Global Clinical Trials Forum

20-21 November 2023
WHO Science Division, Geneva, Switzerland

Z1/Z2 and online https://who.zoom.us/s/93888610500
Program overview

Session 1: Global and regional clinical trial experience
Progress update on the WHA75.8 implementation
Key discussions and initiatives in regions and countries

Session 2: Barriers and priority actions to strengthen clinical trial ecosystem
Clinical trials in context of epidemics and pandemics
Funding models, regulatory and ethics streamlining
Informative, impactful clinical trials and sustainable research capabilities strengthening

Session 3: Enabling clinical trials that provide high quality evidence on interventions
Enable trials in pregnant women and children, and in primary healthcare and intensive care
Patient and community engagements

Session 4: Collaboration on the way forward
Private sector’s support
Breakout group work: actions on the way forward

Presentations, round table discussions, Q&As, share your opinions on Slido, and join the group works (in-person only)
Background
Mapping
Consultations
Key themes emerging
In the pandemic a few large trials generated much useful evidence and changed global practice.
In the pandemic, 1000s of trials were low quality
Key problem statements with the current ecosystem

- Regulatory systems involving multiple approval bodies may be overly complex and **not always proportionate to risk**; as a result of this complexity, good trials are too expensive, take too long, ... costing many lives
  - How can we advance **the benefits of compelling well-designed trials** while maintaining appropriate safeguards?

- **Many trials do not contribute to high quality evidence**: *NB most uninformative trials are likely in high income countries, because most trials are in high income countries*
  - Most health policy/guidelines recommendations are not based on high certainty evidence (Intern Med J 2020 Jan;50(1):30-37) and therefore **most decision-making is not based on high certainty evidence**
  - There are **insufficient “levers” to prevent badly designed trials** that will not answer the scientific question

- **Major gaps in clinical infrastructure and capabilities exist in many countries with high disease burdens**; existence of capacities in high income countries does not guarantee efficient conduct of informative trials
**Guidance**
- TAG constituted
- Public consultation Deadline Sep 22
- Likely to be finalized in 2024
- Online training materials to be developed in coordination with ICH, Ethics, Funders

**Mapping**
- Networks
- Funding
- National Regulations
- Sites/institutional capacities

**Consultations**
- 4th Member State consultation completed
- Private sector consultations: Geneva, May & Kigali October 2023
- Regional consultations: PAHO Oct 4-5, AFRO Oct 17-18, SEARO, Nov 10-11, EMRO Nov 14-15
- Global forum meeting with stakeholders (clinical researchers, ethics, regulatory, funders, patient, community organizations, private sector)
Single collated WHO clinical trials website created

1. Existing relevant WHO and TDR guidance and resources
2. Existing relevant non-WHO guidance
3. Collation of 42 non-WHO initiatives identified relevant to WHA 75.8
4. 23 Inputs to public consultation where permission was provided to post the entire submission
5. Collated list of over 100 Clinical trial networks for endemic (NCD and ID) and epidemic diseases
6. Status of regulatory bodies related to clinical trials oversight
7. Global information on clinical trial activity, eg ICTRP and R&D observatory

Website: Implementation of the resolution on clinical trials (who.int)
WHO asked for inputs on status quo, and examples of good practices, improvements needed, Q4 2022

• 273 inputs were received, of which 53 were from Member States, including government agencies from the health and non-health sectors, and 63 were from non-State actors
• Where WHO has received permission to make the full responses public, they have been made available on the WHA 75.8 website (1)
• The responses have been summarized in the report to WHO’s Board (2)
• A longer supplementary report is also available (3)

1 https://cms.who.int/our-work/science-division/research-for-health/implementation-of-the-resolution-on-clinical-trials
3 https://www.who.int/publications/m/item/supplementary-report-on-implementing-wha-resolution-75.8-on-strengthening-clinical-trials-to-provide-high-quality-evidence-on-health-interventions-and-to-improve-research-quality-and-coordination
Mapping of clinical trials by disease area and region
(PRELIMINARY)

- Clinical trials were mapped to WHO regions as well as the disease areas neoplasms, cardiovascular diseases, and infections
- Disease areas were defined using Medical Subject Headings (https://www.ncbi.nlm.nih.gov/mesh/)

- 2018-2022
11 key aspects of clinical trial governance were identified.

A comprehensive search of legislation, standards, and guidance documents was conducted, sourced from:
- Governmental and Ministry of Health websites
- US International Compilation of Human Research Standards 2021
- Clinregs.com
- Legal and academic databases

Source text from the associated legal document was captured to confirm if the country has a legislative requirement for each clinical trial aspect.

Legislation from 89 WHO member countries has been located.

**Breakdown by WHO regions:**
- Africa – 20
- Americas – 15
- Eastern Mediterranean – 3
- Europe – 36
- South-east Asia – 6
- Western Pacific – 9

**Breakdown by World Bank income groups:**
- High – 40
- Middle – 16
- Low-middle – 12
- Low – 21

Legislation for an additional 39 countries has been identified, although direct text access remains unavailable.
Mapping of clinical trials legislation

Percentage of countries with legislation for each of the 11 clinical trial aspects

- **63%** of the 89 countries mandate **registration in a registry** before commencing clinical trials.
- **37%** of the 89 countries possess legislation **requiring the reporting of results** following completion of the clinical trial in a registry.
- **98-99%** of countries have legislation relating to **informed consent**, **regulatory approval** and **ethical oversight**.
Background Information on Stakeholder Survey

• Survey was developed in collaboration between the WHO and The Global Health Network (TGHN), a WHO Collaborating Centre for research information sharing, e-learning and capacity development. Survey management and analysis was conducted by TGHN.

• Live for a 2 week period, Aug-Sep 2023.

• Developed in 4 languages (English, Spanish, French, Portuguese).

• Distributed via WHO and TGHN networks and communication channels (mail lists, social media, online platforms etc).

• **Global Response Total**: 2,953
Key points from inputs received on structure/existing guidance

- Highlighting recent existing guidance/guidelines that WHO should complement / build on including:
  - ICH E6 R3
  - ICH E8 R1
  - CIOMS guidances including one focusing on resource – limited settings, directly relevant on resource limited settings
  - Good Clinical Trials Collaborative Guidance, directly relevant on quality

- Sections in WHO high level guidance on:
  - Design and implementation
  - Strengthening the clinical trial ecosystem
  - Addressing underrepresented populations
  - Recommendations on roles of different stakeholders
Timeline for WHO guidance

- Draft reviewed by external Technical Advisory Group Q2
- Draft after advisory group review for consultation with stakeholders Q3
- Draft posted on WHO website during public consultation Q2-Q3
- Input from several hundred stakeholder groups received
- **Public and further stakeholder consultations Q4**
- Subsequent development of tools to support capacity development
  - Online training modules
2023

Mapping

Guidance Development

Consultations

2024

Implementation tool Development

Support for capacity development

- National capacities in NRAs
- Ethics committees
- Research institutions
- Patient/Community engagement in research
- Inter-agency harmonization/coordination
Key areas of focus for capacity development going forwards according to inputs received

- Developing capabilities for research sustainably, linked to health systems, and kept “warm” through ongoing well designed clinical research; moving away from a “vertical” to a “horizontal” approach while keeping the best aspects of the vertical.
- Enabling international collaborations
- Improving capacities and efficiency in regulatory and research ethics systems
- Developing prioritization processes to highlight key needs, and focus good quality trials on the key needs
- Ensuring scientific validity and social value of research
- Patient and community engagement norms in clinical trials
- Supporting newer models for RCTs (including integration into healthcare, adaptive, digital)
- Improving efficiency and coordination between elements of the trials ecosystem
- Logistics/importation barriers major impediment for some international trials
Major emerging trends in clinical trials

- Digital vs paper records: any guidance that still focuses on paper records is out of date
- Data collection via digital devices: regulatory structures need to enable this
- Understanding of need for greater patient and community engagement: major focus of inputs from stakeholder survey
- Drive toward equity, inclusion and fairness
- Integration of trials into healthcare delivery: many inputs indicate there is major scope here
- Applications of AI and Large Language Models:
- Gene editing and other aspects of genomics...
Lack of representativeness in trials databases: MAJOR ISSUE!

• Under-representation of anyone not from western European ancestry
• Women
• Pregnant and lactating women
• Children
• Antimicrobial resistance
• Emerging ID
• Rare Diseases
• Neglected Tropical Diseases

• There may be some confusion in some cases about protecting the vulnerable vs need for inclusion of underrepresented populations.
Conclusion

Key guidance on best practices for clinical trials – enabling the following:

• **Sustainable clinical research capacities** that enable ongoing clinical research that meets local and global needs:

• **Effective prioritization** for use of these capacities

• Addressing **under-represented populations**

• **Risk proportionate** approaches to well-designed and well-implemented trials.
Funding Acknowledgement
Survey support
Evolution of stakeholder engagement in strengthening the African Clinical Trial Ecosystem

2022-2023
Workshop on Optimizing Efficiency and Impact in the African Clinical Trial Ecosystem

Held on 16-18 May 2023 in Cape Town

- Organising agencies:
  - Africa CDC, AUDA-NEPAD, BMGF, & EDCTP
- Sponsors:
  - BMGF & EDCTP
- Attendance:
  - 60 participants from national, regional, and global stakeholders including researchers, regional organisations, WHO, industry, private sector, community organisation representatives and research funders
- Main areas of discussion as part of the ecosystem
  - Clinical trial design
  - Capacity development
  - Networks
  - Digital technologies
  - Financing
  - Regulatory and ethics oversight
  - Community and public engagements
WHO AFRO regional workshop on strengthening Clinical Trials

The Clinical Trials Ecosystem – Perspectives from the African region

People

- Scientists
- Clinical Research Allied Professionals (e.g. lawyers, data analysts)
- Communities e.g. CTC
- Capacity building -
- Community engagement – Pre, during Post trial engagement – sharing, access
- Career development
- Governments
- Funders
- Donors

Systems

- Sponsors - AVAREF
- Agencies -
- Programs e.g. DAC etc
- Regulators - external regulators
- Ethics Boards
- Grant management
- Functional health systems – subnational and community level
- Academic programs
- Data repositories or observatories etc e.g. Pan African Clinical Trials Registry (PACTR)
- Governance – policy and decision makers
- Clinical frameworks and legal frameworks (especially for health law)
- Coordination mechanism for funders and alignment with national priorities
- Partnerships (PPPs) – mechanisms that can engage private sector and negotiate partnerships well

Infrastructure

- Clinical research networks
- Clinical research Centres
- Hard infrastructure – e.g. offices, labs, IT equipment, software, internet connectivity, power-electricity, electronic masterfiles (eMTF)
- Digital infrastructure for data repositories or observatories

Regional Coordination

(of African governments, Funders (local or external) and donors to align) - e.g. Africa CDC, AM, AUDA NEPAD, WHO AFRO etc)
Catalysis & Prioritisation

Held on 17-18 October 2023 in Lusaka, Zambia
Examples of investments already existing in the African Ecosystem

Examples form EDCTP and Clinical Trials Community (CTC)
Overcoming imbalances?

- Special programmes for ethics and regulation capacity development
- Special programmes for including countries left behind
- Special programmes to build human capacity
- Special programme to build culture of networking and cooperation

Without doing business differently progress will either be slow or with no impact

EDCTP covering 38 sub-Saharan African countries host recruitment sites of EDCTP-funded collaborative clinical studies.

EDCTP-supported ethics and regulatory projects are being conducted in 37 sub-Saharan African countries.
Overcoming imbalances?

- Special programmes for ethics and regulation capacity development
- Special programmes for including countries left behind
- Special programmes to build human capacity
- Special programme to build culture of networking and cooperation

Without doing business differently progress will either be slow or with no impact

EDCTP funded Regional Networks of Excellence: 24 African countries and 7 European countries

EDCTP 401 Fellowship training and retention programme
Encouraging trend of clinical trials in Africa

Number of Clinical Trials Per Year per Country in Africa (Top 20)
Encouraging trend of clinical trials in Africa

Experience in Africa: TB & Malaria Research

Research Centres with experience in TB Research
• 87 Sites
• 21 Countries

Research Centres with experience in Malaria Research
• 350 Sites
• 35 Countries
Next steps

- Phased implementation of coordination at Africa CDC (2023-2028)
- Aligning funders and donors (starting from EDCTP Forum in Paris, Nov 2023)
- Presentation and global consultation at WHO – HQ, Nov 2023
- Presentation at key African events e.g. CPHIA2023, in Nov 2023
The current status of the clinical trials ecosystem in Bangladesh, India, and in southeast areas

Dr. Firdausi Qadri & Prof. Jacob John
Summary of status of clinical trials in SEARO

- WHO South-East Asia Region (SEARO) is home to over a quarter of the world’s population and consists of 11 member countries.

- Bangladesh, Bhutan, the Democratic People’s Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste are member countries.

- The World Health Organization (WHO), uses a set of indicators/tools for the evaluation of national regulatory systems of vaccines or medical products (authorization, vigilance, market surveillance and control, licensing, inspection, laboratory testing, clinical trials oversight, and NRA lot release, quality, and risk management system.

**Maturity level 4:** Republic of Korea; (Regulatory system at an advanced level)

**Maturity level 3:** India, Thailand, and Indonesia (Stable, and integrated regulatory system)

**Maturity Level 2:** Bangladesh, Nepal, Sri Lanka. Bangladesh is very close to getting to Maturity Level 3 by mid 2024 (Partially performs essential regulatory functions)

**Maturity level 1:** some elements of regulatory systems exist
Summary of status of clinical trials in Bangladesh

According to WHA75.8, the steps for strengthening clinical trials are to provide evidence on health intervention and improve research with the ethical implications as well as the regulatory limitations and barriers.

Bangladesh

• The Directorate General of Drug Administration (DGDA) is the regulatory authority for clinical trials in Bangladesh.

• DGDA ensures the legal and ethical framework, protocol approval, authorizing investigational products (IPs), safety and rights of trial participants, GCP inspection, and confirms the trials are adequately designed and have scientific objectives.

• DGDA requires documents for CT approval: approved Protocol by the independent ethics committee, Investigator’s Brochure, Informed consent, agreements between the sponsor and the contract research organization (CRO), Curriculum vitae(s), Good manufacturing practice (GMP) certificate of the IP, Certificate of Analysis of IP, documentation of funding, case record form (CRF), Standard operating procedures (SOPs), and Good clinical practice (GCP) certificate of PI and team members.

• DGDA also provides approval of the CRO.

• Until now 113 clinical trials and 18 CROs have been approved by DGDA in Bangladesh.
Clinical Trials Methods in Bangladesh

The IRB committees

- Are formed by 9-13 members (lawyer, female representative, biostatistician, religious leader, and research methodologist); ~3 months is needed for the review process; fees include 2% of the approved research project

- All the local ethical committees must be registered by BMRC

Registration, Auditing, and Accreditation

Renewal of the registration every 5 years, and report to BMRC on a regular basis.
Clinical Trial Life cycle

- Ethics Committee Approval
- Regulatory Authority Approval
- Clinical Trial Agreement
- Comply with GCP (Participant enrollment, informed consent, safety management, data recording/reporting)
- Sponsor Responsibility (Monitoring, Auditing, data recording/reporting, permit monitoring, auditing, and inspection)
- Interim and annual progress reports and the final report should be submitted
- Data and Safety Monitoring Board
- Insurance of the trial participant against risk (injury or death)
- Quality Assurance/Quality Control
- The clinical trials should be adequately monitored
- Electronic Data Processing System
- Record management
**Barriers**

*key barriers from Bangladesh perspective*

1. Lack of adequate Legal and Administrative Framework or expert CRO related to the requirement, process, and facilitation of clinical trials

2. Lack of infrastructure, capacity, and knowledge to conduct clinical trials

3. Lack of Funds or financial support to conduct clinical trials

4. Lack of coordination between different stakeholders related to clinical trials

5. Lack of awareness among the patients and common people regarding clinical Trials

6. Bangladesh is a generic drug manufacturer. This is why clinical trials are not needed by pharmaceutical companies. Even bioequivalence studies are not compulsory. Only non-inferiority trials for bio-similar products and a few bioequivalence studies are being sponsored.
## Priority actions in Bangladesh

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adequate law, rules and guidelines has to be in place for conduct</td>
<td>It is essential to generate confidence in the system for all stakeholders</td>
<td>It will ensure high standard trials and also facilitate systematic and</td>
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<tr>
<td>of clinical trials</td>
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<td>time bound activities</td>
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<tr>
<td>2. Increase infrastructure, capacity and knowledge of the researchers</td>
<td>Updated knowledge and technology is very important for this highly technical</td>
<td>It will ensure high standard Clinical trials</td>
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<td>&amp; regulators through funding and training</td>
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<tr>
<td>3. Make a business model which will be sustainable by leveraging</td>
<td>Continuous generation of fund is crucial for sustainability of the research</td>
<td>It will ensure continuous financial support</td>
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<tr>
<td>Researcher and Industry collaboration</td>
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<tr>
<td>4. Harmonization of ethical and regulatory guidelines to align all</td>
<td>Harmonization of requirement is very important on relying clinical trial</td>
<td>It will decrease duplication of Clinical trial as well the cost</td>
</tr>
<tr>
<td>stakeholders</td>
<td>data of different regions</td>
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<tr>
<td>5. Increase awareness of Clinical trials to patients and common people</td>
<td>Awareness is crucial to eliminate misconceptions related to Clinical trials</td>
<td>Patients will be empowered and will take decision voluntarily</td>
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<tr>
<td></td>
<td>and increase participation</td>
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<tr>
<td>6. Increase utilization of digital technology in clinical trials</td>
<td>Facilitate faster decision making and improves data integrity</td>
<td>It will improve the quality of Clinical trials</td>
</tr>
</tbody>
</table>
Summary of status of clinical trials in India

- CDSCO oversees drug licensure and clinical trials.
  - DTAB makes recommendations under the Drugs & Cosmetics Act
  - Subject Expert Committees review licensure and trials
- Health Ministry Subcommittee approval
- 70+ CROs supporting research
- Multiple government departments promote clinical trials & and research
  - DHR & ICMR
  - DBT / DST/DAE
- The pharmaceutical industry-sponsored clinical trials are limited to a few urban healthcare facilities in tier 1 & and 2 cities
- Community trust and participation – a work in progress
Barriers

Some barriers from an Indian (academic) perspective

• Trained, experienced investigators and research staff limited to a few centers
  • Lack of core funding for clinical researchers and research infrastructure outside of the industry

• Lack of representativeness
  • Most clinical trial capacity is at large tertiary care settings in cities.
  • DHR & National Medical Council are attempting to rectify this

• Quality and Oversight
  • Ethics committees and external monitoring require strengthening
  • Internal SOPs / QA – variable quality; CROs are expensive!

