Global **Clinical Trials** Forum

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

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

World Health Organization

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)

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Introduction to Forum

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Science Division
WHO, Geneva

20 Nov 2023

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Background

Mapping

Consultations

Key themes emerging

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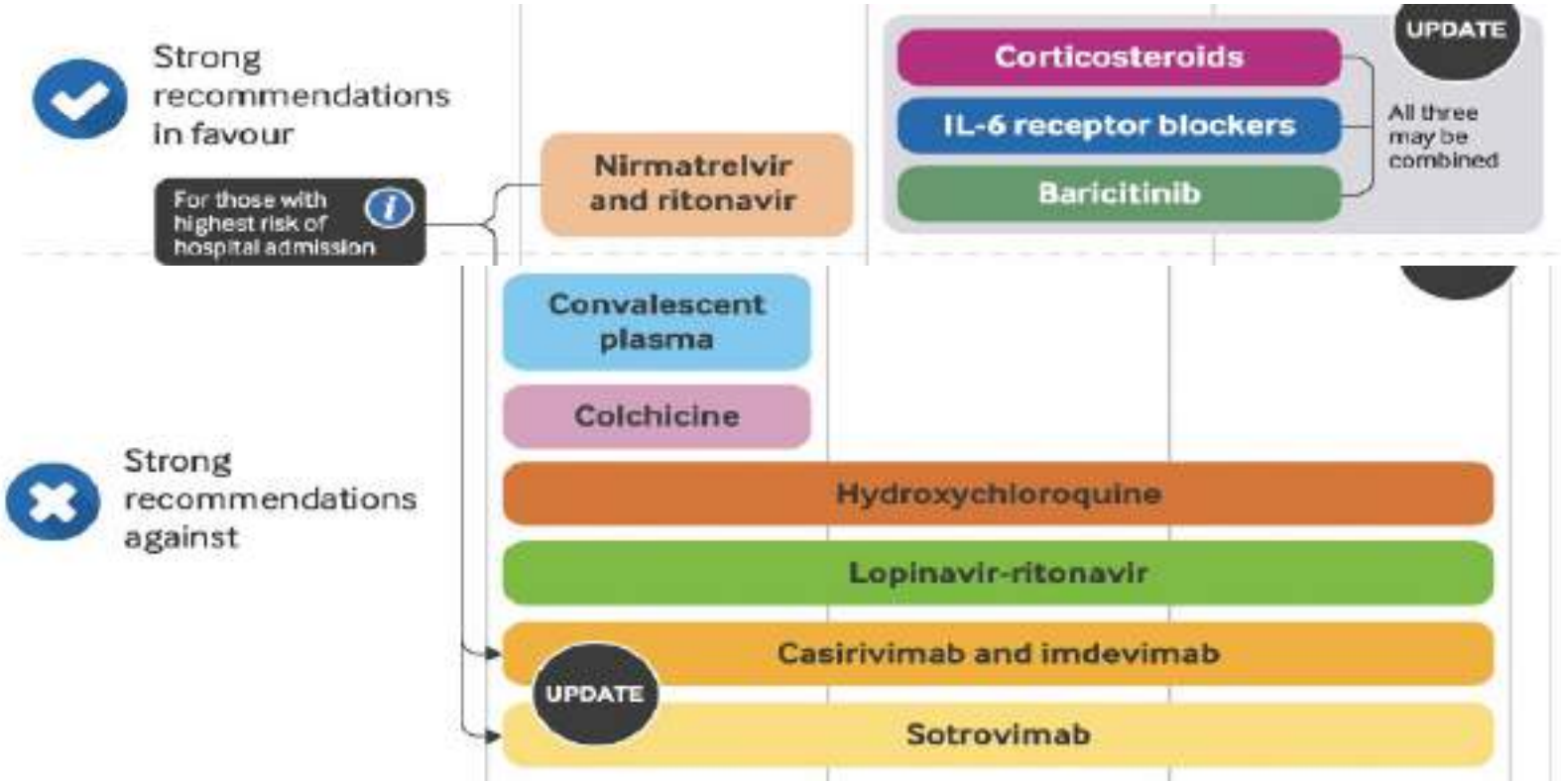
In the pandemic a few large trials generated much useful evidence and changed global practice



