Advancing International Pediatric Clinical Research

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

October 6, 2021

6:00PM – 9:00PM 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

Peter Marks, M.D., Ph.D.

Director of the Center for Biologics Evaluation and Research (CBER) at the US Food and Drug Administration

MD, PhD: New York University
Internal Medicine and Hematology/Oncology training: Brigham and Women's Hospital

Clinical Director, Hematology, Brigham and Women's Hospital

Chief, Adult Leukemia Service, Yale University Chief Clinical Officer of Smilow Cancer Hospital.

2012: Joined FDA, Deputy Director, CBER
2016: Director, CBER

U.S. FOOD & DRUG ADMINISTRATION

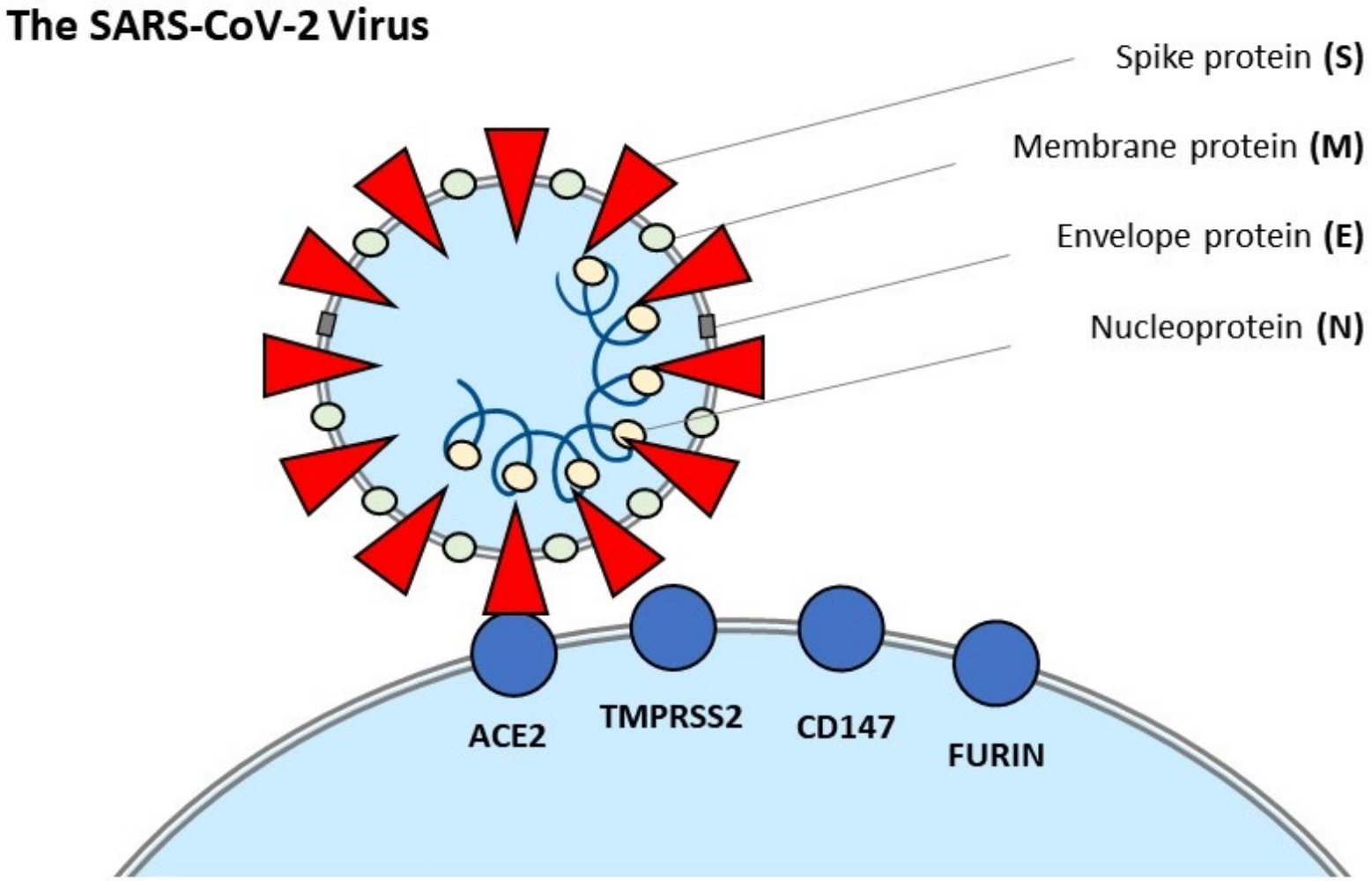
Development of Pediatric COVID-19 Vaccines

Peter Marks, MD, PhD

MRCT Center R13 Webinar

October 6, 2021

COVID-19 Vaccine Targets



U.S. Candidates – October 2021

- mRNA
  - BNT162b2 (Pfizer-BioNTech) – EUA granted Dec 11, 2020
    - Licensure for individuals 16 years of age and up granted to COMIRNATY on August 23, 2021
  - mRNA-1273 (Moderna) – EUA granted Dec 18, 2020

- Non-Replicating Viral Vector
  - Ad26.COV2.S (Janssen) – EUA granted Feb 27, 2021
  - ChAdOx1 (Astra Zeneca-Oxford)

- Protein Subunit
  - NVX-CoV2373 (Novavax)
  - MRT5500 (Sanofi-Translate Bio)

Biologics License Application (BLA)

- Biologics are licensed under section 351 of the Public Health Service Act
- Product must be safe, pure, potent
- FDA considers evidence from adequate and well-controlled clinical trials

Emergency Use Authorization (EUA)

- Put in place after 9/11 to ensure that potentially lifesaving medical products could be available to people in medical need when there is not an approved and available alternative

- The standard used is that the product “may be effective” and its “known and potential benefits outweigh the known and potential risks”

EUA for a COVID-19 Vaccine

- FDA based authorization on clear and compelling efficacy in large well-designed phase 3 clinical trials
- Careful evaluation of quality, safety, efficacy
- Public advisory committee meeting
- Enhanced post-deployment surveillance

COVID-19 Vaccines for Children

- Immuno-bridging from adults for effectiveness
- Need adequate safety data in each age group
- Current age groups (may vary depending on sponsor)
  - Age 12 to 15 years or 12 to 17 years
  - Age 5 to 11
  - Age 2 to 5
  - Age 6 months to 2 years

Pfizer Pediatric Demographics

Characteristic	Age 12-15 Vaccine (N=1131)	Age 16-25 Vaccine (N=537)	Age 12-15 Placebo (N=1129)	Age 16-25 Placebo (N=561)
Female	49.9%	52.5%	48.2%	52.0%
Mean Age (years)	13.6	19.4	13.6	19.6
Median Age	14.0	18.0	14.0	19.0
Black	4.6%	8.8%	5.0%	8.9%
Hispanic/Latino	11.7%	20.9%	11.5%	18.7%
Comorbidity (yes)	21.9%	23.5%	21.3%	25.7%

Pfizer Pediatric Immune Response

Study Group	12-15 Years N=190 GMT (95% CI)	16-25 Years N=170 GMT (95% CI)	GMT Ratio [12-15 Years/ 16-25 Years] (95% CI	Met Predefined Success Criterion
Vaccine	1239.5 (1095.5, 1402.5)	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Yes

Noninferiority is declared if the lower bound of the 2-sided 95% CI for the Geometric Mean Titer (GMT) Ratio is greater than 0.67

Pfizer Pediatric Efficacy

Endpoint	Vaccine 12-15 Years N=1005 Cases	Placebo 12-15 Years N=978 Cases	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence from 7 days after Dose 2 in subjects without prior SARS-CoV-2 infection	0	16	100.0 (75.3, 100.0)

Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period

Pfizer Pediatric Safety

Characteristic	Age 12-15 Placebo Dose 2 (N=1078)	Age 12-15 Vaccine Dose 2 (N=1097)	Age 16-25 Vaccine Dose 2 (N=488)
Injection site pain	17.9%	78.9%	77.5%
Fatigue	24.5%	66.2%	65.6%
Headache	24.4%	64.5%	60.9%
Muscle pain	8.3%	32.4%	40.8%
Chills	6.8%	41.5%	40.0%
Joint pain	4.7%	15.8%	21.9%
Fever	0.6%	19.6%	17.2%

COVID-19 Vaccines for Children

- Adolescents 12 years and older are being dosed as adults right now under EUA and in vaccine trials
- Special considerations in children under 12 years
  - Determination of appropriate dose
  - Duration and number of children for safety follow-up
- The various companies are conducting clinical trials
- Expecting data for one candidate in early October
- FDA will move rapidly to evaluate the data

Reflections on Pandemic Vaccines

- Pediatric development started in earnest following the emergency use authorization of the vaccines
  - Was that the right timing?
  - Could development have started sooner?
    - Immediately following the demonstration of effectiveness in phase 3
    - Immediately following emergency use authorization of the vaccines
- Consider integrating pediatric countermeasure development into any future pandemic response plan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ADMINISTRATION

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

Moderator
Dr. Steven Joffe
University of Pennsylvania
USA

Guest Speaker
Dr. Robert W. Frenck, Jr.
Cincinnati Children's Hospital Medical Center
USA

Guest Speaker
Dr. Calvin Ho
University of Hong Kong
Hong Kong

Guest Speaker
Dr. Isao Miyairi
Department of Pediatrics,
Hamamatsu University School of Medicine
Japan

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

Steven Joffe, MD, MPH

Art and Ilene Penn Professor
Interim Chair
Department of Medical Ethics and Health Policy

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

Initiating Clinical Trials in Children When is the Right Time?

Steven Joffe, MD, MPH

Art and Ilene Penn Professor
Interim Chair
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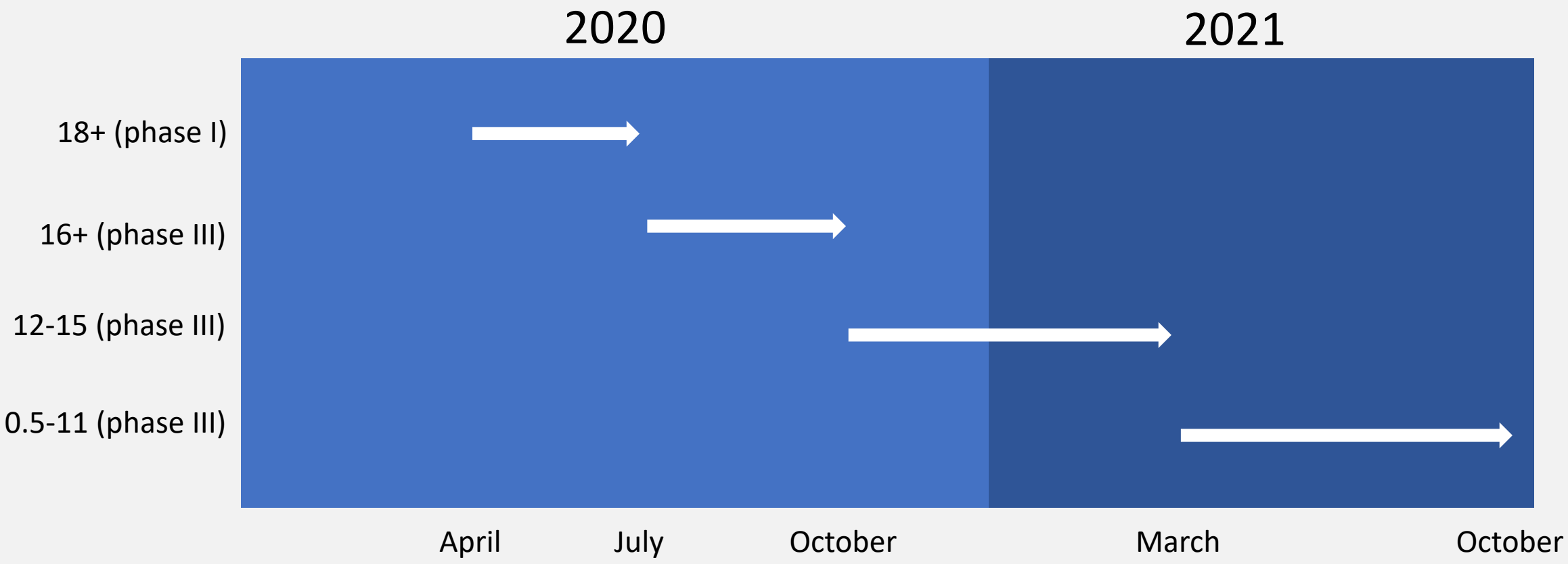
Perelman School of Medicine
University of Pennsylvania

Multi-Regional Clinical Trials Symposium
October 6, 2021

Timeline of Pfizer/BioNTech COVID vaccine trials



Speed/safety tradeoffs

	Potential Benefit	Potential Risk
Move fast	Get effective preventive & therapeutic interventions to children quickly	

Speed/safety tradeoffs

	Potential Benefit	Potential Risk
Move fast	Get effective preventive & therapeutic interventions to children quickly	Expose children in research to unnecessary risk of harm

Speed/safety tradeoffs

	Potential Benefit	Potential Risk
Move fast	Get effective preventive & therapeutic interventions to children quickly	Expose children in research to unnecessary risk of harm
Move slowly	Take longer than necessary to get effective preventive & therapeutic interventions to children	

Speed/safety tradeoffs

	Potential Benefit	Potential Risk
Move fast	Get effective preventive & therapeutic interventions to children quickly	Expose children in research to unnecessary risk of harm
Move slowly	Take longer than necessary to get effective preventive & therapeutic interventions to children	Minimize chance of exposing children in research to risk of harm

Regulatory challenges for beginning pediatric vaccine trials*

- Must offer prospect of benefit (if significant risk)
- Prospect of benefit must justify risk
  - Affected by likelihood that children will develop illness and severity of illness if they do get sick
- The less adult data you have, the less confident you can be about the prospect of benefit and the amount of risk

*Specifics may vary between countries

Practical challenges for beginning pediatric vaccine trials

- Does disease occur in both adults & kids (& is it similar)?
  - If yes, can assess efficacy in adults before studying in kids
  - If no, can look for safety, pharmacokinetics, etc., in adults, but eventually need to test in kids without the benefit of adult data
- How big a problem is the disease for kids?
  - If not a big problem, studying in kids is less urgent
- Where will you run the trials? Who will run them?
  - Investigators, expertise, and sites likely differ

Our panel

Robert W. Frenck, Jr, MD
Professor of Pediatrics
Division of Infectious Diseases
Cincinnati Children's Hospital
University of Cincinnati

Calvin Ho, JSD MSc LLM FRSPH
Associate Professor
Department of Law
Co-Director
Centre for Medical Ethics & Law
University of Hong Kong

Isao Miyairi, MD, PhD
Chair, Department of Pediatrics
School of Medicine
Hamamatsu University

Thank you!

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MULTI-REGIONAL CLINICAL TRIALS

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

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A PERSPECTIVE FROM HONG KONG & SINGAPORE

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MULTI-REGIONAL CLINICAL TRIALS

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

CONSIDERATIONS

- Ethical and Regulatory requirements
  - Ethics approval
  - Clinical trial approval
  - Emergency Use Authorisation
- Consent
  - Fair Offer
  - Best interests
- Favourable Risk vs Benefit Threshold
  - Severity of outbreak
  - Access to vaccines
  - Underlying conditions
- Context: Hong Kong SAR and Singapore

REGULATORY LANDSCAPE: HONG KONG

In Hong Kong, a clinical trial of pharmaceutical products is regulated under the Pharmacy and Poisons Ordinance, which defines a “pharmaceutical product” as:

(1) Any substance or combination of substances that:

(a) Is presented as having properties for treating or preventing disease in human beings or animals; or

(b) May be used in, or administered to human beings or animals with a view to:

(i) Restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action; or

(ii) Making a medical diagnosis; and

(2) Including an advanced therapy product.