• Regulatory pathways – multiple approvals required
  • Do not have clear timelines and transparent decision-making pathway

• Lack of designs that incorporate participant choice and address contextually important outcomes efficiently

• Costs and challenges with disseminating research findings

• Community trust, engagement, and participation a significant challenges for preventive trials
## Priority actions

### Perspectives from academic research in India

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Build research networks</strong> with capacity in design, conduct, analysis and dissemination focusing on under-represented areas</td>
<td>Outside of the industry, there are no clear career pathways for aspiring clinical researchers, and clinical research infrastructure is expensive.</td>
<td>Well networked, research teams primed for high impact collaborative research</td>
</tr>
<tr>
<td>2. <strong>Simplify regulatory pathways</strong>, providing single window for application, clear timelines and tracking applications online</td>
<td>Regulatory hurdles deter clinical researchers from initiating or collaborating on internationally funded trials</td>
<td>Timely transparent regulatory approval process that decreases regulatory burden</td>
</tr>
<tr>
<td>3. Build capacity of IRBs and CROs to provide oversight without making trials prohibitive.</td>
<td>While compliance to GCP and ensuring quality are paramount, Well-equipped CROs and their protocols are prohibitively resource intensive</td>
<td>GCP compliance at a cost that is affordable, and at sites that reflect real-life situations</td>
</tr>
<tr>
<td>4. <strong>Enhance stakeholder and community engagement and trust</strong> by building long-term partnerships</td>
<td>Participation in clinical trials is often transactional. Building community and other stakeholder trust requires long-term engagement.</td>
<td>A community that is confident of the trial processes and safety nets and actively volunteers to co-develop / test relevant solutions</td>
</tr>
<tr>
<td>5. <strong>Develop methods</strong> and training for clinical investigators to answer the most relevant question for the context</td>
<td>Conventional methods and outcome measures are often proxies that do not adequately answer real-world questions</td>
<td>Newer methods that are both efficient and address real-world impact be developed</td>
</tr>
</tbody>
</table>
Summary of discussion

Discussions

- Infrastructure
- Clinical Monitoring
- GCP inspection
- Sponsor
- Bioequivalence study
- WHO prequalification
- CRO technical and hospital facility
- Gaps identification

Follow-up actions planned in the region

Reaching maturity level 4

1. Law, regulation, and rules should be implemented in the SEARO countries for the conduct of clinical trials
2. Infrastructure, capacity, and knowledge of the researchers & and regulators through funding and training
3. Make a business model that will be sustainable by leveraging Researcher and Industry collaboration
4. Harmonization of ethical and regulatory guidelines to align all stakeholders
5. Increase awareness of Clinical trials to patients and common people
6. Utilization of digital technology in clinical trials
Thank you
Clinical Trials Strategy in Singapore

Li Yang HSU
National University of Singapore
Summary of status of clinical trials in Singapore

Singapore has met most of WHA75.8 and seeks to further improve the efficiency of conducting clinical trials. It is also collaborating in and establishing regional clinical trial networks to address national and regional health priorities.

• April 2021 – Clinical Trials Strategy adopted by Health & Human Potential Exco in Singapore
  1. Address existing weaknesses and roadblocks for clinical trials
  2. Talent development for clinical trials
  3. Develop funding mechanisms/support for clinical trials
  4. Establish a National Clinical Trials Strategy Committee and a National Coordinating Body
  5. Build on identified priority areas for trials
  6. Adopt future-oriented support pillars and value platforms
TOP 6 THERAPEUTIC AREAS OF CLINICAL TRIALS CONDUCTED IN SINGAPORE (2016 – 2021)

Clinical Trial Phases

Clinical Trial Phases by Numbers

Clinical Trial Phases by Percentages
1. Slow contracting time between funders/institutions

2. Slow ethics approval and clearance

3. Slow site start-up turnaround time

4. Lack of regional clinical trial experience
• Support investigator-initiated trials to improve the healthcare system
• Enhance the clinical trials ecosystem in Singapore
• Attract more industry-sponsored trials to Singapore
Master Clinical Trials Agreement (2022)

- Common clauses including (i) Institution(s) and Sponsor's obligations and responsibilities, (ii) Payment, (iii) Confidentiality and (iv) Data protection and privacy have been agreed upon in the MCTA, thus speeding up the agreement review process.

- Single template for sponsors to engage PHIs for multi-center trials.
- Useful for sponsors (new biotechs/start-ups) with no prior agreements with PHIs.

- MCTA clauses can be individually adopted to supplement existing agreements.
- The MCTA is available in MS Word document for ease of customization.
Regional Clinical Trial Networks (from Singapore)

• Majority are cancer research networks

• Two infectious diseases research networks (relatively new)
  • ADVANCE ID
  • PREPARE

• Hurdles:
  • Funding of networks and trials
  • Contracting and capacity building
ACORN-HAI Epidemiological Survey

3100 patients enrolled = 1078 VAP + 2022 BSI
Conclusion

• Deliberate strategy for clinical trials in Singapore

• Multiple barriers experienced, even now. Largely due to contracting and start-up of studies

• Regional clinical trial networks are attractive and important. Challenging to establish from Singapore.

• Happy to share further details/experiences.
Thank you
Preparing for the next pandemic: what we do in China

Dr Bin Cao
China-Japan Friendship Hospital, Beijing, China
Outbreak of COVID-19
Early COVID trials – Jan 2020

December 30 2019
Cluster of pneumonia of unknown origin reported by China National Health Commission

20 days

First patient enrolled
Lopinavir/ritonavir RCT

Original Article
A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial
Current COVID trials – 2022-2023

Lack of a platform trial, we still test antivirals one by one by using traditional RCT

https://en.chinacdc.cn/research/achievements/202307/t20230720_267982.html
Preparing for our next threatening

2009-2019
China CDC

2015-2017
CAP-China
to increase clinical trial capability, and strengthen clinical trials policy frameworks, particularly in developing countries

2023, 22-29th week
Preliminary pathogen surveillance of ARI by CAP-China
CAP-CHINA VISON

CAP-China network 1.0 (2019)
Only report viral pathogens in CAP

CAP-China network 2.0 (2026)
Surveillance of common pathogens ILI and LRTI

CAP-China network 3.0 (2030)
Surveillance + trial

Cross-section
China surveillance
Platform plus basket trial

Flu, rsv, hcov, hmpv et al
Patient characters
Acknowledgement
First WHO Global Clinical Trials Forum

EMRO

Faiez Zannad
Emeritus Professor Cardiology and Therapeutics
Clinical Scientist and Clinical Trialist
Inserm, Université de Lorraine.
Disclosures

- Participation in advisory boards or clinical trials oversight committees with 89Bio, Applied Therapeutics, Bayer, Boehringer, BMS, CVRx, Cardior, Cereno pharmaceutical, Cellprothera, CEVA, KPB, Merck, Novartis, NovoNordisk, Owkin, Pfizer, Otsuka, Roche Diagnostics, Servier, US2.2

- Equities at Cardiorenal and Eshmoun Clinical research

- Founder of Cardiovascular Clinical Trialists Forum.

Ex-Advisor at MOH, Tunisia (2014-2015)
Projected change from 2015 to 2040 in percentage of disease burden due to noncommunicable diseases (NCDs), by score on the health system capacity index

Thomas J. Bollyky, Tara Templin, Matthew Cohen, and Joseph L. Dieleman HEALTH AFFAIRS VOL. 36, NO. 11:
DAPA-HF - A global trial
4,744 patients  20 countries

North America
- Canada  223
- USA  454

Western Europe
- Denmark  99
- Germany  186
- Netherlands  135
- Sweden  68
- UK  62

Central/Eastern Europe
- Bulgaria  266
- Czech Rep.  210
- Hungary  250
- Poland  290
- Slovakia  166
- Russia  422

Asia-Pacific
- China  237
- India  237
- Japan  343
- Taiwan  141
- Vietnam  138

Latin America
- Argentina  297
- Brazil  520
Results in HICs are not necessarily generalizable to LMICs

<table>
<thead>
<tr>
<th>Income Group</th>
<th>Hospitalizations per total person-years</th>
<th>Age- and sex-standardized hospitalization rate per 100 person-years (95% CI)</th>
<th>Deaths per total person-years</th>
<th>Age- and sex-standardized mortality rate per 100 person-years (95% CI)</th>
<th>Relative risk of death, model 1b HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-income countries</td>
<td>434/3682</td>
<td>11.7 (10.5-12.9)</td>
<td>716/4032</td>
<td>19.1 (17.6-20.7)</td>
<td>2.49 (2.25-2.68)</td>
</tr>
<tr>
<td>Lower-middle-income countries</td>
<td>2177/12954</td>
<td>17.3 (16.5-18.1)</td>
<td>2205/15847</td>
<td>15.7 (15.0-16.4)</td>
<td>1.98 (1.85-2.11)</td>
</tr>
<tr>
<td>Upper-middle-income countries</td>
<td>2238/9784</td>
<td>22.6 (21.7-23.6)</td>
<td>1188/12638</td>
<td>9.3 (8.8-9.9)</td>
<td>1.09 (1.01-1.17)</td>
</tr>
<tr>
<td>High-income countries</td>
<td>4429/14340</td>
<td>29.9 (28.9-30.8)</td>
<td>1926/21511</td>
<td>7.8 (7.5-8.2)</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

LIC = Lower rate of Hospitalization and Higher rate of Death in patients with heart failure

More people live in Middle East + Africa, but fewer trials contributed:

- Middle East Africa: 20% of world population
- 6.5% of Clinical trials

Doubling the current share of 6% would create 21000 jobs, 3 Billion $ income and provide cutting edge therapies to 60,000 new patients.

Source: Clinicaltrials.gov
LMICs (Eastern EU + Asia, NOT Africa) drive enrolment in heart failure trials due to higher enrolment rate (MRI data base > 40,000 pts enrolled in > 20 studies)
The depressingly stagnant growth of clinical trials in Middle East - Africa
Industry view ROW as the next frontier in global health business, but not necessarily in global health research.
Clinical research in Africa and Middle East: roadmap for reform and harmonisation of the regulatory framework and sustainable capacity development

Interventions should be systemic and coordinated interventions, including:

1. Equitable research collaborations with international organisations, favouring institutional international collaboration, beyond personal relationships between individuals.

2. Support and involvement of citizens from the region with international clinical research expertise and leadership.

3. A dedicated clinical research training curriculum. Enhancing and restructuring of the medical curriculum in universities to include clinical research syllabus for undergraduate and graduate studies.

4. Durable local research capacity, including sustainable research networks – clinical Investigation centres, biobanks and core laboratories.

5. Implementation of eHealth, starting with electronic medical records.

6. Setting priorities favouring trials with objectives best aligned with local burden of diseases.

7. Incentivising investments, from international pharmaceutical and biotech companies that would feed into the clinical research culture and infrastructure.

8. Earmarking funding sources dedicated to clinical research capacity building and granting local priority research programs.

9. Creating a favourable environment for local CROs and academic CROs operations.

10. Mandating on-line registration and monitoring of all clinical trials conducted in the Region, ideally using existing international registries (clinicaltrials.gov and/or WHO).
Promoting clinical research capacity building in EMRO

EMRO meeting last week in Cairo discussed
• Need for specific guidance on key strategies for capacity development in EMRO
  • Need for monitoring maturity level of capacity development to support country capacity development.
Il faut faire aujourd'hui ce que tout le monde fera demain.

Cocteau
Regional experience in clinical trials
Focus on Pakistan

Dr Saeed Hamid
Professor of Medicine
Consultant Gastroenterologist
Director, Clinical Trials Unit
Aga Khan University
Karachi, Pakistan
Pakistan - Demographics

Population 2022 - 241,499,431
  Rural - 147,748,707
  Urban - 93,750,724

Population < 50 years - Nearly 50%

Medical Coverage -
  Public 30%
  Private 70%

Diabetes - 30% of pop.
Hepatitis C - 7% of pop.
Pakistan - Focus Therapy areas

Clinical Trials By Top 10 Therapy Areas

- Infectious Disease: 239
- Central Nervous System: 167
- Gastrointestinal: 98
- Metabolic Disorders: 94
- Cardiovascular: 86
- Hematological Disorders: 68
- Oncology: 57
- Women's Health: 47
- Respiratory: 45
- Dermatology: 44

<table>
<thead>
<tr>
<th>Therapy Area</th>
<th># Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious Disease</td>
<td>239</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>167</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>98</td>
</tr>
<tr>
<td>Metabolic Disorders</td>
<td>94</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>86</td>
</tr>
<tr>
<td>Hematological Disorders</td>
<td>68</td>
</tr>
<tr>
<td>Oncology</td>
<td>57</td>
</tr>
<tr>
<td>Women's Health</td>
<td>47</td>
</tr>
<tr>
<td>Respiratory</td>
<td>45</td>
</tr>
<tr>
<td>Dermatology</td>
<td>44</td>
</tr>
</tbody>
</table>
Pakistan - Top clinical Trial sites/sponsors

Clinical Trials By Top 10 Sponsors

<table>
<thead>
<tr>
<th>Sponsor</th>
<th># Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aga Khan University</td>
<td>97</td>
</tr>
<tr>
<td>DUHS</td>
<td>39</td>
</tr>
<tr>
<td>GSK plc</td>
<td>35</td>
</tr>
<tr>
<td>KE Medical University</td>
<td>22</td>
</tr>
<tr>
<td>Bayer AG</td>
<td>18</td>
</tr>
<tr>
<td>University of Karachi</td>
<td>18</td>
</tr>
<tr>
<td>Jinnah PostGraduate Medical Centre</td>
<td>16</td>
</tr>
<tr>
<td>Combined Military Hospital</td>
<td>14</td>
</tr>
<tr>
<td>Sheikh Zayed Medical College Rahim Yar Khan</td>
<td>14</td>
</tr>
<tr>
<td>Shaheed Zulfiqar Ali Bhutto Medical University</td>
<td>13</td>
</tr>
</tbody>
</table>
Human Clinical Research
Central Administrative Portal-

CTU Central Portal
Receipt of FULL application from Sponsor/Investigator

Initiation of Simultaneous Review
- Ethics
- Scientific
- Institutional Impact
- Legal contracts
- Financial

External Regulatory Approvals
- National Bioethics Comm
- Drug Regulatory Authority of Pakistan
- Import License

20-Feb-2018
CTU at Aga Khan University Hospital
Capacity Building Grant for COVID Trials