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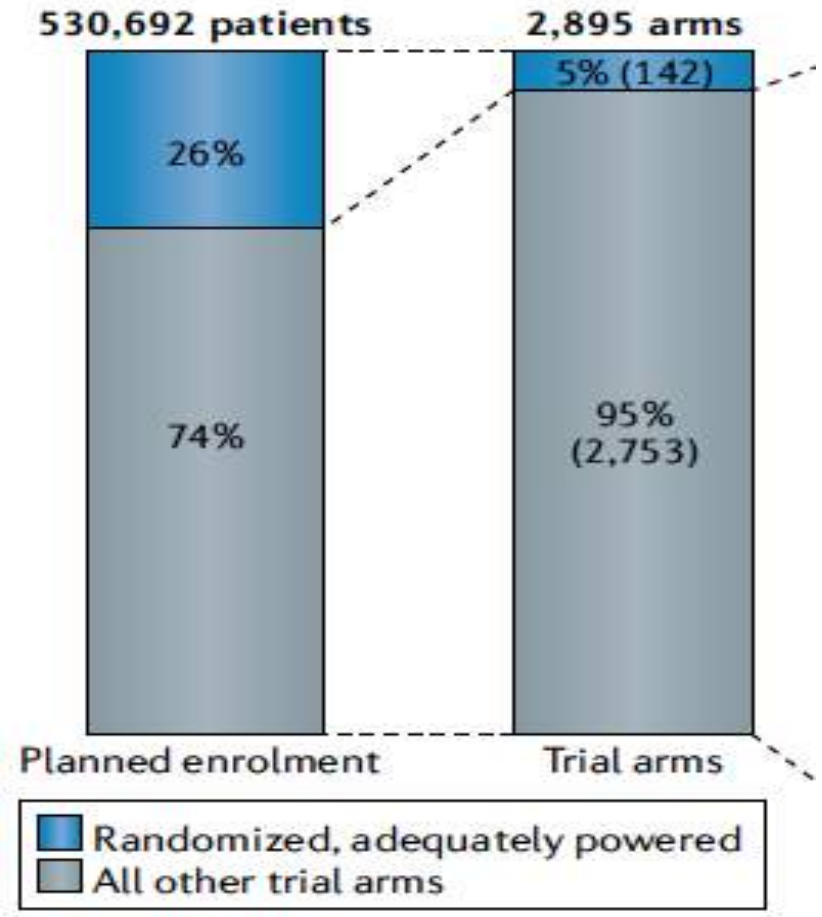
In the pandemic,1000s of trials were low quality



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Nat Rev Drug Discov . 2021 Apr;20(4):254-255. Bugin & Woodcock.

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)

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Strengthening clinical trials to provide high-quality
evidence on health interventions
Regional Consultation


120 ANOS
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Regional Consultation on Health Research Governance
and Management in South-East Asia
7-10 November 2023
World Health
Organization
South-East Asia

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

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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

