Advancing International Pediatric Clinical Research

PART ONE: INFORMING THE FUTURE FROM COVID-19 LESSONS LEARNED

October 7, 2021

8:00AM – 11:00AM 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

Webinar Series: *Advancing International Pediatric Clinical Research*

- Funded 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

The 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.

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 often an afterthought and not routinely offered a seat at the table.**

Project structure: Workgroup & 3 thematic subgroups

- Project Leadership:
  - Dr. Barbara E. Bierer: MRCT Center
  - Dr. Steven Joffe: University of Pennsylvania, PA
  - Elisa Koppelman: MRCT Center
  - Dr. Robert “Skip” Nelson: Johnson and Johnson
  - Dr. Dominik Karres: European Medicines Agency
- Workgroup: 80 + members representing multiple stakeholders; strove for geographic diversity; monthly 90 min. meetings Oct. 2019—Nov 2020
- Subgroups: 15-20 members; co-led by leadership; monthly 90 min meetings X ~1 year
  1: Decision making at level of child/family
  2. Benefit/risk considerations at level of IRB/E
  3. Challenges: Regulatory cooperation and operations

Webinar series supporting contributions to the 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

Advancing international pediatric clinical research—looking ahead

1. *Informing the future from COVID-19 lessons learned:*
   - 6 October 2021; 6-9 pm EDT
   - 7 October 2021; 8-11 am EDT
     - Keynote
     - Panel 1: Initiating clinical trials in children—*Is there a right time?*
     - Panel 2: Infrastructure needs*: How do we create and sustain a network for the conduct of ethical pediatric clinical trials*

2. Early 2022 : Decision making post IRB study approval including pediatric participant voice
3. Spring 2022 : Decision making at ethics committee level including strengthening of ICH E11, concept of an ethical floor
4. Fall, 2022: Regulatory convergence to facilitate international cooperation
5. Early 2023: TBD

Prof. Mojisola Christianah Adeyeye

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Fellow, Nigerian Academy of Science
Fellow, Nigeria Academy of Pharmacy

Advancing International Pediatric Clinical Research: informing the future from COVID 19 lessons learned

BY

Prof Mojisola Christianah Adeyeye, PhD, FAS

Director General, NAFDAC

&

Steering Committee Chair

African Medicines Regulatory Harmonization (AMRH)

AUDA-NEPAD

OUTLINE

- Introduction
  - Paediatrics Clinical Trial in perspective
- Why paediatric clinical trials in Africa?
- Rationale for conducting paediatric trials
- Challenges in paediatric trials
- COVID 19 Reviews and Lessons learned
- NAFDAC Regulatory efforts in Advancing Paediatrics Clinical Trial
- Conclusion/Recommendation
- Acknowledgement

Introduction

Pediatric Clinical Trial in perspective:

- High-quality, cost-effective pediatric clinical trials is key to the development of therapeutic, Prophylaxis solutions to disease burden in pediatric populations globally.
- Requires a robust research and regulatory infrastructure and a properly trained workforce to implement scientifically sound and ethically justifiable trials
- Therapeutic products licensed for adults are frequently used in pediatric populations without sufficient safety, dosing, or pharmacokinetic data.
- Regulators, Researchers and Society share the ethical responsibility of providing the resources necessary to mine the knowledge needed to guide therapeutic decisions for children.

Introduction cont'd

- In advance societies, government regulations and policies both required and provide incentives for the conduct of pediatric clinical trials, thus providing an opportunity to close the knowledge gap in pediatric biomedical innovation.
- However, the pediatric research enterprise must be carried out with due diligence under regulatory oversight to address deficiencies in our current preclinical and clinical research systems that generates data in other to avert irreproducible and poor data for children population.
- It is reported, In 2012, the U.S. Food and Drug Administration (FDA) Safety and Innovation Act (FDASIA) strengthened prior initiatives in pediatric product development and made permanent the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA), which have helped to increase the number of pediatric clinical trials

Introduction cont'd

- The results: Between 1998 and 2011, FDA issued ~340 written requests for new pediatric studies and subsequently approved more than 450 labeling changes associated with BPCA and PREA studies
- In Europe, after initial implementation of the Pediatric Regulation, most applications for new medicines started coming in with a pediatric plan
- Evidence for a more robust pediatric product–development pipeline also comes from the Pharmaceutical Research and Manufacturers of America, which reported on nearly 300 medicines in development to address health needs in children
- Because rare genetic diseases (~6,500 in total) primarily affect children, additional momentum for pediatric trials has come from the rare diseases' community. and the FDA Office of Orphan Product Development are working to advance product development for rare diseases.

NAFDAC PEDIATRIC CLINICAL TRIALS: LEGAL FRAMEWORK

NAFDAC ACT Cap N.1 LFN 2004: An Act to establish the National Agency for Food and Drug Administration and Control with the functions, among others, to regulate and control the importation, exportation, manufacture, advertisement, distribution, sale and use of food, drugs, cosmetics, medical devices, bottled water and chemicals.