• PATH (Program for Appropriate Technologies in Health).
• Funding: $130,000
• Scope: Enhance capacity for conducting large throughput vaccine studies.
  Three sites: AKU CTU, CMS and Karimabad Hosp.
  Facility improvements.
  Lab and Pharmacy equipment.
  HR capacity.
  Trainings.
• Outcome: Placed on the BMGF list of trial ready global sites.
## COVID-19 Clinical Trials at CTU

<table>
<thead>
<tr>
<th>STUDY NAME</th>
<th>WHO</th>
<th>SPONSOR</th>
<th>PI</th>
<th>Sample size</th>
<th>Year</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CanSino</td>
<td></td>
<td>Beijing Institute of Biotechnology</td>
<td>Dr Faisal Mahmood</td>
<td>3000</td>
<td>2020</td>
<td>Final follow up</td>
</tr>
<tr>
<td>Livzon Trial</td>
<td></td>
<td>Livzon Mabpharm Inc China</td>
<td>Dr Faisal Mahmood</td>
<td>800</td>
<td>2021</td>
<td>Follow up</td>
</tr>
<tr>
<td>COPCOV Trial</td>
<td></td>
<td>Oxford University, UK</td>
<td>Dr Asim Beg</td>
<td>650</td>
<td>2020</td>
<td>Follow up completed</td>
</tr>
<tr>
<td>WHO Solidarity</td>
<td></td>
<td>WHO</td>
<td>Dr Nosheen Nasir</td>
<td>60</td>
<td>2020</td>
<td>Closing phase</td>
</tr>
<tr>
<td>ACT</td>
<td></td>
<td>PHRI Canada</td>
<td>Dr Aysha Almas</td>
<td>50</td>
<td>2021</td>
<td>Follow up completed</td>
</tr>
<tr>
<td>Meplazumab Trial</td>
<td></td>
<td>Jiangsu Pacific Meinuoke Biopharma</td>
<td>Dr Nosheen Nasir</td>
<td>8</td>
<td>2021</td>
<td>Second phase</td>
</tr>
</tbody>
</table>
CanSino Ad5-nCoV Vaccine Phase III Trial

- **Sponsor:** Beijing Institute of Biotechnology
  CanSino Biologics Inc.
- **Scope:** Global Phase III Trial of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in Adults 18 years of age and older.
- **Subjects:** Global-40,000, Pakistan-10,000
  AKU- 2900
- **Outcome:** First and only COVID vaccine to be produced in Pakistan (NIH).
D-LIVR

- **Sponsor:** Eiger Bio-pharmaceuticals, USA
- **Scope:** A Phase 3 Study of Efficacy and Safety of 50 mg Lonafarnib/100 mg Ritonavir BID with and without 180 mcg PEG IFN-alfa-2a for 48 Weeks in Patients with Hepatitis Delta Virus Infection.
- **Subjects:** 55/400 enrolled.
- **Outcome:** Potentially the first oral drug to be FDA approved for hepatitis Delta infection.

Hepatitis Delta in Pakistan
RIFASHORT

• Sponsor: MRC (St George's University, London, UK).

• Scope: An International Multicenter Controlled Clinical Trial to Evaluate 1200mg and 1800mg Rifampicin Daily in the Reduction of Treatment Duration for Pulmonary TB from 6 months to 4 months.

• Subjects: 35 recruited.

• Status: Completed-published
<table>
<thead>
<tr>
<th>Year</th>
<th>Study Title</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2023</td>
<td>A Randomized, Double-masked, Parallel-group, Multicenter Clinical Study to Evaluate the Efficacy and Safety of AVT06 Compared with EU-Eylea® in Subjects with Neovascular (wet) Age related Macular Degeneration (ALVOEYE)</td>
<td>Alvotech Swiss AG - Switzerland</td>
</tr>
<tr>
<td>2023</td>
<td>Active 2D - A Phase 3, multicenter, randomized, double-blind, 24-week study of the clinical and antiviral effect of S-217622 compared with placebo in non-hospitalized participants with COVID-19</td>
<td>Shionogi &amp; Co., Ltd.</td>
</tr>
<tr>
<td>2022</td>
<td>A Phase III, Randomized, Observer-Blind Study to Evaluate the Safety and Superiority in Immunogenicity of PTX-COVID19-B Administered as Booster Vaccination Compared to Vaxzevria® in Adults Aged 18 Years and Older Who Were Previously Vaccinated with Vaxzevria</td>
<td>EVEREST MEDICINES (HK) LIMITED</td>
</tr>
<tr>
<td>2023</td>
<td>Effectiveness Of novel approaches to Radical cure with Tafenoquine and primaquine (EFFORT)- A randomized controlled trial in P. vivax patients</td>
<td>Menzies School of Health Research, Australia</td>
</tr>
</tbody>
</table>
Pakistan as a preferred clinical trials site - Enabling Factors

Resources and Capabilities

• Large Treatment naïve population
• Well trained physicians.
• Possibility for patients to access innovative therapies.
• Lower costs for procedures, diagnostic tests and visits.
• Presence of international CROs
What do we need going forward?

- Automation in clinical trials submission and approvals.
- Regulatory Capacity.
- Better understanding of clinical trials procedures and regulation by relevant authorities.
- A network of inter-connected CTUs
- Discipline specific consortia- Oncology, GI, MCH, Vaccines etc
- Well trained research staff- for recruitment and retention.
- Internal funding mechanisms for multi-center national studies.
DRAP Process Improvements- 2022/23
Regional Experience in Clinical Trials - PAHO

Carlos Alvarez-Moreno – Colombia
Evandro Lupatini - Brazil
Summary of status of clinical trials

The agenda was organized based on discussion questions in four thematic areas that pose great challenges for the region:

1. Conducting high-impact clinical trials;
2. Research capabilities;
3. Clinical trial networks;
4. Ethical and regulatory efficiency.

Brasilia, October 04-05

12 countries:
• Representatives of the MOH;
• Regulatory agencies;
• Clinical research centers;
• Universities;
• Ethics committees;
• Private institutions;
• PAHO and WHO representatives.
Summary of status of clinical trials

1. Target research funding based on critical weaknesses identified locally;
2. Develop coordinated processes between regulatory networks;
3. Expand adaptive platform testing and transition to high-priority continuous clinical trial deployment models, considering national, regional, and global priorities.
Barriers

**Documents from the Brazilian National Research Ethics Commission (Conep)**

1. Need for technological modernization to improve ethical analysis processes;
2. Lack of alignment with other national and regional guidelines (e.g. National Health Council);
3. Need to promote regional regulatory harmonization (LATAM);

**Regional Workshop – PAHO**

1. Inadequate funding sources;
2. Regulatory assessment timelines for investigational medical devices;
3. Inadequate mechanisms for patient and community engagement;
4. Deficit of professionals trained in clinical research. Not just principal investigators but the entire ecosystem;
5. Networks of research centers and researchers are scarce in the region and challenging to retain;
6. Redundancy of regulatory and ethical activities and lack of harmonization between countries in the region.
### Priority actions

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| 1. Greater integration of clinical trials in medical practice and health decisions. | Creating networks at a regional or global level will allow clinical questions of interest in public health to be answered in less time. What was achieved in the pandemic can be carried out routinely. | • Improve the quality of care;  
• Offer the best possible treatment based on the best available evidence;                                                   |
| 2. Greater emphasis on research design that can robustly answer key questions and produce reliable evidence. | Studies with adequate designs to answer key questions allow evidence to be brought to communities more quickly.                                                                                       | • Time and resources savings;  
• Prevent duplicate efforts;  
• Obtain robust and reliable evidence.                                                                                           |
| 3. Have a community engagement team in clinical research centers.       | Community engagement teams are essential in community empowerment and the success of clinical trials.                                                                                                    | • Better perception of clinical research by the community;  
• The community more easily accepts more efficient clinical trials and their results.                                             |
## Priority actions

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Stimulate the training of health professionals in clinical research.</td>
<td>Regional formal and non-formal continuing education programs can help qualify professionals in each disciplinary area (clinical coordination, clinical monitoring, research pharmacy, ethics committee, researchers, etc.)</td>
<td>• Increase in courses, diplomas, and master's degrees in clinical research; • Robust clinical ecosystem in each country and region.</td>
</tr>
<tr>
<td>5. Creation of large-scale national and international research networks on diseases or geographic areas with gaps, with effective coordination mechanisms.</td>
<td>The formation of networks of clinical research centers will allow clinical studies to be conducted more efficiently.</td>
<td>• Optimize the implementation, conduct, and monitoring of clinical trials;</td>
</tr>
<tr>
<td>6. Establish a network of national and regional ethics committees facilitating the research protocol review and approval process.</td>
<td>The harmonization of regulatory processes in different countries will facilitate the formation of networks of ethics committees and health agencies.</td>
<td>• Optimize approval times and development of multicenter and multi-country clinical studies.</td>
</tr>
</tbody>
</table>
## Roles and responsibilities

<table>
<thead>
<tr>
<th>Stakeholders</th>
<th>Roles</th>
<th>Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Researchers, health workers</td>
<td>To identify gaps, design research protocols and conduct clinical trials.</td>
<td>Monitor public health problems at local, regional and global level and propose responses.</td>
</tr>
<tr>
<td>2. Trainers (WHO, Governments, NGOs, Universities, Private Sector)</td>
<td>Offer training Create national, regional, and global networks.</td>
<td>Monitor progress and identify gaps.</td>
</tr>
<tr>
<td>3. Organizations and Governments</td>
<td>Support human resource training. Provide appropriate resources for developing and sustaining clinical research centers.</td>
<td>Ensure the provision of resources, good governance, and a sustainability model.</td>
</tr>
<tr>
<td>4. Governments</td>
<td>Contribute to the harmonization of clinical research policies.</td>
<td>Contribute to the strengthening of clinical investigation.</td>
</tr>
<tr>
<td>5. WHO</td>
<td>Contribute to the harmonization of clinical research policies and centers.</td>
<td>Provide guides and technical documents to harmonize the different components of clinical research.</td>
</tr>
<tr>
<td>6. Hospitals</td>
<td>Support to the development of clinical research centers. (infrastructure, human resources, etc.) Redistribute and prioritize clinical research.</td>
<td>Ensure the Good Clinical Practice compliance. Facilitate and stimulate the conduct of clinical studies</td>
</tr>
<tr>
<td>7. Funding agencies and Private Sector</td>
<td>Redistribute and prioritize clinical research. Equitably support the development of clinical research centers and support clinical studies</td>
<td>Monitor the proper use of resources. Participate as Sponsor in clinical trials ecosystem</td>
</tr>
</tbody>
</table>

World Health Organization

1st Global Clinical Trials Forum, 20-21 November 2023, WHO Science Division, Geneva, Switzerland
# Summary of discussion

## Discussions

### Regional Workshop – PAHO

2. Research capabilities.
4. Ethical and regulatory efficiency.

## Follow-up actions planned in the region

1. Establish a regulatory cooperative system to streamline multi-country clinical trial authorization;
2. Design and implement mechanisms to avoid repetitive ethical review processes of multicenter studies;
3. Design and carry out three pilot clinical trials on priority topics collaboratively in the region;
4. Strengthen opportunities for collaborative work, within the framework of this regional network, through the creation of:
   a. Registry of research centers with the capacity and authorized to carry out clinical trials;
   b. Platform that provides methodological support for clinical trials and can ensure the design and conduct of high-impact clinical trials.
5. Create a regional network for clinical trials;
6. Design and implement policies to retain human talent in research.
Gracias!
Obrigado!
Thank you!
Lessons from a large-scale, pragmatic, adaptive platform trial

Peter Horby on behalf of RECOVERY team

WHO, Geneva, 20-21 November 2023
Four effective treatments for high-risk patients

Dexamethasone

Tocilizumab

Baricitinib

Ronapreve (casirivimab + imdevimab)
Empagliflozin

Eight ineffective drugs

Hydroxychloroquine

Azithromycin

Aspirin

Lopinavir-ritonavir

Convalescent plasma

Colchicine

Higher dose steroids

PANDEMIC SCIENCES INSTITUTE
1. Quality by design

- Focus on elements that are **essential** to reliable estimation of central question
  - Reality of participants
  - Randomisation
  - Follow-up completeness
  - Safety of participants
  - Analyses
- Eliminate procedures that are superfluous to central question

---

Eight minutes to randomise

<table>
<thead>
<tr>
<th>N</th>
<th>[Min, Max]</th>
<th>Mean (SD)</th>
<th>Median [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>48595</td>
<td>[0, 89]</td>
<td>8.30 (5.39)</td>
<td>7 [5, 10]</td>
</tr>
</tbody>
</table>
2. Quick & proportionate ethical & regulatory review

- No site investigator CVs
- No special labelling of repurposed drugs
- No fixed sample size
- SSARs not all SAEs

### Approvals within days

<table>
<thead>
<tr>
<th>Application</th>
<th>Purpose</th>
<th>Submission date</th>
<th>MHRA</th>
<th>REC</th>
<th>Live</th>
<th>Submission to live</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td></td>
<td>13 March</td>
<td>17 March</td>
<td>17 March</td>
<td>19 March</td>
<td>6 days</td>
</tr>
<tr>
<td>Subst. amend. 1</td>
<td>Add hydroxychloroquine</td>
<td>23 March</td>
<td>25 March</td>
<td>24 March</td>
<td>25 March</td>
<td>2 days</td>
</tr>
<tr>
<td>Subst. amend. 2</td>
<td>Add azithromycin</td>
<td>7 April</td>
<td>8 April</td>
<td>8 April</td>
<td>8 April</td>
<td>1 day</td>
</tr>
<tr>
<td>Subst. amend. 3</td>
<td>Add tocilizumab</td>
<td>14 April</td>
<td>16 April</td>
<td>16 April</td>
<td>23 April</td>
<td>9 days</td>
</tr>
<tr>
<td>Subst. amend. 4</td>
<td>Include children</td>
<td>27 April</td>
<td>5 May</td>
<td>30 April</td>
<td>9 May</td>
<td>12 days</td>
</tr>
</tbody>
</table>
3. Linkage with routine health care data

Short follow-up form

>99% completeness of primary outcome

Increased reliability of results

Figure 6.1: Results of randomised comparisons using eCRF, linkage or pre-specified combination

<table>
<thead>
<tr>
<th></th>
<th>Tocilizumab (n=2222)</th>
<th>Usual care (n=2354)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 28 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eCRF only</td>
<td>883 (39%)</td>
<td>839 (30%)</td>
<td>0.83 (0.75-0.93)</td>
</tr>
<tr>
<td>Linkage only</td>
<td>610 (30%)</td>
<td>722 (34%)</td>
<td>0.94 (0.87-1.06)</td>
</tr>
<tr>
<td>Combined</td>
<td>621 (31%)</td>
<td>729 (38%)</td>
<td>0.98 (0.89-1.09)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eCRF only</td>
<td>665/1764 (32%)</td>
<td>700/1803 (39%)</td>
<td>0.83 (0.65-0.91)</td>
</tr>
<tr>
<td>Linkage only</td>
<td>610/1175 (35%)</td>
<td>759/1803 (41%)</td>
<td>0.85 (0.69-0.98)</td>
</tr>
<tr>
<td>Combined</td>
<td>619/1175 (35%)</td>
<td>754/1803 (42%)</td>
<td>0.94 (0.77-1.12)</td>
</tr>
</tbody>
</table>

*Analysed only those on mechanical ventilation or non-invasive ventilation at assessed randomisation.
4. National infrastructure & leadership

• National clinical trial agreement template

• National costing framework - Schedule of Events Cost Attribution Tool (SoECAT)

• Urgent Public Health Research status

• National leadership

‘While it is for every individual clinician to make prescribing decisions, we strongly discourage the use of off-licence treatments outside of a trial, where participation in a trial is possible. Use of treatments outside of a trial, where participation was possible, is a wasted opportunity to create information that will benefit others.’
5. Point-of-care trial

Make it (almost) as easy to enroll as to treat

- Reduces distractions from critical components
- Allows participation in routine clinical care settings (not just academic centers)
- Facilitates larger samples sizes & enhanced statistical power
- Facilitates participation & representativeness
- Increases probability of meaningful results that improve care

At peak 500 enrolments per day
EU initiatives to support clinical trials

WHO clinical trials forum, 20-21 November 2023

Presented by Ana Zanoletty, Head of Clinical Trials Transformation Workstream
Data Analytics and Methods Task Force, European Medicines Agency
The European clinical trials environment

Problem statement

• Need for more multinational clinical trials which drive decision-making
• Need for an overarching strategy that bring stakeholders together
• Multiple actors requiring clear roles and responsibilities
• Strong healthcare and research infrastructure in the EU

Vision for EU

• EU as an attractive region for clinical research
• Enabling larger and more impactful CTs, with seamless coordination among regulators and stakeholders
• Smart CTs that are meaningful to the research community and patients, through regulatory, technological and process innovation
• Fostering collaboration by empowering, engaging and supporting stakeholders
1. The European Clinical Trials Regulation (CTR) and CTIS

Before the Clinical Trials Regulation
Clinical trial applications were submitted separately to regulators and ethics committees in each EU Member State.