2 https://apps.who.int/gb/ebwha/pdf_files/EB152/B152_13-en.pdf

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

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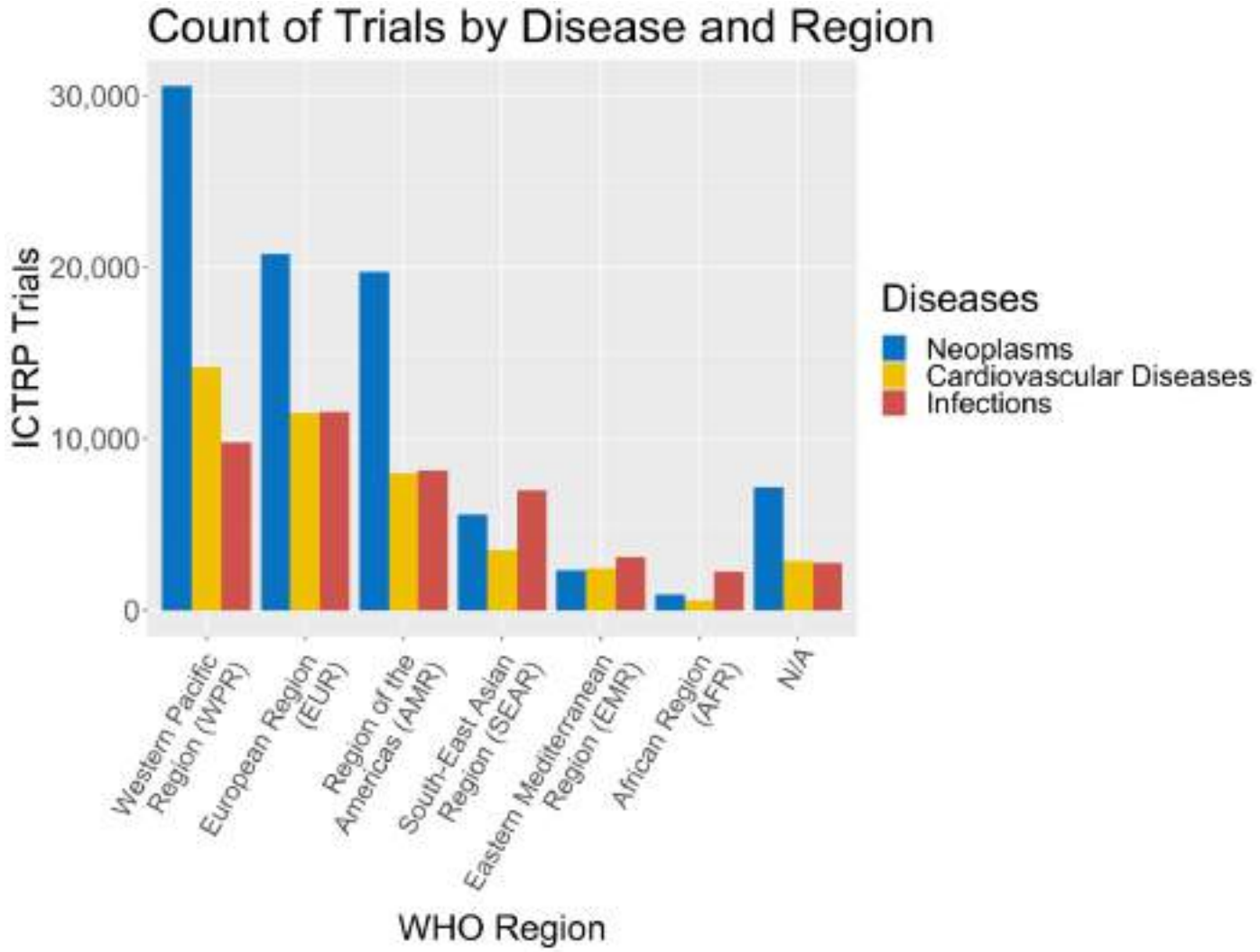
Mapping of clinical trials by disease area and region (PRELIMINARY)

- 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



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Mapping of clinical trials legislation (preliminary)

Defining

11 key aspects of clinical trial governance were identified.

Searching

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

Summarizing

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

89

- 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

39

- Legislation for an **additional 39 countries** has been identified, although direct text access remains unavailable.