The Pharmacy and Poisons Board of Hong Kong has adopted the definition of “clinical trials” provided by the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in its Good Clinical Practice (GCP) guideline.

REGULATORY LANDSCAPE: SINGAPORE

In Singapore, all clinical trials of therapeutic products, Class 2 cell, tissue and gene therapy products (CTGTPs) and medicinal products (e.g. Chinese Proprietary Medicines, health supplements that are being investigated for the treatment or prevention of disease) are regulated by the Health Sciences Authority.

Regulatory framework depends on product type:

- Therapeutic products and Class 2 CTGTPs: Health Products Act and Health Products (Clinical Trials) Regulations
- Medicinal Products: Medicines Act and Medicines (Clinical Trials) Regulations

The principles of the ICH-GCP are applied.

Like Hong Kong, ethics approval must be obtained independently of regulatory approval. Principles set out in the Declaration of Helsinki of the World Medical Association are applied.

HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

01 MAR 2021

CLINICAL TRIALS GUIDANCE

SAFEGUARDS AND CONSENT REQUIREMENTS IN VULNERABLE TRIAL PARTICIPANTS

GN-IOCTB-06 Rev. No. 003

Figure 2. Guide to Assessing Acceptable Levels of Risk and Burden in Relation to the Benefit

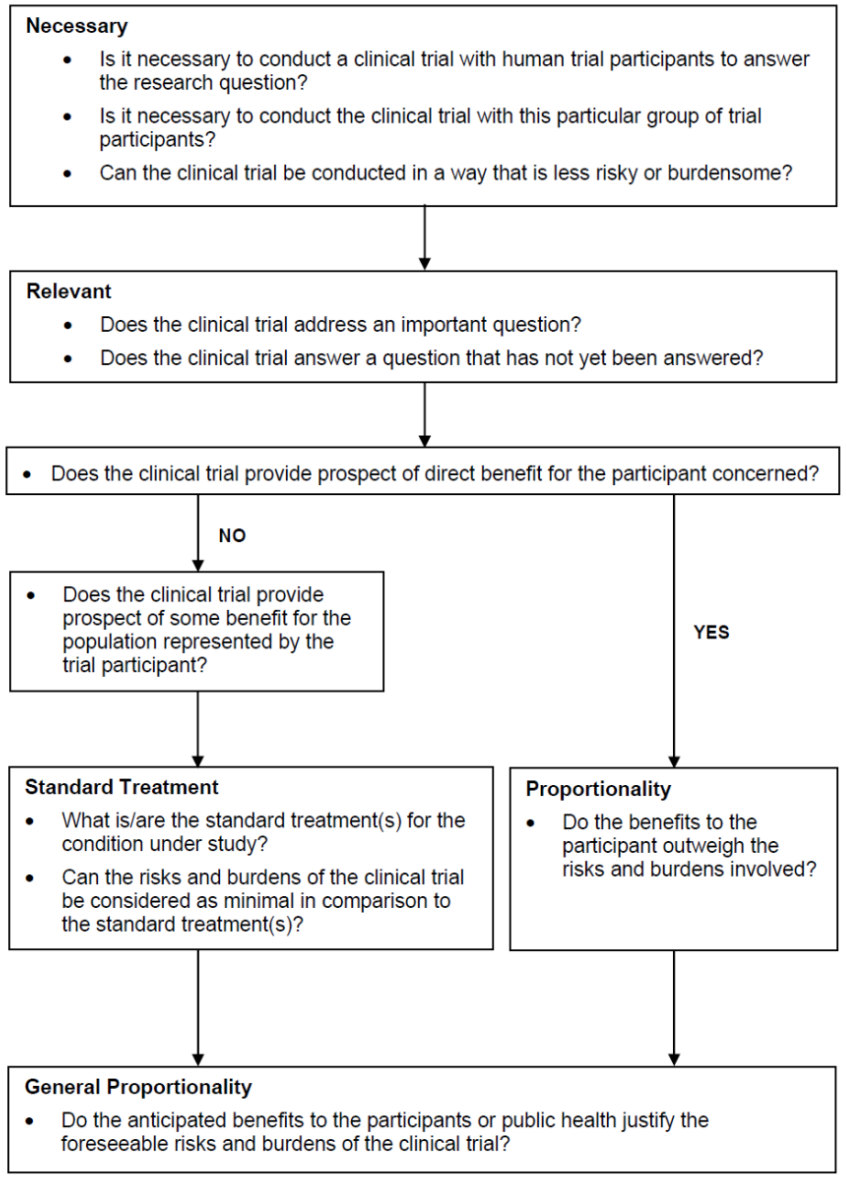
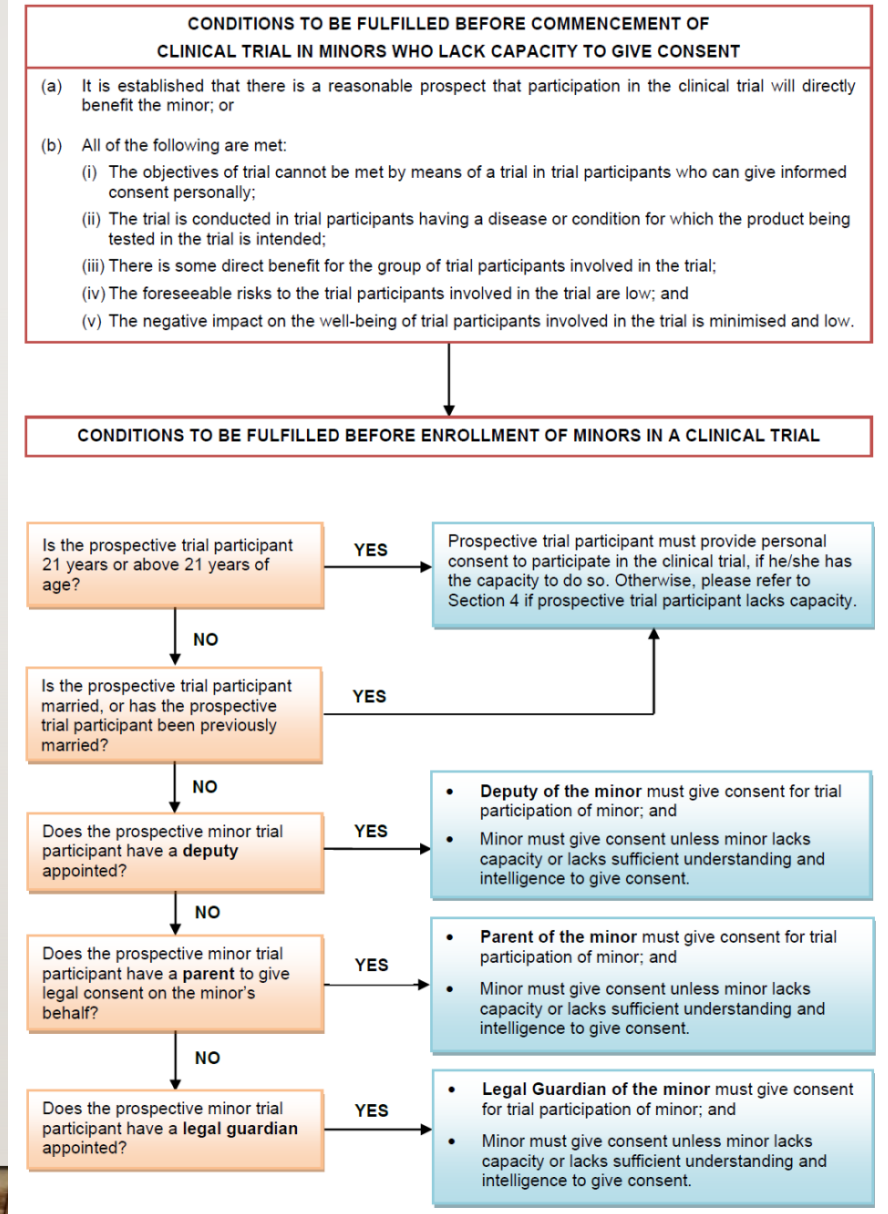