After the Clinical Trials Regulation
Single clinical trial application covering regulatory and ethics submission in up to 27 Member States
Applies as of **31 January 2022**

The Clinical Trials Information System (CTIS) is the single submission portal, workspace and public registry which **harmonises the submission, assessment and supervision of clinical trials** in the EU/EEA.

Public health
Facilitates multinational trials to address key health issues, increase transparency & enables patient enrolment.

Research and innovation
Enables medical innovation through collaboration and access to clinical research data.

Global hub for clinical trials
Aims to ensure the EU/EEA remains an attractive clinical research hub globally.
2. Accelerating Clinical Trials in the EU (ACT EU)

ACT EU is a business change initiative led by the EMRN to transform the EU clinical research environment in support of medical innovation and better patient outcomes.

Priorities for 2023-2024

- **CTR implementation**
  - KPIs
  - Sponsor surveys
  - Transition CTD/CTR
  - Increased transparency

- **Support to non-commercial sponsors**
  - Mapping support
  - Definitions
  - Regulatory support
  - Funding

- **Multi-stakeholder platform**
  - Stakeholder advisory group
  - Multi-stakeholder events

- **Scientific advice**
  - Mapping
  - Consolidated SA pilot CTA/MAA

- **CTs in public health emergencies**
  - Increased collaboration
  - Fit-for-purpose regulatory flexibilities
  - PHE CTA package

See [ACT EU website](http://act-eu.eu) for more information.
3. CTR Collaborate - CTCG collaboration initiative

Optimises alignment between NCAs and ethics bodies to ensure harmonisation and seamless cooperation for safe, high-quality trials

Anchored to ACT EU

- **Survey** to map landscape of part I assessment NCA/ethics
- Lists of **issues and proposed solutions** to optimise work procedures
- Joined (NCA and ethics) **update of best practices**
- **Implementation of best practices** via CTCG roundtables/workshops to harmonise and collaborate
- **Communication** with NCA/ethics/sponsors
4. Creation of EU Ethics Group

**Initiative from Ethics committees in cooperation with European Commission and collaboration with CTCG**

Position of ethics committees in assessment of clinical trials changed with CTR:

- only one authorisation letter per MS integrating the ethics committee’s opinion
- CTR timelines for assessment
- mandatory use of a Clinical Trial Information System (CTIS).

Urgent need for increased alignment between the research ethics committee system of the different MSs in the EU.

Aims to strengthen cooperation between EU ethics committees in the EU/EEA; facilitate exchange of experience; align best practices and provide training.
In summary

1. Problem statement
2. Vision for EU CT environment
3. How?
   1. CTR & CTIS
   2. ACT EU
   3. CTCG CTR Collaborate
   4. Creation of EU Ethics Group

INCREASED COLLABORATION BETWEEN EU CT GROUPS

Contacts:
ACTEU@ema.europa.eu | ctcg@hma.eu | m.al@ccmo.nl (EU Ethics Group)
Any questions?

Official address  Domenico Scarlattilaan 6  ●  1083 HS Amsterdam  ●  The Netherlands
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Send us a question  Go to www.ema.europa.eu/contact

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High-quality informative clinical trials during epidemics & pandemics

The WHO R&D Blueprint for Epidemics` experience and future approach

Ana Maria Henao-Restrepo MD MSc
Lead WHO R&D Blueprint for Epidemics
WHO Health Emergencies programme
The Constitution of the World Health Organization defines that one of WHO’s key roles is to “promote, conduct and coordinate research in the field of health”.

In May 2015, the Sixty-Eight World Health Assembly welcomed the development of a blueprint, in consultation with Member States and relevant stakeholders, for accelerating research and development in epidemics or health emergency situations where there are no, or insufficient, preventive, and curative solutions, taking into account other relevant work streams at WHO...

https://www.who.int/news-room/articles-detail/who-design-and-consultation-process-on-a-new-medical-countermeasures-platform-for-pandemics
Coordinating and accelerating global research must promote universal values

Regarding a collaborative effort to ensure access to MCMs during pandemics, some have emphasized the importance of speed and sometimes cost in responding to future pandemics. It is equally important to take a broader view that recognizes the primary importance of quality, equity, and trust in access, and trust in the products safety and efficacy.
An approach to fast-track assessment of candidate MCMs and support pandemic prevention and control

1. **Prioritization**
   - WHO Independent expert process to prioritize candidate vaccines
   - A WHO process for prioritization of candidate vaccines by an independent WHO Technical Advisory Groups on candidate vaccine and treatments prioritization
   - Decisions are informed by outcomes of the prioritization process on minimum number of candidate product doses required for research during outbreaks and that need to be available.

2. **Availability**
   - Agreement on availability and access to candidate vaccines and therapeutics
   - Ministries and researchers in affected countries are in the driving seat and integrated into the response. CORE protocols for viral and bacterial families design and approved in advance.

3. **Clinical trials**
   - CORE protocols and platforms to promptly initiate trials with equitable access to research
   - A partnership model and signed agreements with Ministries of Health and developers with access to MCMs considered, and a framework for insurance and liability arrangements.

4. **Agreements**
   - Prior agreement on legal collaboration, insurance, indemnity and liability
   - Signed agreements with contributors; aimed at a simple approval process for releasing of funds and simplifying financial reporting.

5. **Funding**
   - Access to readily available funding through committed financing mechanism

6. **Collaborative approach**
   - To foster an open flexible collaborative mechanism that allows a variety of contributors
   - Including pathogen and trial experts, local researchers, and outbreak response teams to help adjust and implement research as needed.
On a path to accelerate access to Ebola vaccines: The WHO's research and development efforts during the 2014–2016 Ebola epidemic in West Africa

A novel trial design with the country in the driving seat & 26 global institutions collaborating

Expanded Access with rVSV ZEBOV GP (unlicensed doses), for outbreaks reported between 2016 - 2022

12 EVD (Zaire) outbreaks and 3,721 EVD confirmed cases reported

MOH designated researchers initiated studies within 2 weeks of outbreak declaration

Over 350,000 people at risk vaccinated including >100,000 HCWs/FLWs

Informed consent for all and individual data collection from 250,000
With the support of hundreds of experts worldwide WHO has discussed trial designs and developed protocols that get adjusted in every epidemic.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>R&amp;D Roadmap</th>
<th>Vaccines</th>
<th>Therapeutics</th>
<th>Diagnostics</th>
<th>Research priorities for other areas of research and innovation.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Landscape Candidate Vaccines</td>
<td>TPP Vaccines</td>
<td>Trial design Vaccines</td>
<td>Simple protocol available</td>
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<tr>
<td>Pathogen X</td>
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Study design options to reduce UNCERTAINTY during an epidemic

For candidate products that may have evidence on safety and may likely be effective against outcomes important for public health, but for which there is remaining uncertainty.

- Studies of biomarkers
  - Animal Rule
  - Immunobridging
  - Comparisons using immunomarkers

- Randomized clinical trials
  - Placebo controlled trials
  - Simple large randomized trials

- Open-label randomized trials
  - Randomization during deployment

- Observational studies
Randomized studies during epidemics and pandemics are **feasible** when:

- There is **uncertainty** about a product's benefit
- Supply of **doses may be initially limited**, and RCTs are a fair way to distribute them (in the trial context)

**Defining (at the outset) the questions of public health importance that will be addressed is necessary**

- During epidemics decisions (e.g. authorization for the deployment of millions of doses) are made after a review of the **totality of the evidence**
Do RCTs during epidemics **always** have to be blinded to limit indirect effects of knowledge of intervention?

Some, **but not all**, randomised trials must be blinded

- **Unbiased assessment of outcomes (e.g. death)**
  e.g. the findings for mortality cannot be appreciably biased by an open-label design without placebos or by variation in local care or patient characteristics.

- **Use of time allocation to define comparison for a definitive outcome**
  (e.g. randomization to now and later)

- **Use of alternative designs (e.g. factorial design)**

- **Clear SOPs** – to address potential risks and compliance is important
Prioritization of Treatment Study Designs

There was consensus on the need for randomization to evaluate the safety and efficacy of these investigation therapeutics with minimal bias. Experience from previous trials such as PALM and PREVAIL was considered. Table 2 summarizes the different study designs discussed during the meetings among a group of trialists and Ugandan researchers.

As of October 31, 2022, some treatments are provided in Uganda under MEURI protocol or compassionate use. Experts agreed that study designs 1-3 were credible and would provide evidence of efficacy, while design 4 should be excluded.

Ugandan clinicians and other experts determined that study design 3 was the most feasible given the local context, while still maintaining the benefits of randomization. The proposed study design includes secondary randomization to desexamethasone for all participants.

Table 2. Summary of Proposed Trial Design Options

<table>
<thead>
<tr>
<th>Option</th>
<th>Trial Design Option</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Standard of care (SOC) + Monoclonal versus SOC + Antiviral versus SOC + Monoclonal + Antiviral versus SOC alone (Full factorial design) Secondary randomization corticosteroids</td>
<td>Including a SOC arm will provide the most valid and interpretable estimation of potential treatments effect. This design is efficient and could provide results relatively quickly.</td>
<td>As the candidate therapeutics are already in use, the SOC arm considered less acceptable for a disease with very high baseline mortality.</td>
</tr>
<tr>
<td>2</td>
<td>SOC + Monoclonal versus SOC + Antiviral versus SOC alone Secondary randomization corticosteroids</td>
<td>Including a SOC arm will provide the most valid and interpretable estimation of potential treatments effect. This design will provide understanding on the impact of the monoclonal and the synergistic impact of the combination therapy.</td>
<td>As the candidate therapeutics are already in use, the SOC arm was considered less acceptable for a disease with very high baseline mortality. The design does provide direct information on the effect of the antiviral alone.</td>
</tr>
<tr>
<td>3</td>
<td>SOC + Monoclonal versus SOC + Antiviral versus SOC + Monoclonal + Antiviral Secondary randomization corticosteroids</td>
<td>If on SOC alone cannot be randomized, this design can provide evidence on any differential effect of monoclonal antibodies vs antiviral, and on any efficacy of the two combination.</td>
<td>If the synergistic effect of a monoclonal plus an antiviral is low, the sample size could increase.</td>
</tr>
</tbody>
</table>

Seamless progression from phase 1 to Phase 3

- **Phases 1 and 2**: Individual randomization among vaccines (no placebo)
  - Cluster-randomized (immediate versus delayed)
    - Enrolment of up to 100 HCVs/FLVs in affected areas
  - Phase 1: Enrolment of up to 200 (100 per arm) participants (contacts of MAVID cases including HCVs/FLVs)
    - Safety analysis of Phase 1 data by DSMC (7 and 14 days post-vaccination) with formal recommendation on whether to continue to recruit.
- **Phase 2**: Enrolment continues (up to 1000 contacts)
- **Phase 3**: Participants will also be included in Phase 3 analyses

Factorial design

- Randomisation 1: Monoclonal antibody vs no additional treatment (1:1)
  - Monoclonal antibody vs no additional treatment (1:1)
  - Emergent therapy vs no additional treatment (1:1)
- Randomisation 2: Antiviral vs no additional treatment (1:1)
  - Low-dose corticosteroids vs no additional treatment (1:1)

Selection of candidates based on WHO expert working group recommendations.

“Both MAb114 and REGN-EB3 were superior to ZMapp in reducing mortality from EVD”.

Roles of researchers, vaccinees, and vaccinators in simplified open-label randomized trials conducted during vaccine deployment

A key requirement in such a study is that it should not interfere with ordinary vaccination.

Nothing extra should be added to what the vaccinators have to do with each individual.

Follow-up depends on what’s locally possible (e.g. electronic records, surveillance and lab results)

<table>
<thead>
<tr>
<th>Planning</th>
<th>Trial Researchers</th>
<th>Vaccinees</th>
<th>Vaccination Personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>instead of usual vaccine allocation procedures, use randomization to determine which persons to vaccinate and when and where they will be vaccinated</td>
<td>Receive detail about and attend vaccination appointment</td>
<td>Administer vaccine and record vaccination in accordance with usual procedures</td>
</tr>
<tr>
<td>Implementation</td>
<td>Infor the vaccinators and participants when and where vaccine will be delivered</td>
<td>Monitor vaccination status and incidence of Covid-19 from health records</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>Report vaccination compliance; analyze outcomes according to assigned vaccine (intention-to-treat principle)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Simplifying vaccine/therapeutics trials in the context of epidemics/pandemics is ongoing

- **INTEGRATING** trials as part of the epidemic response
- **DESIGNING IN ADVANCE** CORE protocols
- **ENROLLING SUFFICIENT** numbers needed to assess effects on **SEVERE** disease
  - **SMALLER** numbers are needed to assess effects on overall disease incidence, and **SMALLER STILL** for assessing immune parameters (e.g. subset studies at a few of the centres may suffice)
- **SIMPLIFYING** every aspect of the process of approval of the whole trials and approval of collaborating centres
  - **SEEKING APPROVAL IN ADVANCE** CORE protocols
  - **ADAPTING** review and monitoring avoiding multiple and repetitive review processes ensuring review processes are agile, rapid, and rigorous.
Simplifying vaccine/therapeutics trials in the context of epidemics/pandemics is ongoing.

- SIMPLIFYING informed consent process
- SIMPLIFYING (electronic) data collection, particularly at entry but also at follow-up
  - Restrict attention to the FEW variables that are of material relevance to answer the important questions
- ENSURING that a group of WHO collaborating centres can support international trials with comprehensive data collection and randomization procedures **WITHIN DAYS OF DETAILED REQUEST**

**COMPLEX IS NOT EQUAL TO BETTER QUALITY**
During epidemics and pandemics, randomized trials are a reliable way to address uncertainty **if** they generate data to answer questions of public health importance.

As of Aug 02, 2023 there were **4634** randomized trials of COVID treatments.

### Solidarity trial vaccines

<table>
<thead>
<tr>
<th>Country</th>
<th>N sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombia</td>
<td>6</td>
</tr>
<tr>
<td>Kenya</td>
<td>5</td>
</tr>
<tr>
<td>Mali</td>
<td>14</td>
</tr>
<tr>
<td>The Philippines</td>
<td>10</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38</strong></td>
</tr>
</tbody>
</table>

Randomised trials in the context of epidemics need to be SIMPLE and of HIGH QUALITY and…

- **Affected country** (and local researchers) must be in the driving seat
- **CORE Protocols** must be discussed and pre-approved in advance
- Epidemics often occur in areas with very **limited infrastructure**
- Trials must be **integrated** into the epidemic response team

**SIMPLE DOES NOT MEAN LOW-QUALITY**
Some examples of the differences between trials and trials integrated into the epidemic response

<table>
<thead>
<tr>
<th>Teams involved in design and implementation</th>
<th>Outside epidemics</th>
<th>In the context of epidemics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialized research teams national and international</td>
<td>Research centers designated by the MOH, <strong>epidemic response teams and clinicians in affected countries</strong> as part of an international collaboration</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Questions to be answered</th>
<th>Outside epidemics</th>
<th>In the context of epidemics</th>
</tr>
</thead>
<tbody>
<tr>
<td>As part of an individual product R&amp;D plan</td>
<td>Design to address key uncertainties to inform public health decisions</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selection of interventions</th>
<th>Outside epidemics</th>
<th>In the context of epidemics</th>
</tr>
</thead>
<tbody>
<tr>
<td>As part of an individual product R&amp;D plan</td>
<td>Ideally as part of a <strong>transparent global process</strong> using defined criteria and data available at the time of the epidemic</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time for preparation</th>
<th>Outside epidemics</th>
<th>In the context of epidemics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months to years</td>
<td><strong>CORE protocols</strong> discussed during the inter-epidemic period</td>
<td></td>
</tr>
</tbody>
</table>

Start of randomization **within 2 weeks** of epidemic declaration because there is a small window of opportunity
Some examples of the differences between trials and trials integrated into the epidemic response

<table>
<thead>
<tr>
<th></th>
<th>Outside epidemics</th>
<th>In the context of epidemics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Process for the study implementation</strong></td>
<td>Mostly aiming to fulfil international guidelines</td>
<td>Committed to fulfil international guidelines with a clear sense of <strong>what is feasible</strong> and community engagement</td>
</tr>
<tr>
<td><strong>Logistics</strong></td>
<td>Defined by infrastructure of specialized research center and defined SOPs</td>
<td>Adjusted to the epidemic response team, while complying with defined SOPs</td>
</tr>
<tr>
<td><strong>Quality assurance</strong></td>
<td>Use of CROs and audits Variable percentage of verification of records</td>
<td>Use of CROs and audits <strong>100% verification of records</strong></td>
</tr>
<tr>
<td><strong>Trust</strong></td>
<td>Relies on regulatory processes</td>
<td>Relies on regulatory processes <strong>Careful community engagement</strong> and transparency are very important</td>
</tr>
</tbody>
</table>
Prioritizing the world’s greatest pathogen threats

There are over 1,400 species of human pathogens in the world. These include viruses, bacteria and fungi.