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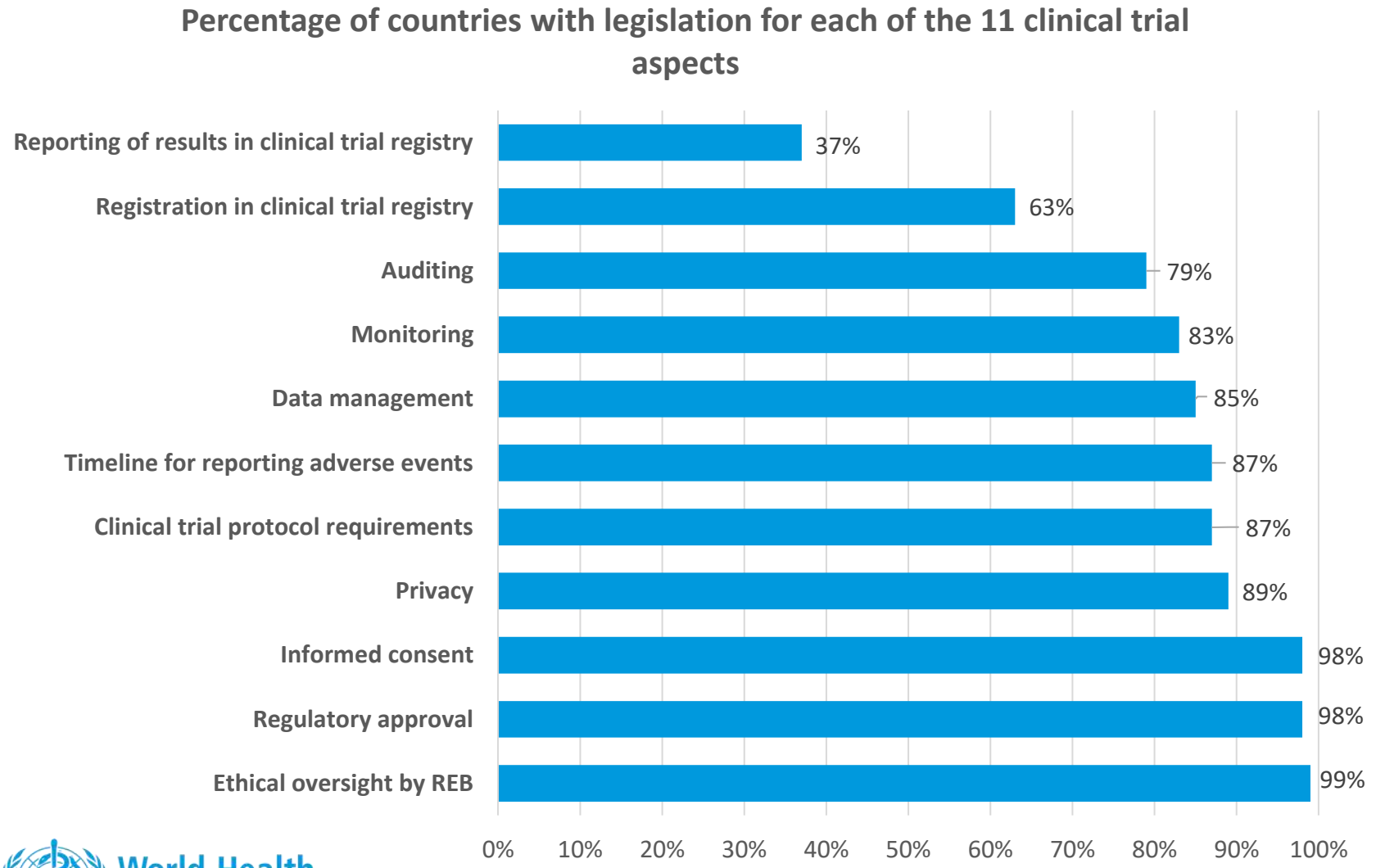
Mapping of clinical trials legislation