Figure 3. Flowchart on safeguards and consent requirements in minors



In Hong Kong, the age of majority is 18 years under the Age of Majority (Related Provisions) Ordinance

Figure 7. Safeguards and Consent Requirements for clinical trials in emergency situations (Part 1)

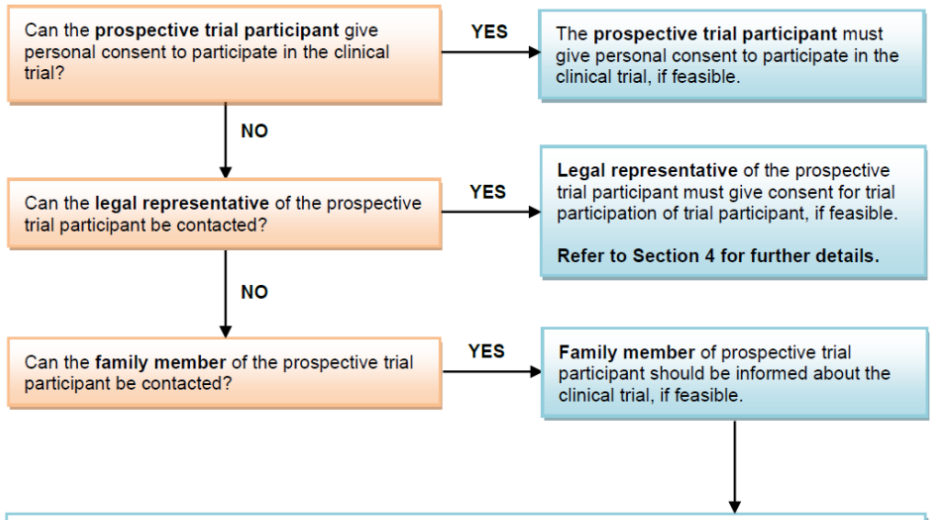
CONDITIONS TO BE FULFILLED BEFORE COMMENCEMENT OF CLINICAL TRIAL IN EMERGENCY SITUATIONS

(i) The clinical trial is subject to the requirements for a Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC);

(ii) The Institutional Review Board (IRB) has reviewed and approved the circumstances in which consent need not be obtained; and the procedures for obtaining consent and/or informing family members at the earliest feasible opportunity, in the trial; and

(iii) Written certification by the Principal Investigator and 2 independent specialists of the conditions described in Section 5.2 have been submitted to HSA.

CONDITIONS TO BE FULFILLED BEFORE ENROLLMENT OF TRIAL PARTICIPANTS IN A CLINICAL TRIAL IN EMERGENCY SITUATION

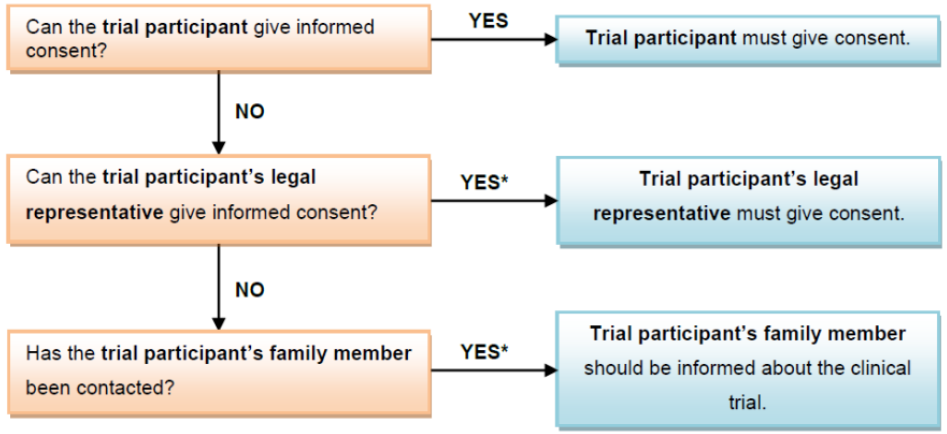


If consent cannot be obtained from the prospective trial participant or prospective trial participant's legal representative, and no family member has objected to the prospective trial participant's trial participation (if feasible), the prospective trial participant may be enrolled in the clinical trial if an investigator and 1 independent specialist provide written certification of the conditions described in Section 5.3.

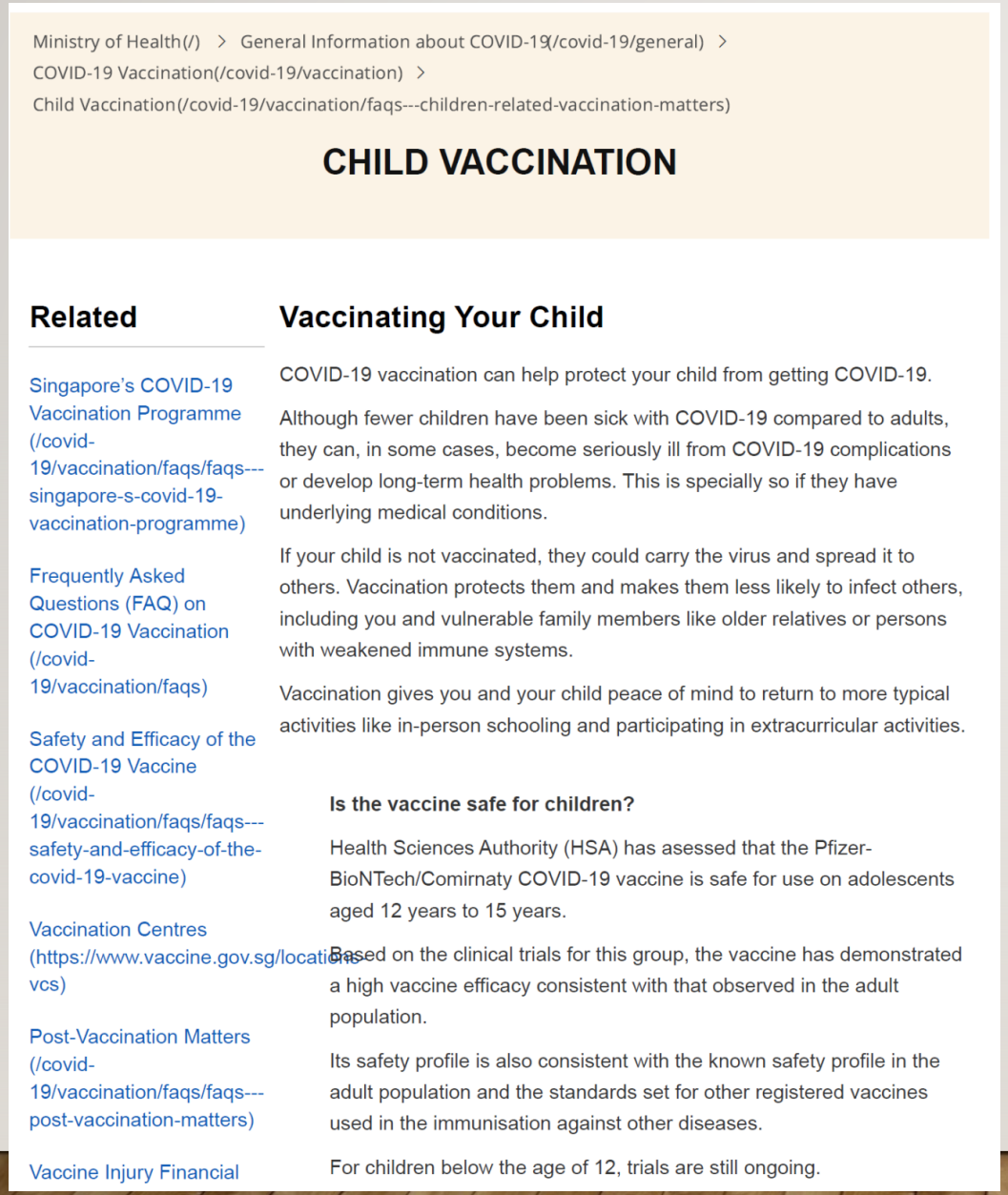
Figure 7. Safeguards and Consent Requirements for clinical trials in emergency situations (Part 2)