To guide future research efforts, the World Health Organization (WHO) R&D Blueprint for Epidemics launched on 21 November 2022, a global initiative to scientifically review all pathogens that could cause a future global pandemic (like-COVID-19) or an epidemic of international concern.

How are the most dangerous pathogens shortlisted?

200 plus
Global experts are independently reviewing and shortlisting pathogens of pandemic threat.

30
Viral families are being studied to ensure all viruses that can infect humans are reviewed for any pathogen X.

1
Bacteria group is being studied to scientifically screen for any bacteria pathogen X.

Pathogen X
A yet unknown pathogen not currently infecting humans but could be pathogenic due to: their zoonotic risk; mode of transmission; global warming; tropical deforestation; or other factors.

Key scientific criteria to shortlist

- How transmissible are they?
- How virulent are they?
- Are there sufficient vaccines or treatments in the event of an epidemic or pandemic?

Pathogens reviewed and not shortlisted: These are viruses or bacteria unlikely to cause an epidemic or pandemic or there is equitable access to safe and effective vaccines/treatments.

Pathogens reviewed and shortlisted: These are viruses or bacteria that have epidemic or pandemic potential but where there is equitable access to safe and effective vaccines/treatments.

Pathogens reviewed and shortlisted: These are viruses or bacteria that have epidemic or pandemic potential and where there are no or insufficient vaccines/treatments.

Pathogens reviewed and shortlisted: These are viruses or bacteria where the epidemic or pandemic potential is currently unknown but shortlisted as potential pathogen X.
To be prepared to integrate research during epidemic

- Continue to foster **collaboration** for evaluating candidate vaccines and therapeutics within epidemic responses, led by Ministries of Health and national research teams.

- Continue to involve national researchers and authorities to contribute to design of CORE protocols for each viral and bacterial family towards final consensus on key trial design attributes.

- Expand to develop **viral and bacterial families' roadmaps** via collaborative global networks of designated researchers in “at risk” countries via engagement in a framework for clinical research preparedness to ensure clinical research is promptly integrated into future epidemic responses.
On behalf of hundreds of colleagues across the three levels of WHO, we would like to thank the over 50,000 researchers and hundreds of Ministries of Health officials who have joined our research efforts; the funders who have facilitated critical research; and the thousands of volunteers who have generously contributed to the studies worldwide.
Extra slides
Improving vaccine effectiveness studies: a vital step before the next pandemic

Observational studies lack precision when either vaccine uptake or variant prevalence is too low or too high for statistical stability, but they could provide insights if cases and controls are adequately matched for potential confounders.

During epidemics non-randomized (so-called real-world) studies are widely disseminated, but sometimes cannot reliably demonstrate or refute moderate effects.
Research undertaken before an epidemic is critical – with one key focus being the global prioritisation, detection and monitoring of new or existing pathogen threats.

Research in the interepidemic period

Identify and prioritise research in the interepidemic period

Surveillance and early detection

Diagnosis and treatment

Health emergency preparedness and response

Enabling research

Research integrated in the outbreak response

Vaccines and therapeutics research in the outbreak response

Clinical management

Vaccines and vaccines and drug access

Public health measures

The delivery of effective medical countermeasures and wider policies to combat a disease outbreak is underpinned by a wide range of research areas. They all coordinate and work together enabling the global research effort before and during an outbreak.

Some sources of information

Search for documents/material

<table>
<thead>
<tr>
<th>Disease</th>
<th>Webpage</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19</td>
<td><a href="https://www.who.int/teams/blueprint/covid-19">https://www.who.int/teams/blueprint/covid-19</a></td>
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<td>Monkeypox</td>
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<td>Ebola/Marburg</td>
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<td>Disease prioritisation</td>
<td>Prioritizing diseases for research and development in emergency contexts (who.int)</td>
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<td>WHO Monkeypox Research - What study designs can be used to address the remaining knowledge gaps for monkeypox vaccines?</td>
<td>Consultation</td>
</tr>
<tr>
<td>Towards the development of a global CORE protocol for evaluation of treatments for MPX Leveraging the Congolese Experience</td>
<td>Consultation</td>
</tr>
<tr>
<td>WHO monkeypox research: What are the knowledge gaps and priority research questions?</td>
<td>Consultation</td>
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<td>Landscape vaccines</td>
<td>Technical document</td>
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<td>Technical document</td>
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<td>TPP for RVF virus vaccine</td>
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<td><a href="https://www.who.int/docs/default-source/blue-print/call-for-comments/tpp-rift-valley-fever-vaccines-draft3-0pc.pdf?sfvrsn=f2f3b314_2">https://www.who.int/docs/default-source/blue-print/call-for-comments/tpp-rift-valley-fever-vaccines-draft3-0pc.pdf?sfvrsn=f2f3b314_2</a></td>
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<td>Efficacy trials of Plague Vaccines: endpoints trial design, site selection</td>
<td>Meeting report, April 2018</td>
<td><a href="https://cdn.who.int/media/docs/default-source/blue-print/plaguevxeval-finalmeetingreport.pdf?sfvrsn=c251bd35_2">https://cdn.who.int/media/docs/default-source/blue-print/plaguevxeval-finalmeetingreport.pdf?sfvrsn=c251bd35_2</a></td>
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<td>Landscape of plague vaccines candidates</td>
<td>Landscape of vaccines</td>
<td><a href="https://www.who.int/publications/m/item/who-target-product-profile-for-plague-vaccines">Landscape of Plague vaccine candidates (who.int)</a></td>
</tr>
<tr>
<td>WHO TPP for plague vaccines</td>
<td>Target product profile for vaccines</td>
<td><a href="https://www.who.int/publications/m/item/who-target-product-profile-for-plague-vaccines">https://www.who.int/publications/m/item/who-target-product-profile-for-plague-vaccines</a></td>
</tr>
</tbody>
</table>
## Some sources of information

| Document                                                                 | Type                             | Link                                                                 |
|-------------------------------------------------------------------------|----------------------------------|                                                                      |
| Establishing a Global Coordination Mechanism of R&D to prevent and respond to epidemics - Toward implementation of the GCM | meeting report March 2017         | [https://www.who.int/docs/default-source/blue-print/gcm/blue-print-gcm2017-meetingsummary.pdf?sfvrsn=3f78ce1c_2](https://www.who.int/docs/default-source/blue-print/gcm/blue-print-gcm2017-meetingsummary.pdf?sfvrsn=3f78ce1c_2) |
| Establishing a Global Coordination Mechanism of R&D to prevent and respond to epidemics: Scoping Meeting | meeting summary, November 2016   | [https://www.chathamhouse.org/sites/default/files/events/2016-11-10-Global-Coordination-Meeting-Summary.pdf](https://www.chathamhouse.org/sites/default/files/events/2016-11-10-Global-Coordination-Meeting-Summary.pdf) |
| 4th WHO R&D Blueprint Consultation on vaccine evaluation in public health emergencies | meeting report, October 2017    | [https://www.who.int/docs/default-source/blue-print/working-group-for-vaccine-evaluation-(4th-consultation)/boston-meeting-report.pdf?sfvrsn=5c7ada89_2](https://www.who.int/docs/default-source/blue-print/working-group-for-vaccine-evaluation-(4th-consultation)/boston-meeting-report.pdf?sfvrsn=5c7ada89_2) |
| WHO R&D Blueprint meeting on pathogen genetic sequence data (GSD) sharing in the context of public health emergencies, 28-29 September 2017 | meeting report, September 2017   | [https://indico.un.org/event/24764/material/slides/5.pdf](https://indico.un.org/event/24764/material/slides/5.pdf) |
Funding models that best support both sustainable capacity and project deliverables

Tom Nyirenda - EDCTP
Historical and colonial links laid the foundation of research in Africa

Critical role of European national institutes and universities
Consequences of historical approach


*Only 5% of publications had south-south linkages*
From individualism to partnerships: 2006 and beyond

Good partnership principles and model funding models have emerged

Effective research capacity strengthening:
A quick guide for funders

Four approaches to supporting equitable research partnerships
Barriers

*Most obvious ones*

- Non-inclusive decision processes on the objectives of research and capacity development
  - Mal-alignment among funders
  - Mal-alignment with local regional and country priorities
  - Lack of local ownership and leadership – therefore no local commitment
- Lack of transparency
- Lack of joint monitoring and evaluation of the collaborations
  - Fragmentation in dissemination and application of research results
  - Inequitable sharing of gains and losses
- Perpetual lack of critical mass for research capacity
EDCTP example of layered programmes within a partnership

The Partnership structure

Implementation model

Outputs

- Products (Drugs/ Vaccines/ diagnostics)
- Competent authorities: AVAREF/ AMA
- Research networks
- Upgraded research sites
- Alumni network
- PACTR
- Afro-Euro funding pot
- New research culture
- Collaboration with Industry
Thank you

Those who shared views:-
• Dr Peter Kilmarx - NIH
• Dr Divya Shah - Wellcome
• Dr Mark Palmer – MRC UK
• Dr Garry Aslanyan - TDR
## Priority actions

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
<th>Outcome</th>
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<tbody>
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</table>
# Roles and responsibilities

[Please elaborate on the roles and responsibilities of stakeholders involved in each proposed action]

<table>
<thead>
<tr>
<th>Stakeholders</th>
<th>Roles</th>
<th>Responsibilities</th>
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<tbody>
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</table>
Summary of discussion

*Please summarize the key discussion points at the GCTF to guide the actions in the focus area of work*

<table>
<thead>
<tr>
<th>Discussions</th>
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<tr>
<th>Follow-up actions planned in the region</th>
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</table>
Thank you
Regulatory considerations for overcoming barriers in future international clinical trials

Marco Cavaleri, Hilary Marston, Adam Fimbo, Claudiosvam Alves, Jeaon Yeon Kim, Elisabeth Higgs, Adam Hacker, Mac Lumpkin, David Vaughn
Enable across countries and regions consistent and timely regulatory approval of clinical trials that are scientifically sound and can generate meaningful evidence to trigger regulatory and/or public health authorities decisions

Define frameworks that allow international convergence across regulatory bodies ensuring regulatory certainty on clinical trials conduct in regions and countries
Three primary entities have a role in accelerating clinical trial launch:

- Protocol/product sponsors – rapid design and provision of relevant review information
- Ethics bodies (RECs or IRBs)
- Regulatory authorities ← primary focus of today’s discussion
Lesson learned from COVID-19

Problem statement:

- Fragmentation of clinical research with duplication of efforts and under-powered studies leading to inconclusive results
- Slow approval timelines affecting the capacity to timely enrol patients
- A global approach towards efficiently launching global clinical trials is lacking
- Sequential submissions across the globe with resultant delays, followed by country by country required changes and adjustments leading to continuous resubmissions
- Discrepancies across regulators in the requirements from inclusion/exclusion criteria to endpoints, safety monitoring or statistical testing.
Lesson learned from COVID-19

• Need for harmonised, scientifically sound regional and international clinical trials

• Need for rapid approval and implementation in countries and regions

• A global approach towards efficiently launching global/international clinical trials is lacking

• Prompt issuance of guidance can help in the design stage, rather than waiting for review

• Objectives:

  Define possible actions to secure faster clinical trial approval across multiple countries maintaining appropriate safety, scientific, and ethical oversight in each jurisdiction.

  Explore coordination mechanisms enabling a rapid set-up and implementation of clinical trials that meet the regulatory requirement for clinical trial conduct and support product authorisation and/or policy decisions for infectious diseases.
Regulatory approval of CTs

Problems identified:

- Insufficient coordination within the Member States (MSs), between national competent authorities (NCAs) and ethics committees
- Slow clinical trial application assessment and authorization
- Insufficient coordination across Member States in the case of multinational trials, also due to national requirements that lead to dis-harmony
- Lack of flexibility and certainty in the approval process, e.g. amount of administrative documents
- Lack of interactions across Regulatory Authorities from different Regions
Classified as internal/staff & contractors by the European Medicines Agency.

1. Regulatory approval of CTs in the EU during PHEs
Lengthy time to approval

CTIS Initial submission

Part 1
Time from submission to approval = 13 days

Part 2
Median time from submission to approval = 46.5 days (IQR 41 to 62)

Contracts with country coordinating centre
5 out 7 contracts signed
Median time from CTIS authorisation to signature = 89.5 days (IQR 69 to 137)

CTIS Substantial Modification submission

Part 1
Time from submission to approval = 42 days

Part 2
Median time from submission to approval = 74 days (IQR 62 to 76)
High number documents required at initial submission (particularly if the trial is multi-country):

- AXL-Solidact = 535 documents (for 10 countries)
- MOSAIC = 329 documents (for 8 countries)

Document burden is increased by the need to upload different versions of a same document

The document burden is also complicated by requirements of each country:

- Inconsistency between country documents requirements,
- Different legal requirements between countries.

Are all documents in all their different formats critical to the approval of the trial?
Potential Strategies for Efficient Regulatory Review

Increase collaboration and coordination between regulatory authorities to streamline approval process.

Increase multi-lateral regulatory discussions across countries and regions to foster a shared perspective that could allow rapid convergence on clinical trials design in variable geographies.

Provide forums for continuous engagement between regulators and the clinical research community and clinical trials networks to allow a shared understanding of the scientific and public health goals and facilitate agreement of clinical trials design.

Explore actions that could reduce the administrative burden and address bottlenecks in clinical trial start to enhance a transparent, smooth and fast review process.

Consider how to build/share expertise locally on country and region-specific regulatory requirements for clinical trials to facilitate efficient submission and review of global trials.
Modernizing The Conduct of Clinical Trials Harmonizing Good Clinical Practice Guidelines – ICH E6(R3) – GCP

ICH E6 is unique as the only harmonized guideline among the global regulatory community for clinical trial conduct

• E6 sets a foundation for practical/feasible expectations for GCP to facilitate clinical trials across settings
  o Proportionality and risk-based approaches with a focus on quality while keeping the emphases and focus on participants’ safety and reliability of trial results

• Encourage a fit-for-purpose approaches

• Incorporate learning from innovative trial designs and lessons from public health emergencies/pandemics

• Minimize burden and focusing resources on what matters most to make clinical trials more efficient globally
  o For example, no blanket training requirement and training should correspond to the role expected to be played in the trial

Potential Strategies for Efficient Regulatory Review

- Leveraging ICH M11 protocol template can simplify review
- Could pursue as a baseline submission, to which minimal additional local documents can be added
- Could develop a database of country-specific requirements to facilitate
- Note that other elements of review (e.g., CMC) are beyond the purview of this discussion
Regulatory elements to support multi-local trials

- Additional helpful elements may include incorporation of decentralized elements, such as remote informed consent, use of local providers for appropriate protocol elements.
AVAREF – A successful example of collaboration

- The African Vaccine Regulatory Forum (AVAREF) is a network of African National Regulatory Authorities (NRAs) and Ethics Committees (ECs) that uses harmonization and reliance as pillars for capacity building.

- As a result of AVAREF’s efforts, vaccines against meningitis, malaria, rotavirus, pneumococcal pneumonia, and Ebola have been developed, and medicines against neglected tropical diseases (NTDs) such as human African trypanosomiasis and leishmaniasis are currently under development.

- Harmonized guidelines for clinical trials have been developed. Regular joint reviews and GCP inspections are organized.

- It has been able to reduce the timelines considerably and now sponsors receive timely feedback on their applications for authorization of clinical trials.
Regulatory framework for enabling CTs conduction

Possible solutions to be discussed

- Mentoring and capacity building to support regulatory systems in LMICs
- Leveraging existing regulatory authority programs and infrastructure for success models and best practices, e.g. AVAREF and other opportunities for regional reliance and harmonization
- Consider possibility of joint reviews in selected cases, e.g. emergencies, large trials in endemic diseases
- Agree standardized submission templates globally for clinical trial authorization submissions that account for any local or region-specific requirements.
Regulatory framework for enabling CTs conduction

Aspects to be considered

- Developing the vision for an adequately-sized and well-equipped clinical trial infrastructure that is constantly operational generating actionable evidence on endemic diseases and health priorities

- Encourage the conduct of clinical trials in countries and networks that
  - Leverages existing regulatory capacity (e.g., existing networks) and best practices (e.g., harmonization, reliance)
  - Includes a focus on capacity building to enhance the clinical trial infrastructure, develop experience within the ethics and regulatory authorities and drive capacity and sustainability

- Consider how to improve currently inefficient processes for importation of investigational products for clinical trials
SUMMARY: Bigger, better and faster clinical trials
*We must seize the opportunity to get better medicines to patients faster*

**NEXT STEPS:**
The constituted Regulatory Working Group will define a set of key principles and proposed actions to improve the international coordination and conduction of clinical trials.