- **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.**

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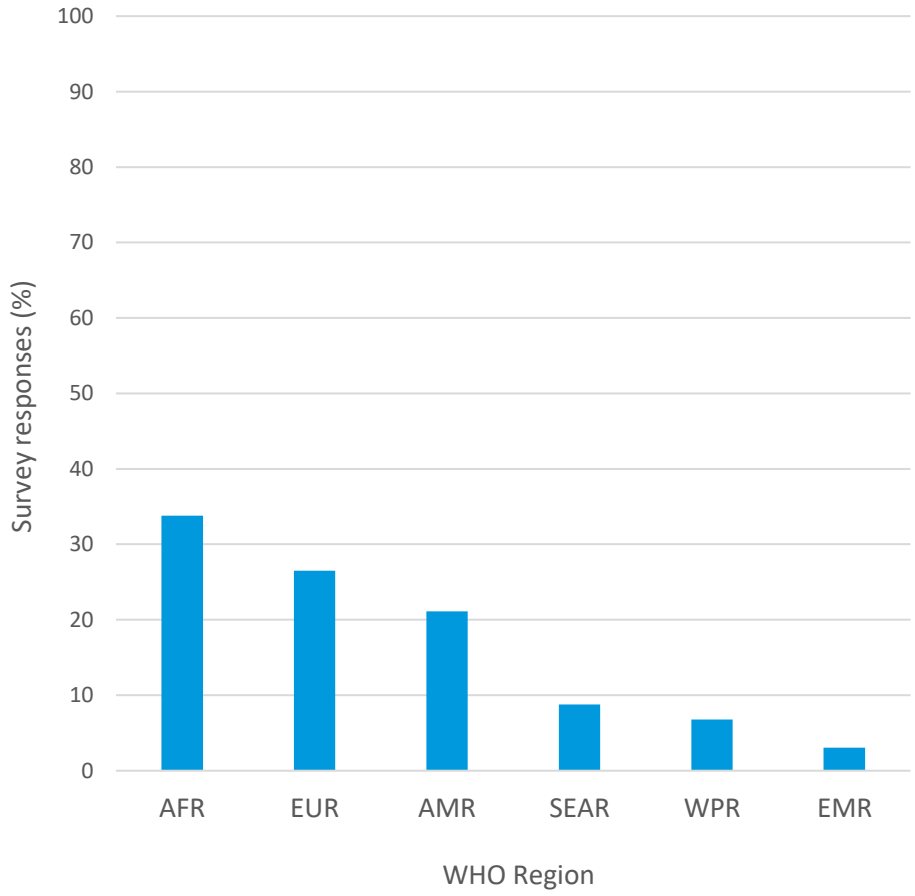
Background Information on Stakeholder Survey

- 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



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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

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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

