.1080/23294515.2018.1472148

Challenges in the Field – Who to ask?

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- Definition of legal guardian
- Desire to shield the patient from true picture

- Even in an adult population only 15% signed consent themselves

Arshad MA, Omar N, Amjad Z, Bashir K, Irfan M, Ullah I. Perceptions and practices regarding the process of obtaining informed consent from surgical patients at a tertiary care hospital. *Ann Med Surg*. 2022;73:103195. doi:10.1016/j.amsu.2021.103195

Challenges in the Field-Lack of Time, structure and resources

High burden of clinical work

Lack of support for data collection and management

Lack of structure

Malik AY. Physician-Researchers' Experiences of the Consent Process in the Sociocultural Context of a Developing Country. *Ajob Prim Res*. 2011;2(3):38-46. doi:10.1080/21507716.2011.616183

Challenges in the Field-Lack of Time, structure and resources

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The Journey of clinical research in Pediatric oncology in Pakistan

- Establishment of a dedicated cancer hospital that organized annual meetings
- Start of Fellowship program and recognition of fellowship training by National body
- Establishment of National Society (PSPO)
- Grant from WHO to start National clinical Trial.
- 3 national level clinical trials approved by NBC

PSPO
Pakistan Society of Pediatric Oncology

Malik AY. Physician-Researchers' Experiences of the Consent Process in the Sociocultural Context of a Developing Country. *Ajob Prim Res*. 2011;2(3):38-46. doi:10.1080/21507716.2011.616183

Conclusion

- There a many practical challenges to conduction ethical clinical research with appropriate informed consent and assent
- These include cultural and language diversity, lack of clearly defined laws regarding assent, complex family structures and overly paternalistic society.
- Need to think outside the box to come up with culturally sensitive solutions

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Advancing International Pediatric Clinical Research

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

Guest Speaker

Dr. Ruben Cuttica
Hospitals General De Niño's
Pedro de Elizalde
Argentina

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

Assent and Consent In the Field: Culture, Context and Respect

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Rubén J. Cuttica, MD, Prof.
Pediatric Rheumatology Consultant
Pediatric Rheumatology Unit
Hospital Pedro de Elizalde
Buenos Aires - ARGENTINA

cutticarj@yahoo.com.ar

HOSPITAL PEDRO DE ELIZALDE
Buenos Aires - Argentina

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- Children's general hospital
- All pediatric sub-specialties
- In and out-patient facilities
- Facilities for phase I to IV clinical trials
- Internal Review Board
- Teaching and Research Department
- Facilities to store biological samples

ARGENTINA

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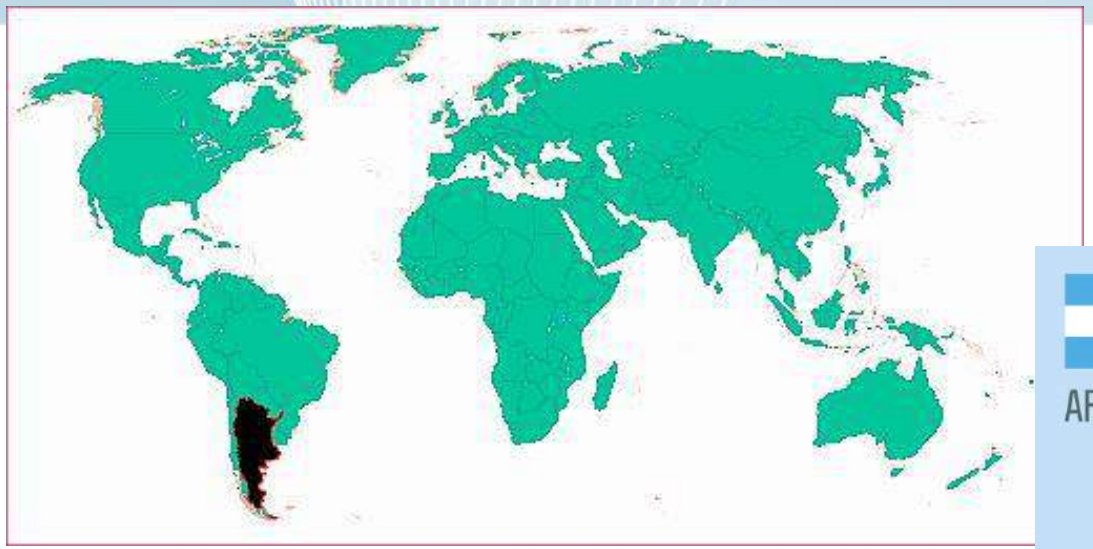

47.000.000 Inhabitants - Surface 3 761 274 km²

3.081.550 in Buenos Aires City
17.875.743 (39%) living in Buenos Aires Province

60% european ancestry

ARGENTINA

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39% younger than 24 y/o
55% is considered poor
median income less than 500 US$ /month

Mostly informal employment

Severe Social and political struggle

Pandemia, isolation and uncertainty

↓

Fear, anxiety and anguish

This is the environment where we ask a patient and his family to participate in a clinical trial

INFORMED CONSENT AND ASSENT ACCORDING TO CIVIL CODE IN ARGENTINA

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Age in years	
0 to < 13	Informed Consent from at least one legal guardian + Informed Assent of the patient according to understanding.
13 to < 16	Patient Informed Consent + Informed assent from at least one legal guardian **in case of risk**.
16 to < 18	Patient Informed Consent + Informed Assent of at least one legal guardian.