AFTER ENROLLMENT OF A TRIAL PARTICIPANT IN A CLINICAL TRIAL IN EMERGENCY SITUATION

- The Principal Investigator must ensure that informed consent is obtained from the trial participant when he/she regains capacity, at the earliest feasible opportunity.
- If the trial participant is unable to consent, the Principal Investigator must make reasonable effort to contact the trial participant's legal representative, to ensure that informed consent is obtained from the trial participant's legal representative at the earliest feasible opportunity.
- If informed consent cannot be obtained from the trial participant or his/her legal representative, the Principal Investigator must make reasonable effort to contact a member of the trial participant's family to inform the family member about the clinical trial at the earliest feasible opportunity.



*** Despite the consent from the trial participant's legal representative or no objection from the family member, the Principal Investigator must continue to make reasonable effort to obtain consent from the trial participant or the trial participant's legal representative, as the case may be.**



Ministry of Health(/) > General Information about COVID-19(/covid-19/general) > COVID-19 Vaccination(/covid-19/vaccination) > Child Vaccination(/covid-19/vaccination/faqs---children-related-vaccination-matters)

CHILD VACCINATION

Related

Singapore's COVID-19 Vaccination Programme (/covid-19/vaccination/faqs/faqs---singapore-s-covid-19-vaccination-programme)

Frequently Asked Questions (FAQ) on COVID-19 Vaccination (/covid-19/vaccination/faqs)

Safety and Efficacy of the COVID-19 Vaccine (/covid-19/vaccination/faqs/faqs---safety-and-efficacy-of-the-covid-19-vaccine)

Vaccination Centres (https://www.vaccine.gov.sg/locations-vcs)

Post-Vaccination Matters (/covid-19/vaccination/faqs/faqs---post-vaccination-matters)

Vaccine Injury Financial

Vaccinating Your Child

COVID-19 vaccination can help protect your child from getting COVID-19.

Although fewer children have been sick with COVID-19 compared to adults, they can, in some cases, become seriously ill from COVID-19 complications or develop long-term health problems. This is specially so if they have underlying medical conditions.

If your child is not vaccinated, they could carry the virus and spread it to others. Vaccination protects them and makes them less likely to infect others, including you and vulnerable family members like older relatives or persons with weakened immune systems.

Vaccination gives you and your child peace of mind to return to more typical activities like in-person schooling and participating in extracurricular activities.

Is the vaccine safe for children?

Health Sciences Authority (HSA) has asessed that the Pfizer-BioNTech/Comirnaty COVID-19 vaccine is safe for use on adolescents aged 12 years to 15 years.

Based on the clinical trials for this group, the vaccine has demonstrated a high vaccine efficacy consistent with that observed in the adult population.

Its safety profile is also consistent with the known safety profile in the adult population and the standards set for other registered vaccines used in the immunisation against other diseases.

For children below the age of 12, trials are still ongoing.

Vaccination for children above 12 years of age in Singapore

Regulatory approval for vaccination of children under 12 years of age will depend on clinical trials data in the US, and regulatory approval from the FDA.

South China Morning Post

News

Coronavirus: Hong Kong children aged 12 to 15 can begin booking vaccination slots from Friday, get jabs on Monday

1372 words
10 June 2021
scmp.com
SCMCOM
English

* Shots available to new age group via individual or group bookings at vaccination centres or through outreach services at schools where enough staff, students and parents sign up

* Primary school pupils may become eligible for the inoculation programme once clinical data shows it is safe, government says

Hong Kong children as young as 12 can book Covid-19 vaccination [https://www-scmp-com.eproxy.lib.hku.hk/knowledge/topics/coronavirus-vaccine/news] slots beginning on Friday and receive the jabs as early as Monday while primary school pupils may become eligible for the shots once clinical data shows it is safe.

The step revealed by the government on Thursday meant an additional 240,000 residents would be covered by the programme, taking the total to just over 90 per cent of the city's population of 7.5 million, but the drive remained sluggish and only about 15 per cent of people were fully inoculated.

"Vaccination is vitally important in protecting adolescents and children from Covid-19 infections, stopping its spread in the community and can raise the whole of society's immunity," civil service minister Patrick Nip Tak-kuen said, adding the next three months would be the "critical stage".

Do you have questions about the biggest topics and trends from around the world? Get the answers with SCMP Knowledge [https://www-scmp-com.eproxy.lib.hku.hk/knowledge], our new platform of curated content with explainers, FAQs, analyses and infographics brought to you by our award-winning team.

Nip urged all unvaccinated residents to receive at least a first shot by late August as he noted the city's 29 community vaccination centres were scheduled to close in late September.

At the same time as the government was struggling to energise the programme ahead of that deadline, authorities were succeeding in tamping down the spread of the virus, with only two new infections emerging on Thursday, one imported from Britain and the other from Mauritania. Fewer than five people tested preliminary-positive for the virus.

As the pandemic stabilises, the prospects for an eagerly awaited travel bubble with Singapore continue to improve, and the Hong Kong government said both sides would review the plans early next month. The city state is also widening its inoculation drive and has sharply brought down its daily caseload, although both sides admitted talks must proceed carefully.

Under the revised rules, Hong Kong children aged between 12 and 15 would be able to receive their jabs in three ways: via individual bookings from Friday 9am onwards at the 24 community vaccination centres offering the BioNTech vaccine, by group vaccinations at the same centres starting from June 21, or through outreach services at schools from June 28 at the earliest, but a minimum number of staff, students and parents must have agreed to be vaccinated.

Nip said vaccinations could be arranged for a school if at least 300 people, including staff and students' parents, were keen on the outreach service. If only a few dozen people showed an interest, they could make use of the group booking service at the vaccination centres and transport would be arranged, he added.

South China Morning Post

News

Coronavirus: what Hong Kong parents need to know about the one-dose BioNTech vaccine policy for adolescents

Elizabeth Cheung and Rachel Yeo

1186 words
17 September 2021
scmp.com
SCMCOM
English

* Experts say protection from one vaccine shot should be sufficient for youngsters in Hong Kong, where risk of Covid-19 infection is low

* Those travelling to high-risk places should still get both doses to boost immunity

Hong Kong's adolescents will now only need one dose [https://www-scmp-com.eproxy.lib.hku.hk/news/hong-kong/health-environment/article/3148893/coronavirus-hong-kong-experts-recommend] of the German-made BioNTech vaccine, after scientific committees under the Centre for Health Protection said on Wednesday that such a move would help reduce the risks of myopericarditis – an inflammation in the heart.

Adolescents aged 12 and above have been allowed to receive the BioNTech vaccine from June 14 this year, although the minimum age threshold for the Sinovac jab remains at 18.

The Post looks at the details and implications of the recommendation.

Do you have questions about the biggest topics and trends from around the world? Get the answers with SCMP Knowledge [https://www-scmp-com.eproxy.lib.hku.hk/knowledge], our new platform of curated content with explainers, FAQs, analyses and infographics brought to you by our award-winning team.