*A draft paper will be discussed at second Forum Meeting next year.*
Thank you
Ensuring High Quality Ethics in Global Clinical Trials

WG Members:

Roli Mathur, Ross Upshur, Sofia Salas Ibarra, Katherine Litler, Andreas Alois Reis
Objectives

High quality ethical research is critical for achieving internationally agreed health related development goals: WHA75.8, 27 May 2022

Vision and Plan towards global equity in clinical research

Effective, Efficient, Resilient, Transparent (Regional Consultation on Health Research and Management, New Delhi 7-10th Nov, 2023)
Challenges

• Integrating ‘ethics’ in the Clinical Research Ecosystem
  • Fragmented Governance Frameworks
  • Responsible Collaborations, Coordination & Stakeholders

• Optimal Investments for Capacity to deliver
  • Preparedness Robust Research, Facilitatory/ efficient
  • Monitoring and oversight
  • Resources & Technology

• Adopting People-centric approaches
  • Ensuring relevance, Scientific and Social Value
  • Equity, Access, Affordability, Customized to local requirements
## Priority actions

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence-Based Research/ Priority Setting/ Local Considerations</td>
<td>85% of research is a waste Inappropriate/ Underrepresented/ incorrect</td>
<td>Identification of National/ Regional/ Global priorities and optimal use of resources</td>
</tr>
<tr>
<td>2. Harmonization, Ethics Governance Frameworks, inter-country collaborations</td>
<td>Lack of coordination, focus, resources, COI, Ethics Dumping</td>
<td>Building an effective, transparent, Networks/ multi-country research</td>
</tr>
<tr>
<td>3. Building Ethics Capacity and Improving Preparedness</td>
<td>Responsive, Timely, Enabling mechanisms</td>
<td>Local/ Regional/ Global capacity, equipped sites, trained HR, better resourced, infrastructure for desired actions</td>
</tr>
</tbody>
</table>
## Priority actions

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4. People Centric Approaches and Sensitivity to local requirements and truthful communications</strong></td>
<td>Mistrust, Fear, inclusion, Protection of Vulnerable, be sensitive to diversity</td>
<td>Build Public Trust, Engagement, Advocacy, Improved communications/Informed consent process</td>
</tr>
<tr>
<td><strong>5. Robust Responsible Research, well-designed, Innovations, transparent</strong></td>
<td>Meaningful Research, fit for the purpose systems, Open to emerging/novel technology</td>
<td>Monitoring, Oversight, quality, efficient, Robust Outcomes</td>
</tr>
<tr>
<td><strong>6. Considerations related to Equity, Access, Affordability</strong></td>
<td>Translation of Research Meaningful Public Health measures</td>
<td>Responsive, Accountable, Policies for Low costs and Sustainable Outcomes</td>
</tr>
</tbody>
</table>

1st Global Clinical Trials Forum, 20-21 November 2023, WHO Science Division, Geneva, Switzerland

ETHICS WORKING GROUP
## Roles and responsibilities

<table>
<thead>
<tr>
<th>Stakeholders</th>
<th>Roles</th>
<th>Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ethics Committees</td>
<td>efficient, effective, resilient, Support research and protection of research participants, Monitoring and Oversight</td>
<td>Timely reviews, Facilitatory and friendly, Guide and Educate</td>
</tr>
<tr>
<td>2. National Agencies/Governments/Regulators</td>
<td>Accountable, Transparent, Timely, Build systems, Guidance/Regulations</td>
<td>Ethics on Board, Multisectoral engagement, priority setting, Listener, Transparent Decisions, Non political</td>
</tr>
<tr>
<td>3. Institutions</td>
<td>Facilitatory, Providers</td>
<td>Structures, resources, facilities, infrastructure, Manpower Training, COI Policies</td>
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</table>
## Roles and responsibilities

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<tr>
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<tbody>
<tr>
<td><strong>4. Researchers</strong></td>
<td>Integrity, Proactive, uphold science and ethics, protection of participants</td>
<td>Responsible research conduct, data collection, analysis and presentation of facts</td>
</tr>
<tr>
<td><strong>5. Sponsors</strong></td>
<td>Updated, support robust science, Capacity Building, Monitoring</td>
<td>Organized efforts for multicounty, Selection of objectives, methods, sites, Training, infrastructure, Funding, DSMB,</td>
</tr>
<tr>
<td><strong>6. Journals</strong></td>
<td>Promote scientific rigor, timely decisions, and encourage LMICs</td>
<td>Timely, Open Access, Accept submissions of positive/ negative results, COI management</td>
</tr>
</tbody>
</table>
Summary of discussion

- Debunking the myth that ethics is just about review
- Investing, reforming, innovating the EC model to a more interdisciplinary approach
- Focusing on underrepresented and marginalized groups
- Adopting a values-based approach to create ‘ethical governance’ models
- Translation, benefit sharing, access and affordability
Follow-up actions from the WG

- Building evidence-based research ethics oversight reform and capacity strengthening (e.g., benchmarking tool etc.)
- Addressing known gaps in ethics review oversight in clinical trials (i.e. development of guidance on adaptive platform trials)
- Facilitating and promoting equitable access to participation and access to the benefits at affordable costs
- Finding ways towards building Public Trust, Engagement and Communicating Better
Conclusion

‘Responsible Research Drives Ethical Outcomes’

High-quality ethics is a shared responsibility.

Ethical considerations are central to the success, ensuring that the benefits are shared fairly, participants are protected, and trust is maintained among nations.
Thank You

ETHICS WORKING GROUP
Features of high impact and informative clinical trials, and how best to enable them

Otavio Berwanger, Mike Clarke, PJ Devereaux, Paul Glasziou, Herman Goossens, Peter Horby, Vivekanand Jha, Martin Landray, Karen Robinson, Nandi Siegfried (alphabetical order)
Objectives

To identify key enabling factors and characteristics of informative and efficient clinical trials that lead to impact

**NOTE:**

- We considered impact to be indicated by trial results which influence practice, policy, clinical guidelines and programmes
- Our focus is primarily on large-scale international clinical trials
What is the Trial Timeline?

We have split this into 4 chronological steps
Synthesize evidence
Combine evidence from primary research into systematic reviews of effectiveness; values and preferences; gender, equity and human rights; and resource use.

Produce evidence
Undertake primary research, including quantitative studies of effectiveness, safety and cost-effectiveness and qualitative studies of uptake, applicability and feasibility.

Evaluate and improve policy and practice
Consider population-based data from registries, quality indicators and programmatic data for use in the evaluation of policies and programmes.

Knowledge translation
Use evidence to inform decision support products, including guidelines, guidance, policy briefs and evidence summaries, and to identify research gaps.

Share evidence with stakeholders
Ensure evidence of beneficial and harmful interventions is made available to decision makers, healthcare providers, and the public, in an accessible and user-friendly way.

Implement evidence
Use evidence to inform policies and programme.

Evidence ecosystem for knowledge translation

Adapted from: http://magicproject.org/research-and-tools/the-evidence-ecosystem/
Barriers

1. Failure to justify, design and place results of new trials within context of what is already known
2. Inequitable distribution of capacity, resources, technology and expertise to lead clinical trials
3. Fragmented and time-consuming regulatory, ethics and contracts approval processes and trial monitoring
4. Insufficient recognition of the value of research by the public, by patients and their communities, and by bodies responsible for planning Human Resources for Health
5. Limited access to, and prohibitive costs of, technologies to support trials
# Priority actions

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<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>1. Knowledge and Capacity</td>
<td>Focus and prioritise clinical trial training (including clinical epidemiology and biostatistics) and regional mentoring to overcome knowledge and capacity deficits</td>
<td>Large-scale, adequately powered trials with credible event rate estimates and credible treatment effects led by investigators from LMIC</td>
</tr>
<tr>
<td>2. Enabling Environment</td>
<td>Streamline regulatory and ethics approval with mutual approval processes to reduce the time and administrative requirements at trial design stage</td>
<td>Single or co-ordinated ethics and regulatory approval process at regional or international level facilitated by WHO and/or national regulatory agencies without compromising safety</td>
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<tr>
<td>3. Tools and Technologies</td>
<td>Limited access to and prohibitive costs of IT support systems (e.g. dedicated CT platform software) results in many CT tasks done manually and not supported in the digital environment.</td>
<td>Fit-for-purpose accessible and scalable platforms for efficient recruitment, data management, analysis and monitoring; recognising limited connectivity in regions</td>
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<tr>
<td>4. Engagement and Partnership</td>
<td>Include public and communities in research prioritization and trial conduct to improve inclusivity and diversity of trial participation</td>
<td>Greater relevance, generalizability, and uptake, of results to all populations</td>
</tr>
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</table>
Priority Actions

- KNOWLEDGE & CAPACITY
- ENABLING ENVIRONMENT
- ENGAGEMENT & PARTNERSHIP
- TOOLS
**KNOWLEDGE & CAPACITY**
- Diverse intellectual leadership
- Support and education for conduct of evidence synthesis
- Prioritization of research questions
- Key design features
- Risk proportionate approaches to design and conduct
- Selection of intervention to enable uptake based on feasibility and integration into health system delivery

**TOOLS**
- “Quality by design” guidelines
- Tools to support design training
- Technologies for convenience of participation, such as in a decentralized, hybrid, or pragmatic manner

**ENABLING ENVIRONMENT**
- Demand creation from community and public
- Funders and ethics bodies to ensure existing evidence justifies new study

**ENGAGEMENT & PARTNERSHIP**
- Prioritization of questions to address unmet public health needs
- Design community-based trials
- Engaged Ethics Committees
- Ensure relevant audience perspectives included e.g. guidelines developers and national decision-makers
**KNOWLEDGE & CAPACITY**
- Leadership and coordination
- Infrastructure for data collection
- Integration of research activities into routine clinical care (embedded trials)
- Reporting of results in context of what is known

**ENABLING ENVIRONMENT**
- Coordination and streamlining by regulatory and ethics
- Considerations of cultural, political and environmental context
- Encourage healthcare providers to conduct research as part of practice

**TOOLS**
- Tools for conduct, data governance and management
- Technologies for convenience of participation
- IT infrastructure for trial conduct, data management and analysis
- Tracking tools and strategies for reduction/mitigation of carbon emissions

**ENGAGEMENT & PARTNERSHIP**
- Active engagement of participants for ensuring inclusivity
- Integration of clinician perspectives
- Community and public engagement
- Equitable collaboration between global partners
**KNOWLEDGE & CAPACITY**
- Selection of intervention that enables later uptake eg implementation feasibility, integration into health system delivery

**ENABLING ENVIRONMENT**
- Prioritization by funders and national authorities
- Efficient translation into relevant licensure, guidelines, and practices
- Update into national policy frameworks and public health programme for large scale roll-out

**TOOLS**
- Technologies and mechanisms to revise national guidelines in a timely manner with new results
- Integration of results into clinical decision support tools
- Functional national HTA agencies

**ENGAGEMENT & PARTNERSHIP**
- Good practices for community and public engagement in research
- Inclusion of perspectives of guidelines developers and national stakeholders
- Inclusion of perspectives of professional societies
### Stakeholders by Priority Actions

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<th>Stakeholder</th>
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<td>Public and communities</td>
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<td>Trial participants</td>
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<td>Principal investigators</td>
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<td>Funding agencies</td>
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<td>5</td>
<td>Regulatory and ethics bodies</td>
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<td>6</td>
<td>Healthcare staff</td>
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## Roles and responsibilities

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<tbody>
<tr>
<td>1. Public and communities</td>
<td>• Engagement &amp; Partnership</td>
<td>Establish structures and networks and/or use existing networks to ensure public and community values and preferences are included.</td>
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<tr>
<td></td>
<td>• Enabling environment</td>
<td>Create demand for trials and shape their questions and designs</td>
</tr>
<tr>
<td>2. Trial participants</td>
<td>• Engagement &amp; Partnership</td>
<td>Participate in trials and potentially advise on trial design</td>
</tr>
<tr>
<td>3. Principal investigators</td>
<td>• Knowledge &amp; Capacity</td>
<td>Ensure quality and safety of trials from concept to design to analysis to results dissemination. Mentoring, training and intellectual property input into development of tools and technologies</td>
</tr>
<tr>
<td></td>
<td>• Tools and technologies</td>
<td></td>
</tr>
<tr>
<td>4. Funding agencies</td>
<td>• Enabling Environment</td>
<td>Avoid unnecessary and wasteful duplication, include sufficient funding for digital technologies to enable efficient trial conduct, provision of trials training and inclusion of routine healthcare staff</td>
</tr>
<tr>
<td></td>
<td>• Tools and Technologies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Engagement &amp; Partnership</td>
<td></td>
</tr>
<tr>
<td>5. Regulatory and ethics</td>
<td>• Enabling Environment</td>
<td>Collaborate and harmonise across regions</td>
</tr>
<tr>
<td>6. Healthcare staff</td>
<td>• Knowledge &amp; capacity</td>
<td>Lead and conduct trials and ensure that all aspects of a trial are conducted according to standards</td>
</tr>
<tr>
<td></td>
<td>• Engagement and Partnership</td>
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Translating evidence into global impact: lessons for HIV research and policy development from the AMBITION trial

Evaluate and improve policy and practice

WHO 2018 clinical guidelines: urgent need for simple treatments for CM suitable for low-resource settings

Synthesize evidence

1. Nested cost-effectiveness study
2. Nested acceptability (LEOPARD) study
3. Nested feasibility study

Published in LGH and PLoS NTD, 2022

Produce evidence

AMBITION RCT:
- single dose vs SOC (7-14 days)
- 844 PLHIV powered for safety & efficacy
- 5 Sub-Saharan African countries
- Gilead donated liposomal Amphotericin B

Published in NEJM, 24 March 2022

Share evidence to stakeholders

1. Advocacy activities throughout trial with PLHIV, Ministries, African clinical collaborations, global funders, generic manufacturers, and Gilead commitment to preferential pricing.
2. WHO in close contact with trial investigators

Implement evidence

Incorporation into national guidelines as part of routine care within 3 months

Knowledge translation

1. WHO Rapid Advice, April 2022
2. Full revised WHO guidelines, July 2022
3. Trial investigators shared results pre-publication

An evidence ecosystem for knowledge translation

Adapted from: http://magicproject.org/research-and-tools/the-evidence-ecosystem/
Summary of discussion

Discussions

Still to come from today’s breakout sessions

Follow-up actions from the WG

• We advocate for a programme of research to collate more examples of impactful trials, and to characterise key features that lead to impact
• Identify other organizations working in this area to harmonise efforts with respect to trial standards, guidelines and regulatory and ethics requirements
Frameworks for clinical trial ecosystem strengthening

Bernhards Ogutu, Libby Higgs, Peter Kilmarx, Dominique Sprumont, Laura Merson, Nicole Lurie, Amelie Rioux, Peter Horby, Anna Laura Ross, Sarah Charnaud, Philip Kenol, Duduzile Ndwandwe
Key Points

There is no one generally agreed and implemented system that covers all necessary elements globally for clinical trial ecosystem strengthening.

However there are many complementary frameworks developed that apply to parts of the clinical trial ecosystem.

Some aspects are well developed and implemented.

eg National Regulatory Authority Global Benchmarking Tool which addresses clinical trial oversight (and other NRA functions).

For Research Ethics Committees, WHO has developed a benchmarking tool which is available.
Key Points

For Individual Clinical Researchers, there is a global WHO TDR competency framework, and a MRCT competency framework.

For institutional research capacities there is no one globally agreed set of clinical trial unit competencies that the group could find; however there are many related sets of work.