Supported by:

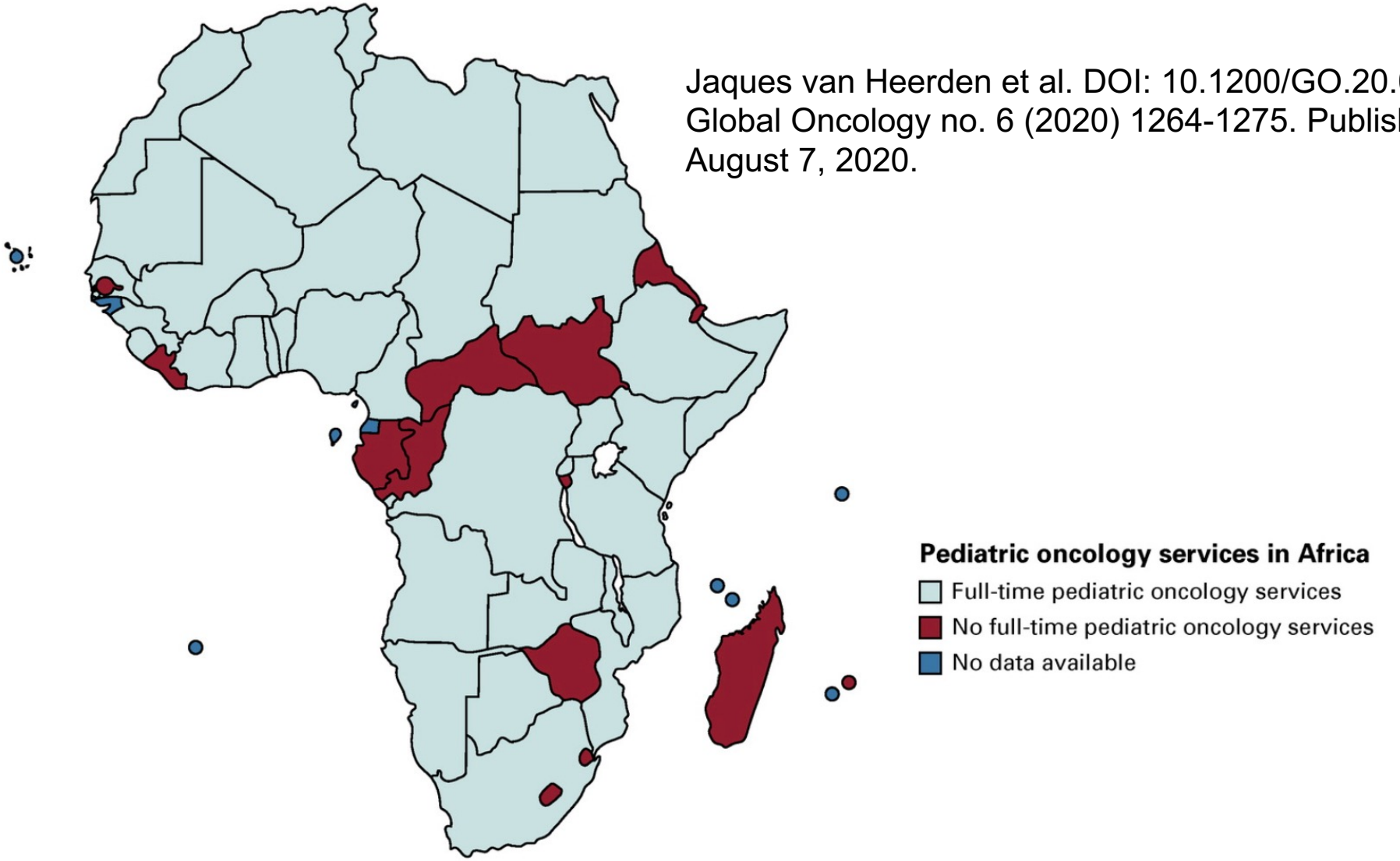
- Sections 5(1) and 5(2) of the Food, Drugs and Related products (Registration, etc.) Act Cap F33
- NAFDAC GCP Guidelines and NAFDAC Good Practices for Pharmaceutical Quality Control Labora tory Guidelines (GPPQCL)
- https://www.nafdac.gov.ng/wp-content/uploads/Files/Resources/Guidelines/DRUG_GUIDELINES/GUIDELINES-FOR-CLINICAL-TRIAL-IN-PAEDIATRIC-POPULATIONS-1.pdf