Click to view image. [https://cdn.i-scmp.com/sites/default/files/d8/images/methode/2021/09/16/ced89aa2-16da-11ec-ab69-f2bfe93835cf_1320x770_215329.jpeg]

Can one dose of BioNTech provide enough protection, or should recipients wait for the age limit for the Sinovac jab to be lowered?

Experts of the scientific committees said one dose of the vaccine would be sufficient to protect youngsters living in Hong Kong, where the risk of Covid-19 infection remains low.

Professor Lau Yu-lung, chairman of the scientific committee on vaccine preventable diseases, said one dose of vaccine could already offer more than 80 per cent effective protection from severe conditions caused by the coronavirus.

Lau said the protection offered by one or two doses would not differ too much, given that the chances of young people developing serious illnesses after contracting Covid-19 were very low, compared with the elderly.

According to a local study published in late June in the Hong Kong Medical Journal, the level of antibodies induced by one dose of BioNTech vaccine was similar to that by two doses of the Sinovac jab. While the amount of antibodies does not directly reflect the strength of protection, scientists believe there is more evidence showing that higher levels generally correspond to greater immunity.

SOME CONSIDERATIONS

- Public health justification to commence vaccination in children above 12 years of age
  - Local clinical trials? Acceptable risk-benefit threshold?
  - Lowering age to below 12 years of age?
    - Access to vaccines not in issue
    - No significant local transmissions in Hong Kong, but only over 50% adult population vaccinated with first dose
    - Significant local transmissions in Singapore, but only 80% adult population vaccinated
- Clinical trial design
  - Placebo use?
  - Safety
- Evidential threshold for emergency use authorisation and full authorisation?


Thank you

Isao Miyairi, MD, PhD

Chair, Department of Pediatrics
School of Medicine
Hamamatsu University
Japan

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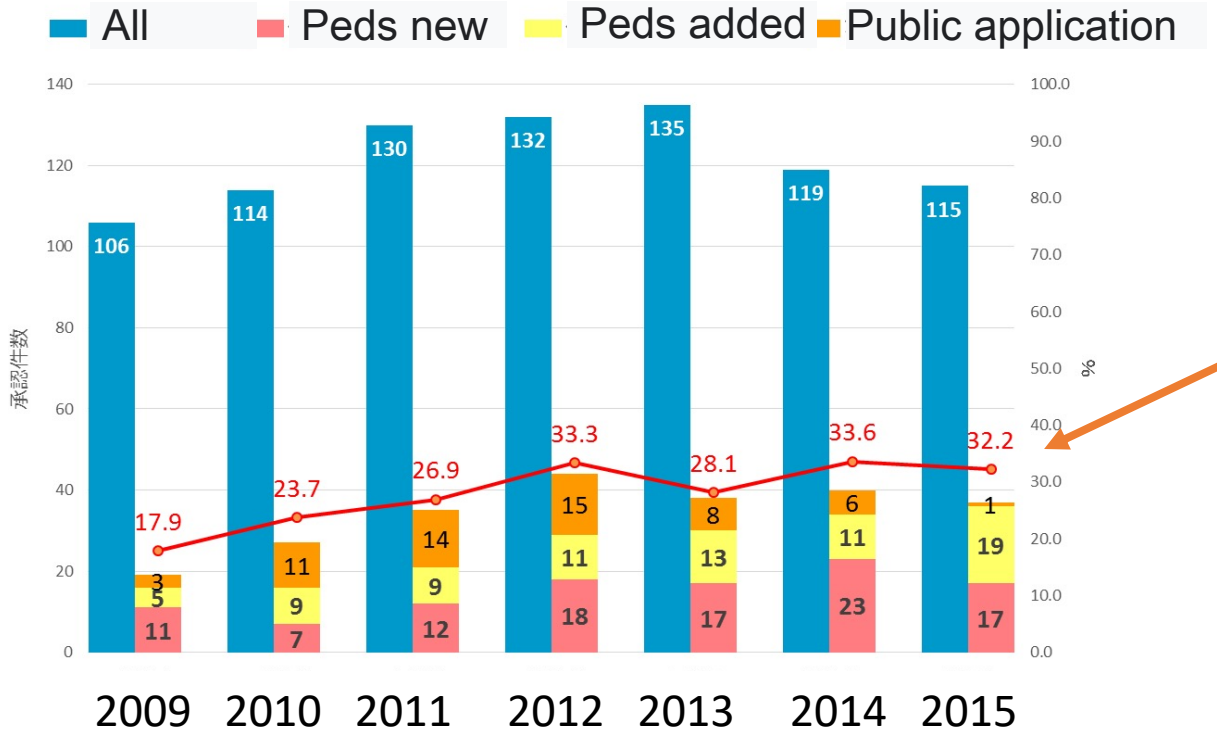
MULTI-REGIONAL CLINICAL TRIALS

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

Problems and lessons learned from COVID-19 (Japan)

- There is generally a drug lag before pediatric formularies reach Japan
  - Pediatric study (investigation) plan is NOT mandatory in Japan
  - Japan is often not included in global clinical trials



Data from PMDA

Efforts have been made and rate of pediatric formulary approval is improving somewhat

Problems and lessons learned from COVID-19 (Japan)

- Clinicians were caught by surprise when the COVID-19 vaccine "suddenly" became available to children 12 years-old and over in Japan, which was based on Special Approval for Emergency (article 14-3 of the PMD Act)

Approval for adults (2 months)

Dec 2020 U.S. FDA approval

18 Dec 2021 Submission by Pfeizer Japan

21 Feb 2021 Approval

Special survey specific for COVID-19 vaccines

- ✓ 100% follow-up survey in very early-phase of vaccination campaign.
- ✓ Symptoms and illnesses for a certain period (about 1 month) after vaccination are collected in approx. 10,000 – 20,000 HCWs.

Approval for children 12 through 15 years (3 weeks)

10 May 2021 U.S. FDA expands authorization after clinical trial

1 June 2021 Approved for kids in Japan

No specific survey for kids in Japan

Information: Courtesy of SATO Junko, Ph.D.
Director of Office of International Programs
Pharmaceuticals and Medical Devices Agency (PMDA)

Problems and lessons learned from COVID-19 (Japan)

- There was hesitancy among clinicians because there was not much communication between the government and clinicians
- Race/ethnicity was not represented in this trial.

- There is a need to involve multiple countries in pediatric clinical trials from the beginning
- There is a need for coordination among regulatory bodies (FDA, EMA, PMDA) to use common definitions and endpoints for drug approval to expedite global trials.
- Always room for better communication

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

Moderator
Dr. Alysha Croker
Health Canada
Canada

Guest Speaker
Dr. Collin Hovinga
Institute for Advanced Clinical Trials for Children (iACT), University of Texas at Austin
USA

Guest Speaker
Dr. Mario Alanis
Center for Innovation in Regulatory Science (CIRS)
Mexico

Guest Speaker
Dr. Hidefumi Nakamura
National Center for Child Health and Development
Japan

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

Alysha Croker, PhD

Manager of the Office of Pediatrics
and Patient Involvement
Health Canada
Canada

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

Collin Hovinga, PharmD, MS, FCCP

Senior Vice President, Clinical and Scientific Development at the Institute for Advanced Clinical Trials for Children (I-ACT for Children); Associate Professor, University of Texas at Austin.