WHO guidance on best practices for clinical trials includes a framework which is close to finalisation, and could be used for ecosystem strengthening, but will need further discussion on associated tools to support clinical trial ecosystem strengthening.
Sustainable Strong Continuous National Clinical Research Ecosystems

Enabling national clinical research governance
Regional & global coordination
Continuous financing

Clinical trial infrastructure capability and capacity
Community engagement

Research ethics oversight

Regulatory systems including efficiency

Continuous strengthening through monitoring, evaluation and learning (MEL)
Sustainable Strong Continuous National Clinical Research Ecosystems

- Enabling national clinical research governance
- Regional & global coordination
- Continuous financing
- Clinical trial infrastructure capability and capacity
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- Enabling national clinical research governance
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- Regulatory systems including efficiency

Continuous strengthening through monitoring, evaluation and learning (MEL)
Clinical Trial Infrastructure Capability and Capacity Pillar: Space for a Maturity Framework

A scoping review of guidance, frameworks and standards for health research capacity identified many guidance documents, but few assessment frameworks.

Can benchmarking standards and a self-assessment maturity framework support sustainable clinical research capacity?
Sustainable Strong Continuous National Clinical Research Ecosystems

Enabling national clinical research governance
Regional & global coordination
Continuous financing

Clinical trial infrastructure capability and capacity
Community engagement

Research ethics oversight

Regulatory systems including efficiency

Continuous strengthening through monitoring, evaluation and learning (MEL)
Global Benchmarking Tool for Research Ethics Committees

Figure 2. The seven categories

1. Legal provisions and regulatory framework
2. REC structure and composition
3. REC resources
4. REC procedures
5. Mechanisms to promote REC transparency
6. Mechanisms for RECs to monitor their performance
7. Responsible research institutions
Sustainable Strong Continuous National Clinical Research Ecosystems

- Enabling national clinical research governance
- Regional & global coordination
- Continuous financing
- Clinical trial infrastructure capability and capacity
- Community engagement
- Research ethics oversight
- Regulatory systems including efficiency

Continuous strengthening through monitoring, evaluation and learning (MEL)
Global Maturity Level Tool for National Regulatory System Strengthening

Available and in use

Well accepted by many countries, with support from WHO to enhance their NRA functionality

Major progress observed in country maturity levels
Current levels of maturity of national regulatory systems

WHO GBT (for medicines and vaccines: as of Nov 2022)

<table>
<thead>
<tr>
<th>Level</th>
<th>Oct 2018</th>
<th>Nov 2020</th>
<th>Nov 2022</th>
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<tr>
<td>ML1</td>
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- **Singapore** achieves the world's first to achieve maturity level (ML4) (Feb 2022)
- **Egypt** and **Nigeria** medicines regulatory systems reach ML3 (Mar 2022)
- **China**'s vaccine regulatory system reaches ML3 (Jul 2022)
- **South Africa**'s vaccine regulatory system reaches ML3 (Oct 2022)
- **Republic of Korea** achieves the highest WHO level for regulation of medicines and vaccines (Nov 2022)

Vaccines developed in countries with weak regulatory systems, i.e., ML1/ML2, are not eligible for EUL or prequalification.
Discussion Points

- Vision for national clinical trials ecosystem

- Further discussion will be needed on the four pillars

- Maturity levels exist for regulatory and ethics pillars

- There are many tools for governance, and clinical trial infrastructure and capabilities; maturity levels not in place here
Backup slides on initiatives identified
Previous initiatives focused on health research systems capacity

National Health Research Systems c2003, updated draft 2023: 17 indicators covering national, institutional and individual researcher metrics

Metrics for national biomedical research capacity 2018 World Bank International Vaccines Taskforce

Analysis of country level capacity for the ESSENCE on health research systems initiative 2022
Previous initiatives focused explicitly on preparedness

Global Preparedness Monitoring Board – includes clinical trial indicators 2023
GHSA R&D Indicators
Previous initiatives focused patient and community engagement

James Lind Alliance bringing patients, carers and clinicians into priority setting
Good Participatory Practice for community engagement in clinical trials
Global Benchmarking Tool for Research Ethics Committees

Available and in pilot use

Developed with countries through consultative process
Previous initiatives focused on governance of research institutions

CIOMS international guidelines of good governance practice for research institutions – to be published very soon 2023

Fair contracting – COHRED 2020

Equitable partnerships resource hub
Previous initiatives focused on research integrity and transparency

WHO ICTRP established 2006 as global cornerstone of research transparency efforts, standards for clinical trial registration and trials reporting

WHO Joint Statement with 23 Research funders 2017 on public disclosure of results from clinical trials

UK Concordat: national policy statement on research integrity
Related initiatives for elements of the clinical trials ecosystem

ICH Guidances

IT and Data Management Standards

Good Financial Grant Management Practice

GCLP and Research Laboratory Standards

UKCRC Registered CTU Network Key Competencies and Evaluation Criteria 2023

- Note no globally agreed framework and indicators for multi-centre clinical trial coordination/leadership through clinical trial units
**Priority actions**

*Please propose up to six key actions to lift the barriers as mentioned before. Please elaborate on the rationale and expected outcome for each proposed action*

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Roles and responsibilities

*Please elaborate on the roles and responsibilities of stakeholders involved in each proposed action*

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Summary of discussion

*Please summarize the key discussion points at the GCTF to guide the actions in the focus area of work*

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Thank you
Please feel free to choose title and close slides from the below alternatives
[Please insert the focus area work of the WG]

[Please insert the names of the WG members]
[Please insert the WG's focus area of work]

[Please insert the names of the WG members]
[Please insert the WG's focus area of work]

[Please insert the names of the WG members]
Thank you
Thank you
Thank you
Enabling clinical trials in primary care

Chris Butler
Professor of primary care
Clinical Director Primary Care Clinical Trials Unit, University of Oxford
Chief investigator of PRINCIPLE and PANORAMIC Trials
Primary health and social care, community care and self care

**Primary care:** Undifferentiated by diagnosis, gender, place, age, Trials in primary care means trials in disadvantaged groups, children, women, pregnancy, older people, rural, and every condition

May kinds of trial questions and design, funding and regulation musty follow context and question: Complex, health services questions, preventative strategies, comparative effectiveness, registration trials pragmatic policy relevant trials
"Hand me down evidence" from hospitals particularly inappropriate in primary care
The sickness iceberg, prevention and early intervention

Figure 3.1  Monthly prevalence of illness in the community and the roles of various sources of health care. (From Green et al., 2001.)

Ian McWhiney
1926-2012
Inverse funding and potential health gain law

1st Global Clinical Trials Forum, WHO Science Division
The Lancet · Saturday 27 February 1971

THE INVERSE CARE LAW

JULIAN TUDOR HART
Glyncorog Health Centre, Port Talbot, Glamorgan, Wales

Summary The availability of good medical care tends to vary inversely with the need for it in the population served. This inverse care law operates more completely where medical care is most exposed to market forces, and less so where such exposure is reduced. The market distribution of medical care is a primitive and historically outdated social form, and any return to it would further exaggerate the maldistribution of medical resources.
Trials should be done in the ‘intended use population’ to be most useful; community buy in to priority questions, outcome measures and implementation
27 March 2020

Cardiff Road Medical Centre,
Cynon Valley
Mountain Ash
South Wales
Managing uncertainty... ????: Only just
No treatment, no research opportunity (for COVID, yes, but also for numerous other clinical dilemmas)

Inverse research participation law
Access to research is often inversely proportional to a participants’ potential contribution and to where the research findings should be most applicable
It is too hard for participants, research staff, and care personnel to do rigorous, sustainable trials in primary care

- **Care Staff:** Primary health and social care is close to breaking point in many parts of the world: care needs to be evidence based through system-strengthening research (embedded, answering questions that improve care)

- **Participants:** Ethical, Administrative, Regulatory, Legal and Nationalism barriers limit participation: e.g. regulations disproportionate and not fit for ‘democratic’ trials (e.g., lack of knowledge and empathy to community research, limited facilities for remote consent, *telephone decretory PIL etc.* WE make them come to the research

- **Researchers:** piecemeal funding; skills shortages (*PRINCIPLE= 7 trials in one*); infrastructure poorly developed; *sub-optimal understanding of probability and Bayesian statistics and open-label trials (addition to placebos)*; lack of empathy with pragmatic, policy relevant research; no research capable pharmacies in the community, 9,000 GP practices in the UK
Facilitators

• Experience of multi-country EU funded ALIC4E trial (PREPARE Consortium); platform and response adaptive randomisation capability; existing trials can be repurposed by amendment

• Nimble peer review and funding for platform to address best treatment for a condition vs. “does a particular treatment work”

• Early dialogue with regulators

• Urgent Public Health status badging (endorsement and prioritization)

• Research ready infrastructure (NIHR Clinical Research Network)

• Covid Therapeutics Advisory Panel of Therapeutics Task Force appraisals and recommendations of interventions

• Digital enablement; positive test result feed and outreach, access to GP Summary Care Record for central eligibility check (eventually)

• NHS capable of rapid implementation
Making it possible to contribute research without leaving your bed or home “*take research to the people trials*” (TRTPT)

- Awareness, trust, potential participant identification and invitation (social media, word of mouth, practice records)
- Website
- Eligibility checked by clinicians from participant history and access to care records
- Remote Consent (with proportionate regulations)
- Central distribution of meds: courier direct to home
- Remote consent; phone, video, texting
- Self-sampling
- Trial partner
- Follow up by links, apps, tests, phone, HCPs to homes, routine data
PRINCIPLE Trial of repurposed medicines

- **Hydroxychloroquine**: 2 Apr 22 May
- **Azithromycin**: 30 Nov 22 May
- **Doxycycline**: 14 Dec 26 May
- **Inhaled Budesonide**: 1 Dec 26 May
- **Colchicine**: 4 Mar 22 May
- **Ivermectin**: 8 Apr 2021 01 July
- **Favipiravir**: 23 Jun 2021 01 July
- **Usual Care**: 

*Articles*

- *Lancet 2021*
- *Lancet Respiratory 2022*
- *BJGP 2022*

*Participants: >10,500 participants*
Identifying what does NOT work critical: Home rune for antimicrobial stewardship
1433 Unvaccinated participants (716 on molnupiravir)

3% Reduction in hospital admission/death

(48 of 709 [6.8%] vs. 68 of 699 [9.7%]; difference, −3.0 percentage points; 95% confidence interval, −5.9 to −0.1)

Interim data not replicated in post-interim data

Bernal, DOI: 10.1056/NEJMoa2116044

Do these findings apply in the vaccinated population in the UK under omicron?

**JVT:** Let’s do a trial in the intended use population to find out!
Recruitment from all four UK Devolved Administrations

>120,000 screened

>6,000 GP practices have recruited at least one participants to PANORAMIC (each red dot represents a GP Practice)
Cumulative recruitment summary into PANORAMIC, trial ongoing

Between 8 Dec ‘21 and 23 April ‘22, 25,708 randomised to molnupiravir vs usual care

500 on a day

TRIAL ONGOING n=>28,300

PRINCIPLE+PANORAMIC: >38,500 randomizations
Disability Champions
Will and Gemima Browning
Molnupiravir

- Did not reduce already low hospital admissions when used as an early treatment in the community for COVID-19 by multiply vaccinated people.
- Resulted in earlier time to recovery, sustained early recovery, reduced severity and duration of all typical COVID symptoms.
- Reduced health care seeking in primary care in some services.
- Reduced viral detection and load in a sub-group on Day7.
- Was well tolerate and safe.

- Health Economics, more virology and effect on longer term symptoms still to come.
Data quality

- >95% primary outcome collected
- >90% completed diary data
- 90% completed 3 months diary/call
- 84% completed 6 months diary/call
- 83% virology sample returned
- Minority ethnic participation reflective of UK population
Primary care trials that are

• Prioritised
• Coordinated
• Mandated
• Resourced
• Embedded in communities and clinical care
• Systems and resilience strengthening
• Sustained
• Simplified
• Internationalised
• and democratised (including TRTP Trials)

• Can happen, and by their nature, will address the ‘inverse research participation law’
Thank you
Paediatric WG
Nigel Rollins and Martina Penazzato
On behalf of
Ebunoluwa Aderonke Adejuyigbe, Tahmeed Ahmed, Per Ashorn, Jay Berkley, Zulfi Bhutta, Guillermo Chantada, Tanzila Ghani, Diana Gibb, Carlo Giaquinto, Rebecca Grais, Glenda Gray, Fyezah Jehan, Edward Kija, Philippa Musoke, Sharon Nachman, Grace Ndeezi, Shane Norris, Fiona Russell, Judd Walson and Jim Zhang
Why invest in paediatric research?

• Rates of decline of infant and child mortality have been levelling off since 2015 despite high or increasing coverage of proven interventions

Why invest in paediatric research?

• Rates of decline of infant and child mortality have been levelling off since 2015

• Growing child populations in LMICs
  o By 2100, 8 of 10 people will live in Africa or Asia
Why invest in paediatric research?

• Rates of decline of infant and child mortality have been levelling off since 2015
• Growing child populations in LMICs
• The investment return for interventions in young children greatly outweigh the return in any adult population (Heckman, Nobel Laureate, Economics)
Why invest in paediatric research?

• Rates of decline of infant and child mortality have been levelling off since 2015
• Growing child populations in LMICs
• The investment return for interventions in young children greatly outweigh the return in any adult population
• Prenatal and postnatal health sets a lifelong trajectory of health and disease

“If we change the beginning of the story, we change the whole story”
Working group objectives

I. To summarise **status of clinical trials implementation** among infants and children

II. To **identify the barriers** to implementation of high-quality clinical trials among infants and children, particularly in developing countries

III. To **identify possible solutions** to implementation barriers and key enablers to successful translation of research evidence into public policy and programmes
Only 10% of ongoing registered clinical trials include children
... And 70% of these are conducted in High income settings
Only 10% in LMICs

International Clinical Trials Registry Platform (ICTRP), October 2023
...where 70% of the under 5 mortality is occurring

Only a fraction of global research priorities are being addressed across the child health domain

- Perceived complexity
- Active exclusion of children from clinical trials
- Few, robust global clinical trial networks to support paediatric research
II. Barriers

Failure of the global research community to efficiently coordinate and align, including processes between national government, communities, researchers, regulators, industry and funders to address the most pressing evidence gaps for infants and children

Common to all areas of research
- DATA & BIOSPECIMEN GOVERNANCE
- RESEARCH LEADERSHIP AND CAPACITY
- INFRASTRUCTURE & LOGISTICS
- TRIAL METHODOLOGY
- NATIONAL LEADERSHIP AND STEWARDSHIP

Disproportionately affecting paediatric research
- ETHICS and REGULATORY
- FUNDING
- RESEARCH CAPACITY
Barriers

Failure of the global research community to efficiently coordinate and align, including processes between national government, communities, researchers, regulators, industry and funders to address the most pressing evidence gaps for infants and children

Disproportionately affecting paediatric research

- ETHICS and REGULATORY
- FUNDING
- RESEARCH CAPACITY
For example....

**Mortality in low resource settings**
- How to reduce the excess mortality in the first 12 months of life among infants born Preterm/LBW?
- How to reduce post-discharge mortality (similar to in-patient mortality)

**Obesity**
- How to prevent childhood obesity and metabolic disease in low and high income settings?

**Sickle cell**
- Improved clinical diagnostics and treatment

**Pneumonia**
- How to identify infants and children needing antibiotics? What medicines to treat and prevent?

**Technologies**
- How can currently available technology e.g. POC CRP or SaO2 be used in low resource settings to improve care pathways and survival

**Health system**
- Risk-differentiated care: How can health systems more effectively use available information to identify and manage high risk infants and children
**Progress is possible if ... in addition to responding to cross-cutting challenges**

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<td>5. Policies and activities enabling research environment including ethical and regulatory aspects</td>
<td>Existing or perceived barriers impede the timeliness and quality of priority research</td>
<td>Alignment of ethical and regulatory principles in support of rapid implementation of prioritized research</td>
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<td>Dedicated research consortia that can ensure high quality evidence generated in a timely manner</td>
</tr>
<tr>
<td>4. Funders to commit to mechanisms for pooled resources with accountability</td>
<td>Fragmentation of resources and research agenda without all relevant inputs</td>
<td>Pooled funding from multiple stakeholders (public and private sector) to support prioritized research</td>
</tr>
<tr>
<td>5. Policies and activities enabling research environment including ethical and regulatory aspects</td>
<td>Existing or perceived barriers impede the timeliness and quality of priority research</td>
<td>Alignment of ethical and regulatory principles in support of rapid implementation of prioritized research</td>
</tr>
<tr>
<td>6. Build the environment for knowledge translation including capacity for future research</td>
<td>To anticipate and accelerate communication of study findings and their implication for policy and practice</td>
<td>Rapid dissemination of study findings and translation into policy change and practice at global and national level + capacity incrementally established for future research</td>
</tr>
</tbody>
</table>
We must all be active contributors....