INFORMED CONSENT AND ASSENT IN CLINICAL TRIALS INVOLVING CHRONIC CONDITIONS

- Patient has some time to follow-up with the medical team.
- The first step is to explain what clinical research is and GCP in pediatric trials.
- Talk about why a patient may be admitted to the trial
- Talk about the current and trial treatment
- Talk about advantages, risks and uncertainties
- Informed consent form is given some time in advance to read it at home
- Set a new appointment to discuss about doubts and clarifications and finally make the decision to sign or not

KEYS TO A SUCCESSFUL INFORMED CONSENT

- Knowledge
- Time
- Dedication
- Privacy
- Quiet environment
- Clear explanations
- Sincerity

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Advancing International Pediatric Clinical Research

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

Guest Speaker

Dr. Muhammed Afolabi
London School of Hygiene &
Tropical Medicine
England

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

Advancing international pediatric clinical research:
Assent and consent in the field: culture, context, and respect

PART THREE

Muhammed Afolabi, MD,MPH, PhD, FWACP, FHEA, FFPH
Clinical Associate Professor
London School of Hygiene & Tropical Medicine, UK
28 June 2022

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Informed consent and assent in African settings

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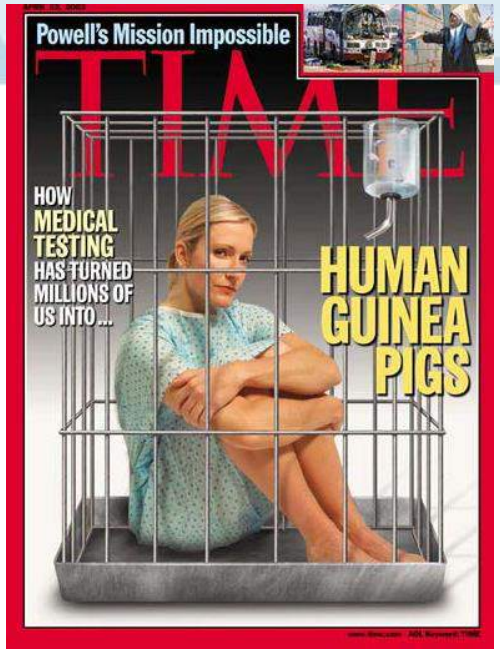
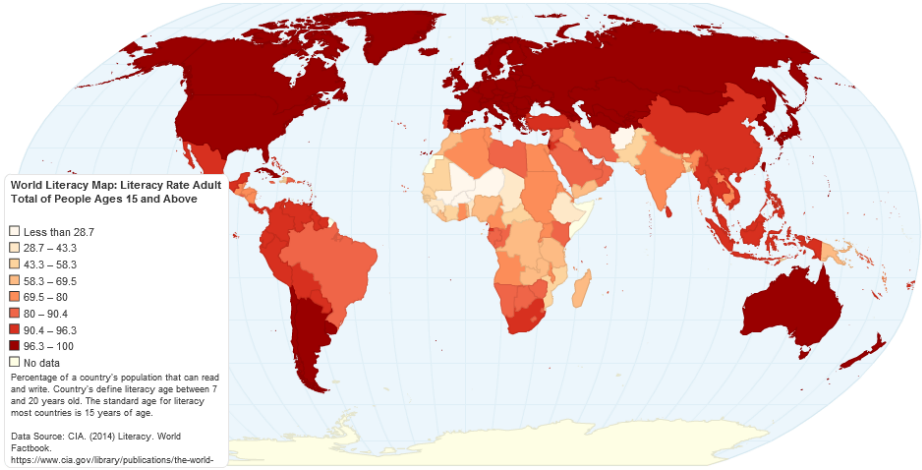
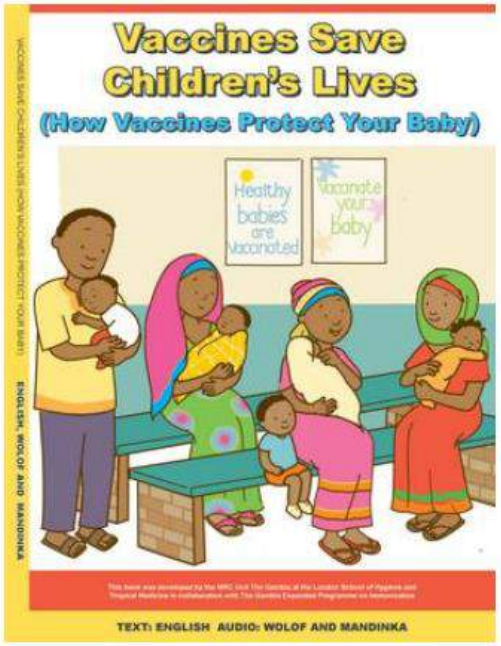