PEDIATRIC CLINICAL TRIALS – NAFDAC FOCUS

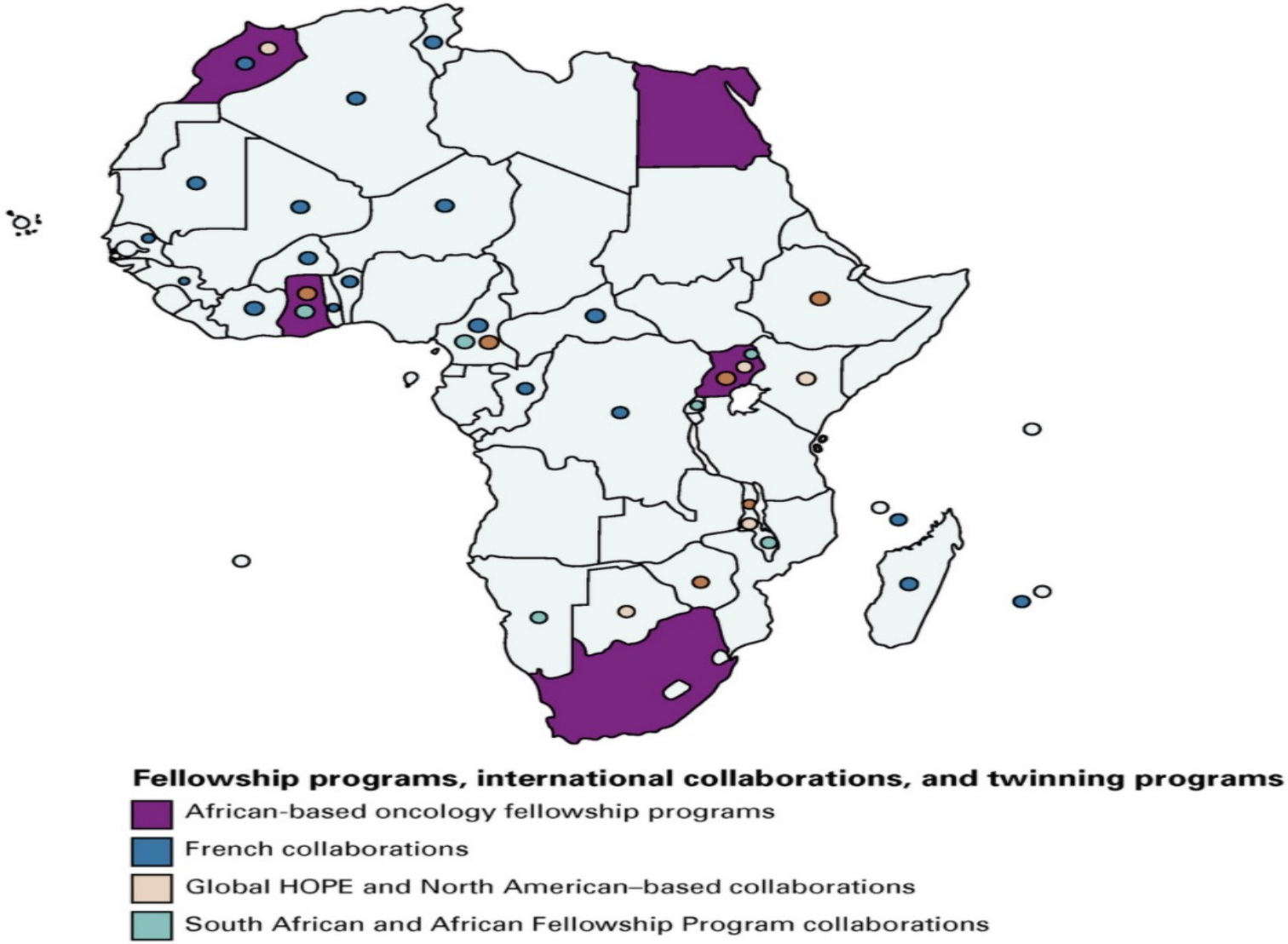
- Safeguard Public Health
  - Ensuring that the medicines that Nigerians consume are safe, efficacious and do that what it is supposed to do in the human body; Clinical trial is the scientific tool for such.
  - Clinical trial no doubt plays pivotal role in achieving this mandate and Vision

Why Clinical trials in Africa - Nigeria

- Inadequate clinical services have yet to be established in the majority of African countries, where childhood cancer survival rates vary from 8.1% to 30.3%
- ClinicalTrials.gov showed that only 12.1% of African oncology studies included children and adolescents.
  - 50.5% were interventional trials - palliative care and leukemia trials
  - < 1% of the pediatric oncology publications come from Africa.
  - Despite low number of pediatric clinical treatment trials in African children and adolescents, there is high quality clinical research



Jaques van Heerden et al. DOI: 10.1200/GO.20.00159 JCO Global Oncology no. 6 (2020) 1264-1275. Published online August 7, 2020.


Fellowship programs, international collaborations, and twinning programs
African-based oncology fellowship programs
French collaborations
Global HOPE and North American–based collaborations
South African and African Fellowship Program collaborations

Rationale for conducting pediatric trials

- Children have the right to the highest attenable level of health enunciated by the convention on the Rights of the child;
  - **Can not be realized if therapy for children is based mere extrapolation from studies carried out in adults**
- Children and adult differ in
  - Physiological capabilities; Pharmacokinetics profile and Pharmaco-dynamics characteristics
  - Metabolic pathways, organ function and metabolic rates.
  - Disparity in terms of receptor functions, effector system and homeostatic mechanism.
- Age, growth and development influence side effect of drugs.
  - Dose of medication is largely dependent on body weight or surface area
  - Influence severity and type of disease and pathological agents

Challenges in pediatric clinical trials

- Conduct of clinical trial in pediatric population has a web of challenges confronting stakeholders;
  - Complexity of clinical trial in pediatric population.
    - Rare Disease amd limited number of subjects
  - The Orphan Drug Act defines rare diseases as disorders affecting fewer than 200 000 individuals in the United States. Elsewhere, it is defined as also having a prevalence ranging from < 1:2000– < 1:50,000