<table>
<thead>
<tr>
<th>Stakeholders</th>
<th>Roles/Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Community</strong></td>
<td>Contribute to prioritization, advocacy and study design and dissemination via community advisory boards</td>
</tr>
<tr>
<td><strong>2. Researchers</strong></td>
<td>Contribute to prioritization, establish collaborations to implement the key priorities and ensure rapid knowledge sharing</td>
</tr>
<tr>
<td><strong>3. Funders</strong></td>
<td>Explore matching funding opportunities to support prioritized research, catalyze engagement of additional funders</td>
</tr>
<tr>
<td><strong>4. National ministries</strong></td>
<td>Contribute to prioritization, provide political support to implementation and knowledge sharing</td>
</tr>
<tr>
<td><strong>5. IRBs and regulators</strong></td>
<td>Gather to review principles and policies in support of rapid implementation of research questions prioritized</td>
</tr>
<tr>
<td><strong>6. WHO</strong></td>
<td>Convene stakeholders and facilitate prioritization, technical advocacy and knowledge translation</td>
</tr>
<tr>
<td><strong>7. Private sector</strong></td>
<td>Contribute to implementation of priority research via financial and technical support</td>
</tr>
</tbody>
</table>
..to realize a first step towards impactful evidence for children

A coordinated, transparent process with an accountability mechanism to complete high quality research that provide policy makers and programme managers with definitive evidence to inform interventions that reduce infant and child mortality and improve health and development

• Over the next 5 years we will have research collaborations to address agreed research priorities in countries
  • High quality evidence to inform policy
  • Builds sustainable research infrastructure
  • Supported by enabling ethical and regulatory environment
  • With accountability mechanism

“every system is perfectly designed to get the results it gets....” (attributed to David Hanna)

Unless there is a step change in how critical clinical trials for infant and child survival, health and development are approached, there is no reason to believe that things will change
Thank you

E bun oluwa A deronke Adejuyigbe, Tahmeed Ahmed, Per Ashorn, Jay Berkley, Zulfi Bhutta, Guillermo Chantada, Tanzila Ghani, Diana Gibb, Carlo Giaquinto, Rebecca Grais, Glenda Gray, Fyezah Jehan, Edward Kija, Philippa Musoke, Sharon Nachman, Grace Ndeezi, Fiona Russell, Shane Norris, Judd Walson Jim and Zhang
Enabling high quality trials in pregnant and lactating women

Arri Coomarasamy
Shivaprasad Goudar
Mercedes Bonet
Mariana Widmer
Outline

• Context & problem statement
• Barriers
• Suggested priorities
• Looking forward to 2030
Pregnancy and lactation

Pregnancies: ~250.4 million per year*
  • Births 134 million**
  • Miscarriages 23 million
  • Abortion 73 million

Lactating women: ~ 60 million women

Maternal deaths: 287,000 per year***
  • Haemorrhage: 74,000 per year
  • Preeclampsia: 40,000 per year
  • Sepsis: 32,000 per year

A maternal death every 2 minutes


Why aren’t matters improving? (1/2)

Numerous reasons: one of which is **scarcity of evidence** on:

- What interventions are effective and safe (i.e., lack of RCTs & other clinical research)
- Scarcity of innovations (commodities including medicines, devices, diagnostics)
- How to best implement and sustain effective practices (lack of implementation research)

<table>
<thead>
<tr>
<th>Disease</th>
<th>RCTs available in MEDLINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>39,332</td>
</tr>
<tr>
<td>Asthma</td>
<td>11,257</td>
</tr>
<tr>
<td>COVID-19</td>
<td>4,914</td>
</tr>
<tr>
<td>PPH</td>
<td>788</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1090</td>
</tr>
</tbody>
</table>

Example of rapid MEDLINE search strategy (Nov 2023):

```
preeclampsia AND (randomized controlled trial[Publication Type] OR randomized>Title/Abstract] AND controlled>Title/Abstract] AND trial>Title/Abstract])
```

Only 2 new drugs for pregnancy-specific conditions in the past 30 years
Scarcity in diagnostics, medicines and devices.
Why aren’t matters improving? (2/2)

Funding – very little

Research projects funded – very few

Number of grants for biomedical research by health category
Source: World RePORT as of November 14, 2023
Number of grants for biomedical research by funder and recipient in 2020 (who.int)
An example: RCTs available for uterotonic treatment of postpartum hemorrhage, topmost killer of women postpartum

**What we wanted!**
Large number of good quality RCTs

**What we found!**
7 studies involving 3738 women
Problem statement

Scarcity of high quality RCTs in pregnant and lactating women

Results in weak and discordant policy and clinical practice recommendations

Compromised efforts to implement, scale-up and sustain effective and safe interventions to improve outcomes
Barriers to high-quality trials

- Ethics processes
- Regulatory processes
- Lack of sponsorship & indemnity
- Lack of research capacity (few research groups and researchers)
- Lack of funding opportunities
- Risk sensitivity (e.g., teratogenicity; long-term development)
- Benefit insensitivity (e.g., long-term benefits of preventing preterm birth)
- Too little profit (pregnancy & lactation are ‘self-limiting conditions’, access price)
- Too expensive to do the trial (e.g., pre-clinical studies, mother & baby may need intensive surveillance, costs of regulatory trials)
### Some unique issues

<table>
<thead>
<tr>
<th>Barrier related to</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Population**     | 1. Pregnant and lactating women need to be treated separately.  
                    2. We normally target the mother and baby dyad in pregnancy. What if there is the possibility of benefit for one but potential for harm for the other?  
                    3. Pregnant women with co-existing medical (e.g. diabetes) or mental health problems should be able to take part in condition-specific trials (e.g. diabetes trials. Should aim to have an “opt-out” design)  
                    4. Pregnant population excluded from trials of outbreaks and pandemics. They shouldn’t be. |
| **Intervention**   | 5. Most trials focus on repurposing of existing drugs (with well known safety profiles), but there is a need for new interventions.  
                    6. Not just drug and device interventions, but also implementation and organisation of clinical care interventions.  
                    7. Physiological changes of pregnancy and potential effects on PK/PD |
| **Outcome**        | 6. Co-primary outcomes with outcomes of importance for mother and baby.  
                    7. Need a focus beyond short-term outcomes & future pregnancies |
Suggested priorities

- ADVOCATE! WHO, ICM, FIGO, Political figures, Celebrities
- Facilitate PPIE
- Secure funding commitment from donors, research councils and industry
- Facilitate sponsorship and indemnity
- Produce framework & guidance for regulatory bodies
- Produce framework & guidance for ethics committees
- Retain core staff
- Retain the learning: ‘a network with a memory’
- Enable a living democratized maternal health research network: Hub and (many spokes) “Always on” “Always busy”
- PPIE: e.g. community groups
- Build and maintain Relationships
- Industry
- Ethics committees
- Funders
- Regulatory bodies
- Facilitate ongoing multi-stakeholder research prioritization
- Deliver on trials
- Conduct methodology research

World Health Organization

1st Global Clinical Trials Forum, 20-21 November 2023, WHO Science Division, Geneva, Switzerland
Looking forward to 2030!

**Active advocacy:**
- Key actors around the globe
- Key messages
- Key events

**Funding at least doubled** between 2025 and 2030

**A stimulated market**

**Frameworks and guidelines** on ethical and regulatory considerations for assessing and conducting trials in pregnant and lactating women

A living **maternal health research network**:
- 7 – 10 hubs across the continents
- 2 – 3 core staff
- 2 – 3 ongoing trials
- At least 1 platform trial
- Several principal investigators
- Harmonized data
- An outward looking resource

**A Roadmap** to guide us, with monitoring framework to track our progress
Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth


Randomized Trial of Early Detection and Treatment of Postpartum Hemorrhage

Thank you

Special thanks to the WHO-convened pregnancy and lactating women research stakeholder group: Arri Coomarasamy (University of Birmingham, UK); Sinead Delany-Moretlwe (University of the Witwatersrand, South Africa); Myriam El Gaaloul (Medicines for Malaria Venture, Switzerland); Ruth Faden (Johns Hopkins Berman Institute of Bioethics, USA); Shivaprasad S Goudar (KLE Academy of Higher Education and Research, India); Metin Gülmezoglu (Concept Foundation, Switzerland); Justus Hofmeyr (University of Botswana, Botswana); Marian Knight (University of Oxford, UK); Anna Mastroianni (Johns Hopkins Berman Institute of Bioethics, USA); Flor Munoz-Rivas (Baylor College of Medicine, USA); Leyla Sahin (FDA, USA).
Clinical Trials in CRITICAL CARE: The Role of Networks

Fernando Bozza, MD, Ph.D

National Institute of Infectious Diseases
Oswaldo Cruz Foundation - Fiocruz
Ministry of Health, Rio de Janeiro, Brazil
Agenda

- Collaborative Networks in Critical Care
- Critical Care and Pandemic Response
- Equitable Governance → The Path Forward
Critical care is a foundation of emergency response

“Recognizing that robust emergency, critical and operative care services are at the foundation of national health systems’ ability to respond effectively to emergency events including all hazards; and to ensure the implementation of the activities required, both proactive and reactive, to minimize the danger and impact of acute public health events...”

(9) to strengthen the evidence base for emergency, critical and operative care interventions by encouraging research and supporting Member States to execute research on emergency, critical and operative care delivery, including by providing tools, protocols, indicators and other needed standards to support the collection, analysis and reporting of data, including on cost-effectiveness;
Clinical research networks are key drivers of quality and capacity

“CALLS ON Member States...”

“to encourage research funding agencies to prioritize and fund clinical trials that are well-designed and well-implemented, including through...”

(a) encouraging investment in well-designed clinical trials, including through clinical trials networks that are developed in collaboration with affected communities, with a view to addressing their public health needs and with the potential for trials to contribute to clinical trial capabilities, including strengthening the core competencies of research personnel, particularly in developing countries;
The ecosystem of critical care research

Networks of Networks

Clinical Trials Networks

ICU Registries
ICU registries provide benchmarking and data infrastructure

14 registries
22 countries
Global research collaborators
Critical care networks build capacity and improve care

CCCTG collaborations

Burns et al. 10.1164/rccm.202001-0098LE
Growing global trend of investigator-led critical care trials groups
Growing global trend of investigator-led critical care trials groups

Launch of critical care research networks
Networks of networks drive rapid collective response
Networks of networks drive massive collective response

COVID-19 Data Platform
~1 million patients
>50% from LMIC
76 countries
>1,800 sites

>180 manuscripts
19 clinical reports
4 clinical dashboards
Evidence for policy, planning, clinical trial designs and regulatory submissions
Introducing: ISARIC LMIC Regional Hubs

> 120 research sites across 12 countries - Brazil, Cameroon, DRC, Ghana, Guinea, India, Kenya, Nepal, Pakistan, Philippines, Senegal and Uganda

Data collected on >24,000 COVID-19 patients

- ISARIC 3.0 represent ISARIC at international and regional levels
- Promote and coordinate regional preparedness and response to outbreaks
- Coordinate and oversee academic training
Network hubs to support international registry enabled clinical trials
How did we organize the clinical research response?

- Using available data: National surveillance systems and ICU registry
- Running trials: Coalition – 8 trials
- Integrating translational research: ISARIC/WHO CCP
- Community based-intervention: vulnerable urban communities
BRICNet COVID trials: March, 2020

Network Initiated

Coalition 1: HCQ n=667
Coalition 2: AZT n=447
Coalition 3: DEX n=299
Coalition 4: ATC n=615
Coalition 5: HCQ n=1300
Coalition 6: TCZ n=129
Coalition 7: Follow-up n=1800
Coalition 9: antiviral n=2000
WHO Brainstorming Session in collaboration with InFACT and ISARIC held on Oct. 4-7, 2023

- Translate the experience of observational trial (O2CoV2) to the design of an intervention
- Link LMIC investigators into the wider Colloquium

100+ attendees from 40 countries over 3 DAYS joined in Toronto
### Beyond COVID-19: Building an Acute Illness Research Platform to Enhance Global Healthcare

#### Start Themes

<table>
<thead>
<tr>
<th>Clinical science is a global good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical science must be rigorous, reliable, and accessible</td>
</tr>
<tr>
<td>Endogenous and external factors modify the individual response to treatment</td>
</tr>
</tbody>
</table>

#### Issues

1. Lack of global data
2. Lack of global research infrastructure
3. Clinical demands on research staff
4. Competition amongst trials
5. Research slow to start
6. Research not embedded in clinical practice
7. Few patients were studied
8. Inequitable research provision globally
9. Causes of heterogeneity:
   - Prognostic and predictive heterogeneity
   - Equity and inclusiveness
   - Different care settings
   - Consequences of heterogeneity:
     - Different treatment effects
     - Inefficient resource allocation

#### Improvements

1. Global trial registry
2. Research networks
3. Comprehensive data
4. Alignment
5. Collaboration
6. Governance
7. Learning healthcare system
8. Clinically embedded platform trials
9. Clinically embedded observational studies
10. Interoperable data systems and capture
11. Biosamples and phenotyping
12. Better biological targets
13. Common Research Framework
14. PIRO (Predisposition, Infection, Response and Organ Dysfunction) Model for staging system for critical illness

#### Needs

- Funders and policy-makers to engage with the international community of independent, clinician-investigator-led research networks to support the infrastructure, specific programs and timelines to realize this.
- A more secure global healthcare ecosystem, better able to act together in response to the known and unknown challenges of the 21st century.

#### Finish

- To offer research participation to all critically ill patients worldwide through embedding research into usual care.

#### Cross cutting themes >

- Patient involvement and engagement
- Mentorship of early career researchers
- Research leadership from the Global South
The Future of Clinical Trials

• We have a strong starting point of international collaboration... and need to close the gap.

Vision

• **Engagement:** Communication, equity and diversity

• **Efficiency:** Simpler, working close to the health system, value for money

• **Coordination:** Multiple funders, innovative models of collaborations
### Equitable Governance: Involving LMICs in ICU Trials

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Principles</th>
<th>Required resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>• How do you establish new models of international collaboration – local leadership X global participation?</td>
<td>• Access</td>
<td>• Professional project management teams</td>
</tr>
<tr>
<td>• How do we professionalize the sites to give sustainability?</td>
<td>• Diversity</td>
<td>• ICU research networks</td>
</tr>
<tr>
<td>• Simplify contracts and Intellectual property?</td>
<td>• Voice</td>
<td>• Funding</td>
</tr>
<tr>
<td></td>
<td>• Inclusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Benefit of research</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Shared knowledge and decisions</td>
<td></td>
</tr>
</tbody>
</table>
Putting into practice

O2 Respiratory Trial provides ideal demonstration project to apply learnings from the COVID pandemic:

- Distributed and equitable governance
- Networks, networks of networks + associated federation of platform trials
- Leadership from LMICs
- Interoperable and representative registries
"The most impactful research in critical care comes from trials groups led by clinician-investigators who study questions arising through the day-to-day care of critically ill patients."

- John C. Marshall, MD

International Forum for Acute Care Trials (InFACT)
WHO GLOBAL CLINICAL TRIALS FORUM

AGREEING A GLOBAL VISION FOR SUSTAINABLE CLINICAL TRIAL INFRASTRUCTURE AND CAPACITY

LILLIAN N. MUTENGU
COMMUNITY & PUBLIC ENGAGEMENT
SCIENCE FOR AFRICA FOUNDATION
Ethical: It is the right thing to do!

Practical: Helps do the right research, the right way!
- Optimizes design and implementation processes that are feasible and acceptable to participants and communities
- Facilitates participant recruitment & retention
- Improves quality of trial implementation which is critical to public trust
- Enhances uptake of products and policies – but this must be built on trust! (e.g., COVID vaccines)
Acknowledges importance of “…inclusion of all trial stakeholders, including representatives of patient groups, according to best practices in the development of clinical trials with affected communities to ensure that the health interventions address their needs …."

Calls on member states to increase capability for “… well designed and well implemented…” clinical trials that include “… all the major population groups the intervention is intended to benefit..” and “… that are developed in collaboration with affected communities, with a view to addressing their public health needs …”

Calls on the WHO DG to review existing guidance for member state implementation of “… scientifically and ethically sound clinical trials ..” that “… meet the needs of major population groups that the intervention is intended to benefit, with a particular focus on under-represented populations…”
From Increased Recognition to Operationalization of CE to deliver on WHA 75.8 Resolution on Strengthening Clinical Trials
CE Operationalization to deliver on WHA.75.8 Resolution on Strengthening Clinical Trials

- Review/revise current GPP for CE in CTs to include guidance and tools on engagement and involvement of underrepresented populations.

- Embed CE in ICH-E6 (GCP). CE Must no longer be a “Nice to do”. If products and interventions developed are to drive better patient and public health outcomes, patients and publics must be systematically included, engaged and involved in CTs from Pre to Post trial.