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U.S. Lessons learned-Collin Hovinga, I-ACT for Children

Only if we understand, can we care. Only if we care, we will help. Only if we help, we shall be saved. .-Jane Goodall

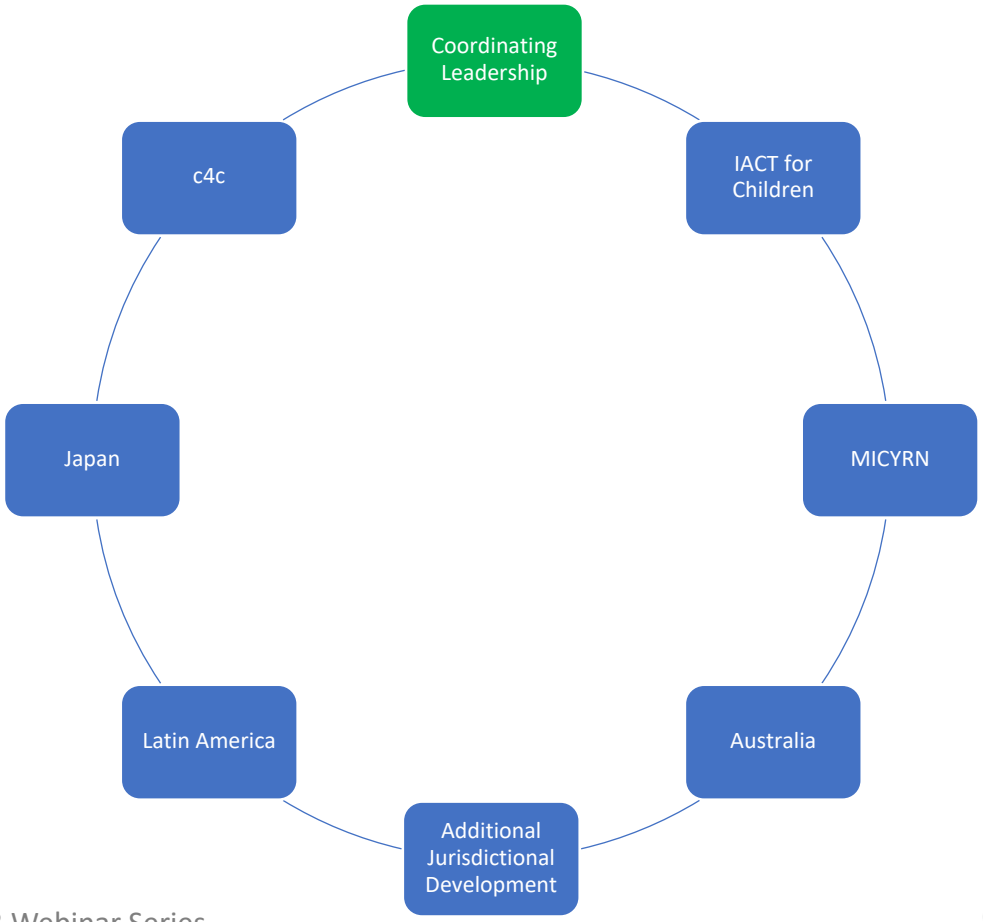
Most clinical research sites have recovered, not all at 100% capacity

- Positive's
  - Novel use of remote services (telemedicine/IP delivery/remote monitoring, consenting)
  - Rapid contract/budget/IRB reviews
  - Highlighted the need for communication and collaboration among stakeholders
- Negative's
  - *Acute impact*:
    - Uncoordinated response to determine how and which research should/can continue
    - COVID19 trial design/deployment-chaotic
  - *Late impact:*
    - More caution at sites/experts to engage in research activities
    - Significant reduction in overall research pediatric activity
    - Workforce loss, turnover

Future Recommendations-Collin Hovinga I-ACT for Children

Every individual matters. Every individual has a role to play. Every individual makes a difference.-Jane Goodall

Global Pediatric Network (aka Research UN)



- Interoperable global network derived from existing infrastructure
- Charged with developing additional worldwide infrastructure
- Multi-national/jurisdictional leadership
  - Site/academic, regulatory, sponsor and patient representation input
- Improve efficiencies and minimize cost by reducing unnecessary reinvention
- Diversify funding strategies

Future Recommendations-Collin Hovinga I-ACT for Children

We have the choice to use the gift of our life to make the world a better place-or not to bother.-Jane Goodall

- Current internetwork collaborations
  - Study feasibility and site selection
  - Site standards
  - Metrics and quality improvement
  - Educational and training
  - Therapeutic area public meetings
- Future state
  - Consultations-experts
  - Real world data
    - Safety
    - Feasibility
  - Parent-Patient engagement (PPI)
  - Recruitment and retention
  - Inventory of strengths and needs
  - Shared strategic goals and accountability from multi-stakeholders

Mario Alanís, PhD

Senior Advisor, Center for Innovation in Regulatory Science, (CIRS)
Mexico

CIRS Centre for Innovation in Regulatory Science

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Background

Latin America and other emerging countries

- Very low share of pediatric clinical trials
- Cost advantage
- Population opportunity
- Insufficient infrastructure
- COVID-19 – missed opportunity

Infrastructure include many aspects

- Scientific and methodological capacity
  - Protocols
  - Data analysis
  - Training
- Collaboration and funding
  - Fragmented research
- Regulatory compliance
  - Pediatric pharmacovigilance
  - GCP and other pediatric guidelines / recommendations

Summary and recommendations

- There is high potential for CT in Latin America, particularly for pediatric, given the population structure.
- Important to develop awareness campaign of benefits: CT can bring important revenue and health benefits
- Adopting mentorship programs and funding
- Countries should aim to align to best regulatory practices
- A focused effort may be needed to maximise a country's clinical trial activities

    Agencies are eager to receive training
    Interested parties could support development of infrastructure
    There is mistrust of studies with only phase 2 studies.

Hidefumi Nakamura, MD, PhD

Director, Clinical Research & Development, Department of R&D Supervision, National Center for Child Health and Development, (NCCHD), Tokyo
Japan

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Network Activities in Japan

Japan Pediatric Society
Drug Development Network (JPeDNet) and
Pediatric Clinical Trial Network, Japan

Hidefumi Nakamura, MD, PhD

Chairman

Committee on Pharmaceutical Affairs, Japan Pediatric Society

Director for Clinical R &D

Department of Research and Development Supervision

National Center for Child Health and Development, Tokyo, JAPAN

Japan Pediatric Society
Drug Development Network (JPeDNet)

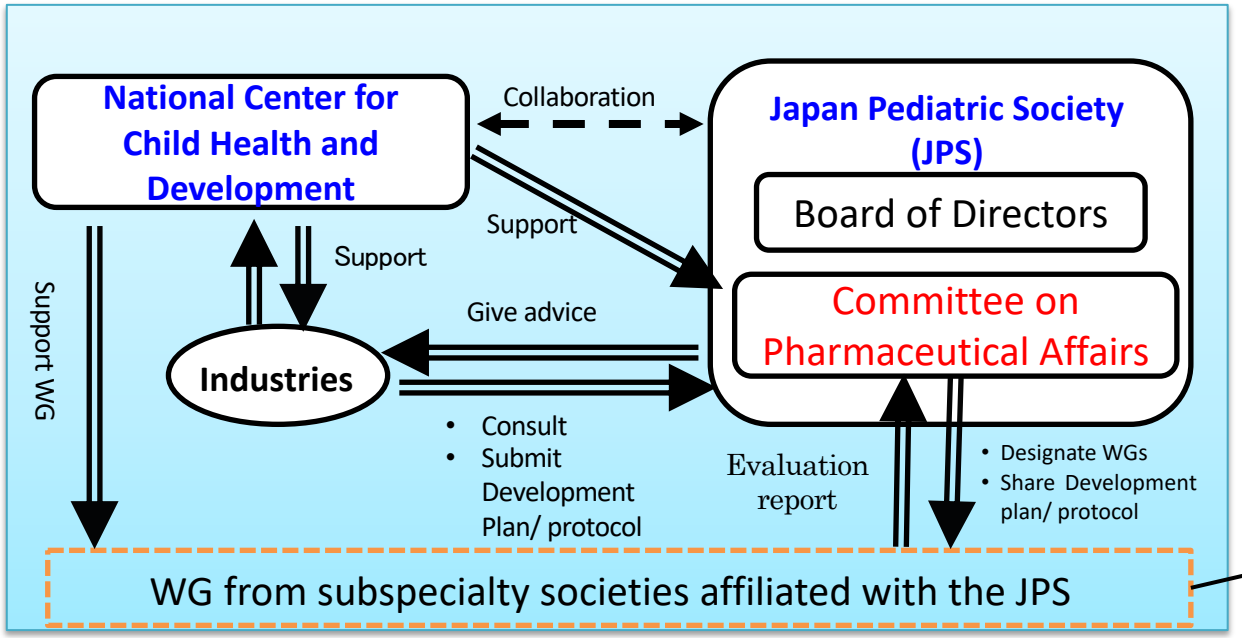
Funding

- ✓ 2017-2019 Japan Agency for Medical Research and Development (AMED)
- ✓ 2020- The Ministry of Health, Labor and Welfare (MHLW)

Core function

- ✓ 17 Working Groups for consultation and advice
  - Specialists knowledgeable in clinical trials and/or in pediatric subspecialty
  - Clinical research coordinators/ nurses from Pediatric Clinical Trial Network, Japan give advice on practical issues.
  - Additional working group if necessary.