Challenges in pediatric clinical trials Cont'd

- Approximately 80% of the thousands of defined rare diseases have an underlying genetic basis and approximately 50% is estimated to affect children
- Many of these rare diseases lack treatments or cures and are fatal, making new treatments potentially transformative for the lives of patients.
- **Responses in clinical rrial may also be genetically driven**
- Difficulty satisfying regulatory requirements for therapeutic study of human diseases:
  - appropriate trial design
  - ethical recruitment to participation,
  - funds to support the research, ,
  - Inadequate sample size for certain children disease –rare diseases

Challenges in pediatric clinical trials Cont'd

- Trial Design- Prospective studies
  - Randomized controlled trial {blinded) is often considered the gold standard for establishing efficacy in a research setting
  - It is costly, time-consuming, and requires large sample sizes.
  - Variability : common diseases have a homogenous clinical course -in certain children disease (rare diseases) which are often genetic such as neuronal ceroid lipofuscinoses, even as single gene disorders, there is considerable variability, even within families.
  - Control groups: Use of controls strengthens trial design by addressing concerns regarding clinical variability. However, in some diseases, many of which cause a shortened lifespan for children, there are ethical concerns about use placebo-controlled trials.
  - N/B; Parents are not willing to give consent to children to be enrolled in placebo-control study

Challenges in pediatric clinical trials Cont'd

- **Natural History and Patient;**
  - Detailed understanding of the natural history and epidemiology of disease is crucial to the design of clinical trial and informed criteria for inclusion and exclusion.
  - Data in salient aspects of most rare disease in children are scarce due to lack of natural history of a disease especially in developed countries.
  - In rare disease for example, the small numbers of patients, geographic dispersion of patients, and small number of interested or adequately trained researchers have all been barriers to systematic collection of natural history data compared to common diseases.
- In Nigeria, there is need to establish prospective data appropriate for use as historical controls in the future.
- A clinical registry of prospectively obtained data may introduce efficiency into future studies by serving as a source for historical controls. Patient contact registries also have the potential to serve as powerful recruitment tools

Challenges in pediatric clinical trials-rare disease Cont'd

- **Outcome Measures**
  - Lack of clinical rating scales to better quantify multifaceted diseases, increase their precision related to small changes especially for diseases of genetic origin which characterize Orphan disease in pediatrics
  - Existing research gaps in biomarker development to support proof of-concept or to serve as surrogate outcomes in pediatric studies.
- **Subject Recruitment and Retention**
  - Timely and adequate recruitment of eligible participants is a challenge for any rare disease.
  - Few patients (sample size), may not be feasible to significantly narrow entry criteria based on disease stage or other characteristics..
  - Geographic dispersion of potential participants requires multicenter or even multinational collaboration on the part of investigators. Such collaboration is rare in most research space.

Challenges in pediatric clinical trials-rare disease Cont'd

- Diseases with significant physical impairments, travel to research centers may pose an insurmountable to research participation.
- Trials involving repurposed drugs, recruitment and retention can also be threatened through off-label use outside of the clinical research

Drug Development and Funding:

- Longer timeline for drug development for rare disease in pediatric population compared to common disease.
- In comparison with common diseases, rare disease therapeutics (Orphan drugs) are assumed to have small markets and thus small economic impact, providing little returns on investment
- Lack of funding from government to fund research and development (R&D) in most developing countries
- Lack of trust by development partners to fund research generally in Africa including pediatric studies due to past experiences.

Challenges in pediatric clinical trials-rare disease Cont'd

Researcher Training:

- There is a paucity of clinical researchers with interest, training, and experience in the design and execution of pediatric trials especially for rare disorders.
- Clinical researchers in academia face challenges of balancing clinical demands and research, navigating regulatory requirements, lack of local infrastructure, and need for training in clinical research.
- Lack of opportunities to provide support, mentorship, and protected time for bench and clinical researchers to develop expertise in many areas relevant to rare disease research.
- Knowledge gaps in regulatory requirements in the research space
- Lack of epidemiological data on pediatric data in developing countries especially for rare disease

Covid 19 Review And Lessons Learned

- As coronavirus disease 2019 (COVID-19) spread across the globe in early 2020, healthcare systems adapted urgently to respond to and understand this newly emerging, highly infectious disease.
- COVID-19 in its symptomatic and most severe form primarily affects adults, particularly the elderly and those with underlying health conditions.
- Children are less severely affected representing <5% of cases. However, in May 2020, a severe post-infectious complication of COVID-19 in children, the pediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS) also known as multisystem inflammatory syndrome in children and adolescents temporally associated with COVID-19 was described8 and is now recognized as a significant cause of COVID-19-associated morbidity.9
- Although the incidence of symptomatic and of severe COVID-19 is lower in children, the current pandemic has an increasing number of implications for children's healthcare and associated research.

Covid 19 Review And Lessons Learned

- Cautious Afterthought of Inclusion of Children in Clinical Trials
  - The COVID-19 pandemic poses many direct and indirect consequences for children's health and associated research.
  - Pfizer Biotech COVID-19 Clincal Research
- Direct consequences include participation of children in COVID-19 research trials, pausing other research in children and the potential implications of a global economic downturn on future research funding.
- Collaborative and networked research together with streamlined research processes and use of remote technology ,
- Maintain streamlined and efficient approaches to research governance and data sharing to facilitate high-quality collaborative research.
- Ensure early inclusion of children in trials of therapies for diseases that affect all age groups.