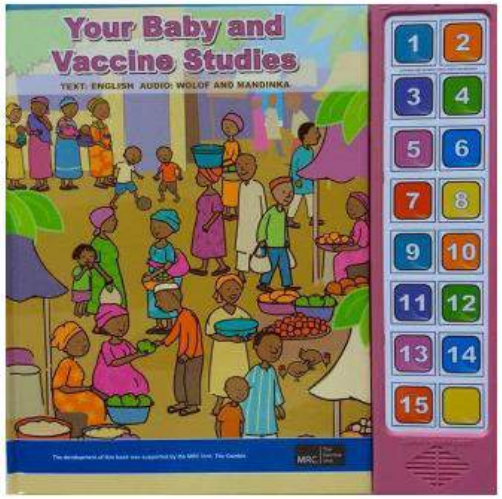
- High preponderance of non-literate and functional illiterate populations
  - 85% of juvenile criminals are functionally illiterate
  - A child born to a non-literate mother is 50% less likely to survive past the age of 5 years.
- [1]Poverty: Illiteracy costs the economy USD $1 trillion each year: 2% of the GDP in developing nations, 1.2% of the GDP in emerging economies
- Poor access to health care
- Local languages exists in oral forms, no standardized writing formats, making translations & back-translations of ICF impractical
- Large power differences between researchers and research participants

[1]https://speakingbooks.com/wp-content/uploads/WLF-FINAL-ECONOMIC-REPORT.pdf

Speaking Book



Vaccines Save Children's Lives (Wolof)
Language: *Wolof*
Country: *Gambia*
Topic: *Immunization, vaccines*
Sponsor: *MRC BioInformatics Unit*



Your Baby and Vaccines
Language: *Wolof*
Country: *Gambia*
Topic: *Health Education, Immunization*
Sponsor: *Pfizer*

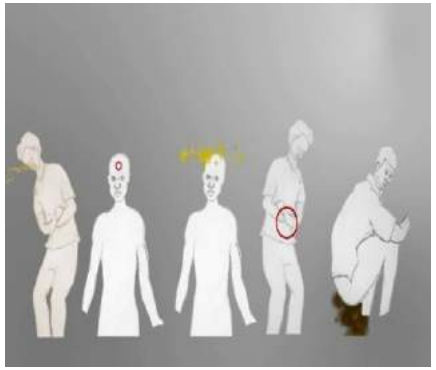
https://youtu.be/TidUsnsOpgc
https://youtu.be/AMuX2DHLyfc

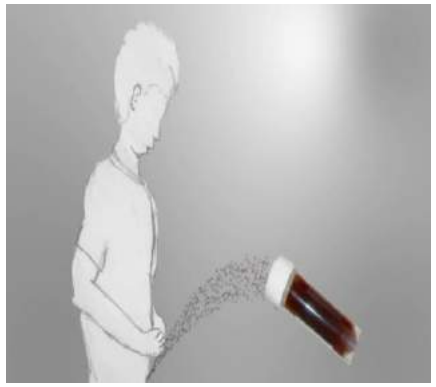
Multimedia consent tool

BMJ Open

Digitised audio questionnaire for assessment of informed consent comprehension in a low-literacy African research population: development and psychometric evaluation

Muhammed O Afolabi,[1,2] Kalifa Bojang,[1] Umberto D'Alessandro,[1,2] Martin O C Ota,[3] Egeruan B Imoukhuede,[4] Raffaella Ravinetto,[5,6] Heidi J Larson,[7] Nuala McGrath,[8] Daniel Chandramohan[2]





A multimedia consent tool for research participants in the Gambia: a randomized controlled trial

Muhammed Olanrewaju Afolabi,[a] Nuala McGrath,[b] Umberto D'Alessandro,[a] Beate Kampmann,[a] Egeruan B Imoukhuede,[c] Raffaella M Ravinetto,[d] Neal Alexander,[e] Heidi J Larson,[e] Daniel Chandramohan[e] & Kalifa Bojang[a]

Many thanks!

PART THREE

- 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

PART THREE

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

PART THREE

MULTI-REGIONAL CLINICAL TRIALS

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

Thank you!