Japan Pediatric Society
Drug Development Network (JPeDNet)



During 2017-2019、cumulative total of 62 specialists (cumulative total of 17 WGs) evaluated and gave advice for 13 medicines/indications

Working groups in Pediatric subspecialty societies	
1	Neonatology
2	Cardiology
3	Neurology
4	Hematology/ Oncology
5	Allergy
6	Inherited Metabolic Diseases
7	Nephrology
8	Endocrinology
9	Infectious Diseases
10	Pulmonology
11	Gastroenterology, Hepatology and Nutrition
12	Psychosomatic Pediatrics
13	Psychiatry and Neurology
14	Oriental Medicine
15	Rheumatology
16	Dentistry
17	Surgery

Give advice on protocols, conduct of trials, and recruitment of patients

Practical advice and collaboration

- JPS Stimulates active involvement of member clinicians in drug development
- JPS Selects the best specialists in Japan as WG members who can
  - give advice on feasibility, better indication, schedule, inclusion and exclusion criteria
  - recommend sites with good performance
- Per request, specialists can also join the kick-off meeting and facilitate discussion on better performance/ enrollment
- JPS can facilitate recruitment of patients
  - by disseminating the information to all possible subspecialty societies
  - in collaboration with other networks including PCTN Japan
    - Subspecialty networks include networks for pediatric cardiology, pediatric hematology/ oncology (JCCG) and pediatric nephrology.

Pediatric Clinical Trials Network (PCTN) Japan

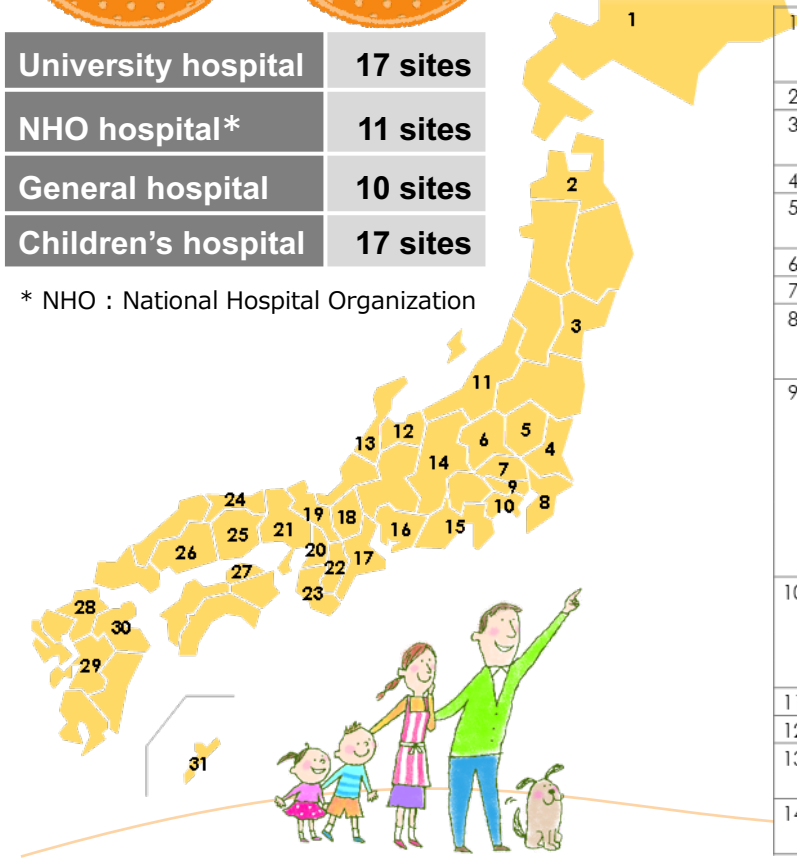
- ✓ Quick feasibility survey and sites recommendation
- ✓ Efficient conduct of clinical trials
- ✓ Central ethics review possible for thirty-nine institutions (marked with ●)
- ✓ Standardization of cost calculation and certain procedures
- ✓ Standardized informed consent and assent form available
- ✓ Training and Education program for clinical research coordinators / nurses
- ✓ Funded partially by the Ministry of Health, Labor and Welfare

55 member medical institutions

6,800 pediatric hospital beds

University hospital	17 sites
NHO hospital*	11 sites
General hospital	10 sites
Children's hospital	17 sites

* NHO : National Hospital Organization



1	● Hokkaido Medical Center for Child Health and Rehabilitation
	◎ Hakodate Municipal Hospital
2	● NHO Hirosaki National Hospital
3	● Miyagi Children's Hospital
	◎ Tohoku University Hospital
4	● Ibaraki Children's Hospital
5	● Dokkyo Medical University Hospital
	● Jichi Medical University Hospital
6	● Gunma Children's Medical Center
7	● Saitama Children's Medical Center
8	● Chiba Children's Hospital
	◎ Tokyo Women's Medical University Yachiyo Medical Center
9	● National Center for Child Health and Development
	● Tokyo Metropolitan Children's Medical Center
	◎ The University of Tokyo Hospital
	◎ Tokyo Medical And Dental University, Medical Hospital
	◎ Juntendo University Hospital
10	● Kanagawa Children's Medical Center
	● Yokohama City University Hospital
	● NHO Sagamihara National Hospital
	◎ Tokai University Hospital
11	◎ Niigata University Medical & Dental Hospital
12	◎ Toyama University Hospital
13	◎ Kanazawa Medical University Hospital
	● NHO Kanazawa Medical Center
14	● Nagano Children's Hospital
	● NHO Shinshu Ueda Medical Center

15	● Shizuoka Children's Hospital
16	● Japanese Red Cross Nagoya Daiichi Hospital
	● Aichi Children's Health and Medical Center
	● Aichi Developmental Disability Center Central Hospital
17	● NHO National Mie Hospital
18	● Shiga Medical Center for Children
19	● University Hospital Kyoto Prefectural University of Medicine
	● NHO Minami Kyoto Hospital
20	● Osaka Women's and Children's Hospital
	● Osaka City General Hospital
	● Takatsuki General Hospital
	● Osaka Habikino Medical Center
21	● Hyogo Prefectural Kobe Children's Hospital
	◎ Kobe University Hospital
22	◎ Nara Prefecture General Medical Center
23	◎ Wakayama Medical University Hospital
24	● Tottori University Hospital
25	● NHO Okayama Medical Center
	◎ Kawasaki Medical School Hospital
26	● Hiroshima Prefectural Hospital
	● NHO Fukuyama Medical Center
	● Fukuyama City Hospital
27	● NHO Shikoku Medical Center for Children and Adults
28	● Fukuoka Children's Hospital
	◎ Kyushu Hospital
29	● NHO Kumamoto Medical Center
30	◎ NHO Beppu Medical Center
31	● Okinawa Prefectural Nanbu Medical Center & Children's Medical Center

Office of PCTN, Japan located at the National Center for Child Health and Development

Discussion

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