Covid 19 Review And Lessons Learned

- The general assumption that children are less severely affected by COVID-19 combined with residual historic reluctance to include children and pregnant women in the early stages of therapeutic trials has contributed to delays in including these groups in COVID-19 trials.
- This has interrupted evidence-based evaluations of potential COVID-19 treatments for hospitalized children and for those who present with more severe forms of the disease. Instead, a standardized approach should be encouraged that best serves the needs of all patients while systematically improving our understanding of the effectiveness and safety of interventions

Covid 19 Review And Lessons Learned

- Several positive outcomes for children's research have arisen during this period.
- One example is recognition from across the research spectrum that rapid, responsive collaboration can be achieved and is essential to effectively and quickly address important clinical questions.
- Information sharing among global collaborations are a credit to the efforts of researchers to bring knowledge and best available practice together and to disseminate it quickly and efficiently via social media and online collaboration.

Covid 19 Review And Lessons Learned

- The second is the recognition that study design may not need multiple complex layers of administration and that approval processes can be streamlined without compromising quality and safety.
- Necessary remote working and use of video conferencing technology has allowed people to become familiar with conducting meetings, delivering teaching, attending seminars and even conferences from multiple locations across the world.
  - The online summer series provided by the Pediatric Academic Society, or the fully virtual European Academic Pediatric Societies meeting are just two examples of how important forums for researchers can be adapted to facilitate dissemination and discussion of results from clinical trials and research studies remotely to influence current clinical practice within a global pandemic.

NAFDAC Regulatory Efforts in advancing Pediatrics Trials

- Development of specific guideline for Clinical trial in pediatric population
  - https://www.nafdac.gov.ng/wp-content/uploads/Files/Resources/Guidelines/DRUG_GUIDELINES/GUIDELINES-FOR-CLINICAL-TRIAL-IN-PAEDIATRIC-POPULATIONS-1.pdf
- Providing enabling environment for stakeholders engagement – through workshops.
  - Had two workshops this year with Principal Investigators
  - Plans are on the way to organize specialized training to biomedical researchers on regulatory perspective of Clinical trials to cover major areas including pediatric studies
- Support and registration of orphan drugs in Nigeria to help the industries develop long term data on safety and effectiveness profile of drugs to fill knowledge gaps and open up opportunities for further Clinical trials in pediatric population

- NAFDAC hopes to develop national guidelines regarding risk stratification of research studies in children in Nigeria

NAFDAC Regulatory Efforts…

- NAFDAC core function is to provide regulatory oversight to all clinical trials
  - Making clinical trials very transparent as part of the Agency regulatory system
  - Providing incentives for pediatric dosage forms manufacturers clinical sponsors
    - Possible Product Registration Waiver as part of ollaborative registration procedure using reliance
  - NAFDAC has launched the first in its kind Electronic Clinical Trial Application Platform called eCTAP (developed by NOVOTEQ and funded by The Gates Foundation)
  - https://www.nafdac.gov.ng/drugs/clinical-trial-regulation/application-for-clinical-trials/
  - Available for all clinical sponsors or applicants including national and international PIs and Clinical Research Organizations, before the implementation of the platform

Conclusion/Recommendation

- Conducting clinical trials in paediatric population is complex. “Getting it right” from the beginning is critical for all stakeholders
- Experimental therapeutics for rare disorders faces many challenges. Despite these challenges, there have been several recent accomplishments.
- It is essential to carry out research in children to ensure that better therapy becomes available to them. However, additional safeguards are necessary to guarantee the rights of children and their families.
- All stakeholders : regulators, patient group, ethic committees, research institutions, practitioners, academia, media, pharmaceutical companies and scientist have to collaborate effectively to ensure that ethical pediatric research is promoted.
- Improved infrastructure and funding for R&D should be a key deliverable for government and research institution to help Clinical trials in special population thrive.

Acknowledgements

- Erika F. Augustine, MD, Heather R. Adams, PhD, and Jonathan W. Mink, MD, PhD Department of Neurology, University of Rochester Medical Center, Rochester, New York.
- Published in final edited form as: J Child Neurol. 2013 September ; 28(9): 1142–1150. doi:10.1177/0883073813495959. -NIH Public Access Author Manuscript
- Fleming, P.F., Gale, C., Molloy, E.J. et al. Paediatric research in the times of COVID-19. Pediatr Res 90, 267–271 (2021). https://doi.org/10.1038/s41390-021-01479-6
- Department of Pediatrics and Clinical and Translational Science Institute, Children's National Medical Center; and School of Medicine and Health Sciences, George Washington University, Washington, DC 20010, USA
- Find articles by Edward M. Connor

- Andrew E. Mulberg1*, Christina Bucci-Rechtweg2 , Joseph Giuliano1 , David Jacoby3 , Franklin K. Johnson1 , Qing Liu1 , Deborah Marsden4 , Scott McGoohan5 , Robert Nelson6 , Nita Patel1 , Klaus Romero7 , Vikram Sinha8 , Sheela Sitaraman1 , John Spaltro1 and Vivian Kessler - Regulatory strategies for rare diseases under current global regulatory statutes: a discussion with stakeholders

1. https://globalgenes.org/rare-facts/ or Global Genes. 'RARE Diseases: facts and Statistics'.
2. https://pharmaboardroom.com/articles/investments-and-deal-activity-in-orphan-drug-products/
3. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) .

THANK YOU!!!

Panel 1: Initiating clinical trials in children—*Is there a right time?*

Moderator
Dr. Angeliki Siapkara
Medicines and Healthcare products Regulatory Agency (MHRA)
UK

Guest Speaker
Dr. Narendra Kumar Arora
INCLEN Trust International
India

Guest Speaker
Dr. Grace Ku
Institute of Tropical Medicine
Belgium

Guest Speaker
Dr. Tanusha Ramdin
University of the Witwatersrand
South Africa

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

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MULTI-REGIONAL CLINICAL TRIALS

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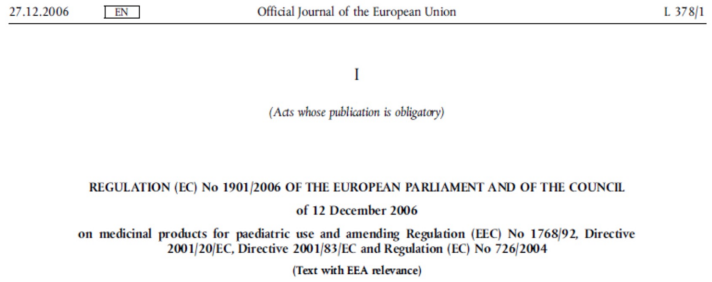
Initiating clinical trials in children—Is there a right time?

- Children should have the same opportunity as adults to use safe and effective medicines
  - Is the decision to seek/support product licence for a given indication essentially commercial ?
  - Absence of MA: absence of controlled clinical trials or trials with negative results ?

- Improve the health of the children ….
  - **Without ?**
  - Unnecessary studies in children
  - Delaying marketing authorisation (MA) for adults


27.12.2006 EN Official Journal of the European Union L 378/1

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(Acts whose publication is obligatory)

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 12 December 2006
on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004
(Text with EEA relevance)

- Cover a paediatric therapeutic need, how and when identified?
- Submitted early in the drug development (end of phase I), expedited programme ?
- What have we (or not) learned from delayed submissions and Long PIP deferrals*:
  - Limited opportunity to influence plans, impact on timely availability of medicines, off label use after the drug has been licensed in adults restricts commitment to enrolment

*Results from the Paediatric Regulation so far 2017 (10 year EC report: http://ec.europa.eu/health/human-use/paediatric-medicines_en)

Covid lesions : UK
what can we use in future paediatric research ?

- **Need for international regulatory collaboration**
  - rapidly identify where regulatory flexibilities and additional support
  - issued guidance to assist those involved in clinical trials disrupted as a result of COVID-19
- **Ability within the system to strongly prioritise on Covid-19 CT applications**
  - a rolling review could begin prior to any regulatory clock start, including expedited regulatory or Scientific Advice (SA) meetings
- **Build upon gained experience throughout the pandemic**
  - a dedicated COVID team within the CT unit to deal with queries and applications in an efficient, expedited manner.
  - contact person within the Health Research Authority (HRA), to enable ethical queries on applications to be dealt with quickly and efficiently.
  - utilising the publication of blogs with information on risk adapted trials and risk adapted monitoring
- **Change of mindset in research : reduce the burden of the trial on trial participants and research staff by adopting different approaches to trial delivery taking into account the trial objectives and protocol so that the participant's trial data are as useful as possible**
  - Examples : planning of visits, receiving IMP, remote follow up, choice of investigations/end points

Initiating clinical trials in children—Is there a right time?

- Pragmatism and flexibility, safety for participants, results that can inform product license

- International, efficient, patient focused trial designs to meet global regulatory requirements
  - Collaborative and constructive dialogue between children, patients/parents' representatives, academics, industry and regulators to facilitate and accelerate treatment development.
  - Collection of data for future trial preparation in a culture of lessons-learned,
  - Dissemination of good practice across paediatric clinical research networks
  - Lobby for greater recognition and awareness amongst healthcare professionals and across society.

- Initiatives to build on the inclusion of paediatric cohorts (i.e.adolescents) within the adult development plans routinely

Narendra Kumar Arora, MD, FAMS, FIAP

Executive Director, International Clinical Epidemiology Network (INCLEN), New Delhi, India

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MULTI-REGIONAL CLINICAL TRIALS

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

Grace Marie V. Ku, MD, MScPH, FPAFP, PhD

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MULTI-REGIONAL CLINICAL TRIALS

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Prioritization of (public) health interventions …and in generating evidence for said interventions

Importance of the **Problem:**

- Economic costs
  - Direct costs
  - Indirect costs
- Social costs
- "Suffering"

Burden of disease

- Incidence
- Prevalence
- Mortality
- Years of life lost (YLLs)
- Years lived with disability (YLDs)
- Disability-adjusted life-years (DALYs)

Directly related to "having the disease" and to current "productivity"

Other effects

?

On informing the future: WHERE WERE WE BEFORE? Lessons learned (?) from the past (Spanish flu) pandemic

"…my father…came on one of his…furloughs…to find both my mother and sister dead… I apparently was chuckling in my cot while my mother and sister lay dead on a bed in the same room."

- Anthony Burgess

Anthony – 1 year 9 months old

Mother – 30 years old

Sister – 4 years old*

*FOCUSED MAINLY ON ADULTS, ESPECIALLY 20-40 Y/O AGE GROUP

"…none of the children covered by the (available) data set were more than two years old during the worst part of the epidemic"

[Reid, Med Hist. 2005 Jan 1; 49(1): 2954. doi: 10.1017/s0025727300008279]

WHERE ARE WE NOW?

- “non-lessons” from past pandemic(s)

  +

- (historical) "hesitancy" in including children (and pregnant women) in the early stages of clinical trials

→Affect current prioritization practices for research involving children at the time of COVID-19

…and not to mention COVID-19 restrictions on children’s mobility (e.g., school closures, <18 years of age not allowed to go out)

For research involving children, considering “experiences” from COVID-19

WHERE DO WE WANT TO GO?

…AND HOW DO WE GET THERE?

Grace Marie V. Ku, MD, MPH, PhD

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Tanusha Ramdin, MD

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Head of Unit, paediatric and neonatal intensive care unit at Charlotte Maxeke Johannesburg Academic Hospital,
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GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

WITS UNIVERSITY

WITS SCHOOL OF CLINICAL MEDICINE

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- At a time when much of the world is still struggling to access COVID-19 vaccines, the question of whether to vaccinate children can feel like a privilege
- SARS-CoV-2 is much less likely to cause serious illness in children than it is in adults
- Some children do still become very ill, and the spectre of long COVID — a constellation of sometimes debilitating symptoms that can linger for months after even a mild bout of COVID-19 — is enough for many paediatricians to urge vaccination as quickly as possible
- In some countries, little is yet known about how COVID-19 affects children.
- Some official tallies of hospitalizations and deaths due to COVID-19 in sub-Saharan Africa, for example, do not break down the cases by age. As a result, paediatricians don’t know which deaths were in children and young people, and how outcomes of COVID-19 might be affected by conditions such as malnutrition, or concurrent tuberculosis or HIV infection

- Paediatricians are concerned about what will happen to children who are co-infected with SARS-CoV-2 and other common viruses that have been kept at bay by social distancing
- Close-knit family structures in a country where children tend to have frequent contact with their grandparents and often travel abroad for school
- Data show that children, and particularly adolescents, can play a significant part in coronavirus transmission
- Transmission by children and adolescents are growing as new coronavirus variants emerge. It’s possible that more-transmissible variants will develop a way to push through whatever it is in a young person’s immune response that makes them more resistant to infection

- Hopes of achieving herd immunity quickly through immunization have waned, so countries need to do the best that they can to keep transmission low
- The indirect impact of COVID-19, school closure and learning could be devastating
- Are wealthier countries that are vaccinating children doing so at the expense of health-care workers and high-risk groups in other countries?
- Should clinical trials on children and COVID-19 vaccinations have commenced a year ago to provide enough evidence on safety and efficacy?
- Improving infrastructure and networking would translate to adequate resources, training and collaborations among different centres within a country and other countries

Panel 2: Infrastructure needs: *How do we create and sustain a network for the conduct of ethical pediatric clinical trials?*

Moderator
Mrs. Pirkko Lepola
FINPEDMED
NORDICPEDMED
Enpr-EMA
Finland

Guest Speaker
Dr. Lisine Tuyisenge
University Teaching Hospital of Kigali
Rwanda

Guest Speaker
Dr. Vasantha Muthuswamy
Former Senior Deputy DG, ICMR
President, FERCI (Forum for Ethics Review Committees in India)
India

Guest Speaker
Dr. Marie Valentin
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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

Pirkko Lepola, BSC, MSC

Executive Secretary of FINPEDMED,
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Chair of the Enpr-EMA Coordinating Group
Finland

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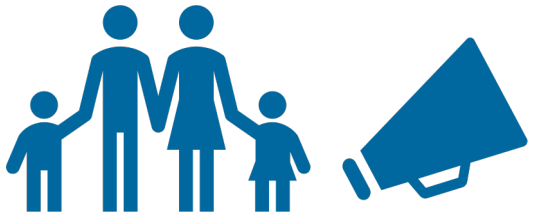
Main challenge categories of pediatric clinical research

Involvement & Awareness



Knowledge & Experience

Ethics & Regulations

Time & Timing

Training & Tools

Infrastructures & Networks

Enablers for sustainable research structures for pediatric CTs

- Availability of targeted funding instruments and funding options
- Flexibility and adjusted timing requirements of global Pharma Industry
- Innovative solutions for language differences and cultural and religious traditions
- Harmonized ethical understanding – with respect of national requirements
- Harmonized legal and regulatory guidance – also for pediatric CTs
- Increased knowledge and expertise for trial design and trial conduction
- Availability of commonly accepted guidelines and tools for trial conduction
- Established research networks and increased global collaboration
- Increased opportunity for patient´s and parent´s involvement

This was fast-info-food for the panelists and for the audience.

Now we´ll see and hear presentations, and more about these topics. In the panel discussion, there is time for Questions, Comments, Suggestions.

Lisine Tuyisenge, MD, MMed

Senior Consultant Paediatrician,
University Teaching Hospital of Kigali
Rwanda

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Infrastructure for conducting research in children

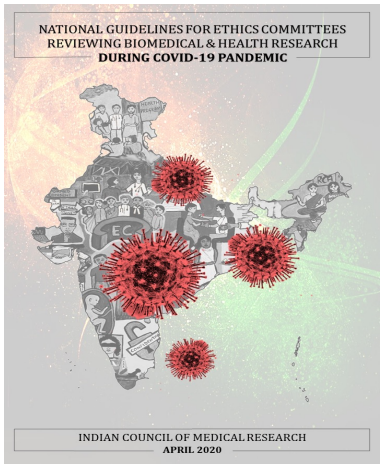
Dr. Vasantha Muthuswamy, India

General guidelines for research in children

- Research proposals should be scientifically sound
- Equation between the potential benefit and the risk or potential harm should be at least as favourable for the proposed research procedure as for the alternatives available to the children
- There should be benefit to children in general and, in most cases, to the individual child participant
- Team of investigators should have requisite expertise- one or more members of the team should be a paediatrician and/or have prior experience of conducting research involving children
- Research involving children should take into consideration the unique physiology, anatomy, psychology, pharmacology, social situation and special needs of children and their families
- Research must be conducted in a child-friendly environment, as far as possible
- In general, drugs should be tested for safety , pharmacokinetics, and at least initial indications of efficacy in adults established before they are tested in children
- It was considered till date appropriate to defer paediatric testing until substantial data are available on the safety and efficacy of a drug in adults
- However, there may be situations where studies involving children would be needed without prior adult studies (e.g. surfactant use in premature babies with RDS)

What happened during the Covid-19 Pandemic?

1. Lockdown has restricted movements – Children as well as adults were not able to reach the research site for new as well as ongoing studies.
2. Interventions could not be delivered initially, leading to interruption of studies. But later domestic delivery of therapeutic products adapted.
3. Different modes of Consent were undertaken to enroll adult research participants – telephonic, digital, etc.
4. Sponsors came up with alternate methods of recruitment, Consent procedures, community engagement, delivery of interventional products etc.
5. Researchers stopped working initially , gradually adopted the new methods.
6. ECs did not know how to conduct online meetings and give appropriate guidance to researchers and other stake holders .



A new norm was set up for effectively conducting research all over the world. New set of Guidelines were released by WHO and individual countries.

This new norm may be made to continue in future also for ensuring effective research enterprise.

Can these new norms be modified to suit child specific research according to the different age group and their capacity to give assent/consent

So what can be the new infrastructure needed for paediatric research?

1. A child friendly environment – Home is the best environment for a child.
2. Training of all stakeholders about the new norms: including the new Informed consent procedures Sponsor/ Researcher/ EC members.
3. Sensitisation of the regulators in all countries to think of including children in the beginning itself with appropriate safety guidelines so that there is no delay in responding to their needs as it happened during the current pandemic.
4. Community engagement and sensitisation on a regular basis to make them realise that for protection of children from any illness, they should participate in research from the beginning, of course with safety norms in position, since they are not small adults to apply the adult norms , but have different requirements at different stages of their life till they become an adult.
5. Networking and collaboration with existing networks to learn from each other to arrive at a global norm for paediatric research.

Marie Valentin, PharmD

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How do we create and sustain a network for the conduct of paediatric trials?

Planning phase

- Think paediatric early in the development (not an afterthought).
- Best us of available/existing data, use of paediatric extrapolation and optimize design of pediatric pharmacokinetic studies (model-based approaches), assess acceptability and palatability within PK trials.
- Promote best practices: include adolescents in adult trials, enroll all paediatric cohorts simultaneously rather than sequentially, systematically use standardized weight band dosing.
- Alignment of paediatric plans and early discussion with regulators.

How do we create and sustain a network for the conduct of paediatric trials?

Prioritization

- Critical first steps to enable a more targeted approach to research and development.

e.g. WHO PAediatric Drug Optimization (PADO) for HIV, HCV and TB (Priority List containing priority formulations to be investigated and developed in the next 3-5 years and Watch List with promising candidates)

Harmonization and alignment

- Sharing of paediatric data, public-private partnerships.
- Harmonization and alignment between partners.

Clinical Trial Oversight

- Build capacity in terms of ethic oversight.
- WHO Good Reliance Practices, make best use of regulatory resources.

(Annex 10 https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf)

How do we create and sustain a network for the conduct of paediatric trials?

WHO Paediatric Regulatory Network (PRN)
Global paediatric working network of regulators as a platform for exchange of regulatory information on paediatric medical products and to support the availability of quality-assured medical products for children
https://www.who.int/teams/regulation-prequalification/regulation-and-safety/regulatory-convergence-networks/paediatric-regulators

GAP·f
Global Accelerator for Paediatric formulations
WHO Hosted Network

Global Accelerator for Paediatric formulations: A collaboration platform supported by an innovative financing mechanism that promotes a faster, more efficient and more focused approach to paediatric clinical studies, formulation development and introduction.
https://www.who.int/initiatives/gap-f

The Rome Action Plan is a compilation of commitments by key stakeholders to accelerate research, development, registration, introduction and uptake of HIV & TB diagnostics and medicines for children living with HIV, with the ultimate objective of reducing morbidity and mortality among this high vulnerable group. https://www.paediatrichivactionplan.org/

How do we create and sustain a network for the conduct of paediatric trials?

Thank You

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Discussion

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