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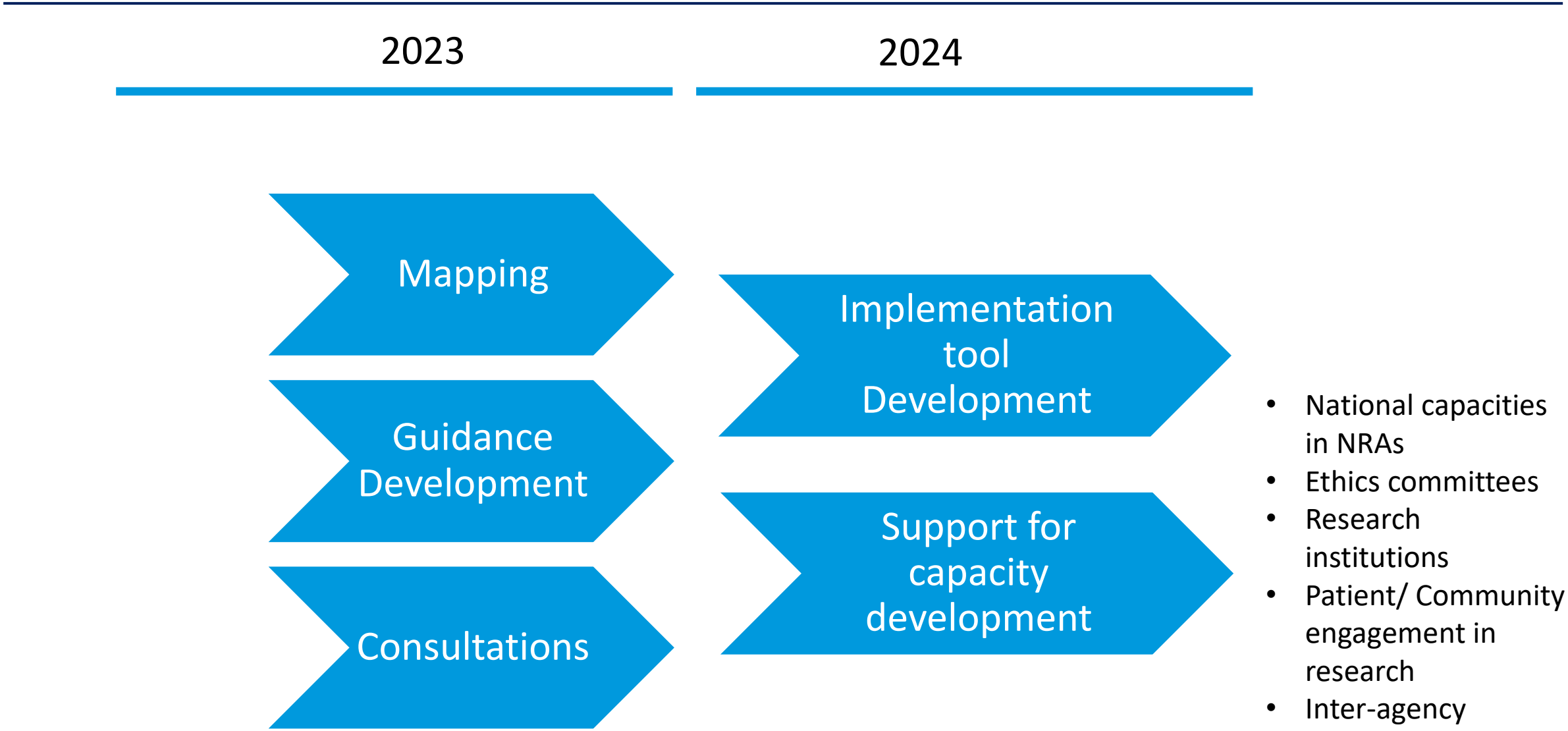

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Key areas of focus for capacity development going forwards according to inputs received

- 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

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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**…

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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.

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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**.**

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Funding Acknowledgement

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Survey support

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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

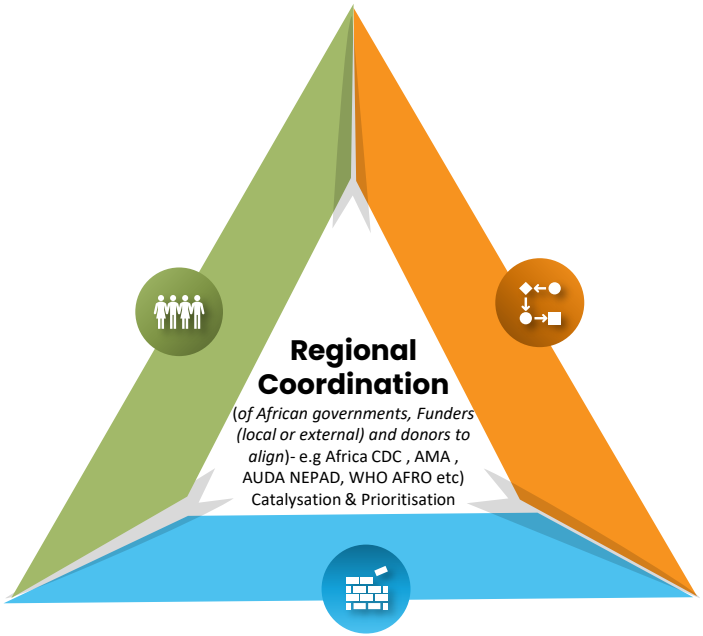
- Organising agencies:
  - Africa CDC, AUDA-NEPAD, BMGF, & EDCTP
- Sponsors:
  - BMGF & EDCTP
- Attendance:
  - 60 participants from national, regional, and global stakeholders including researchers, regional organisations, WHO, industry, private sector, community organisation representatives and research 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

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-supported ethics and regulatory projects are being conducted in **37 sub-Saharan African countries**.

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

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

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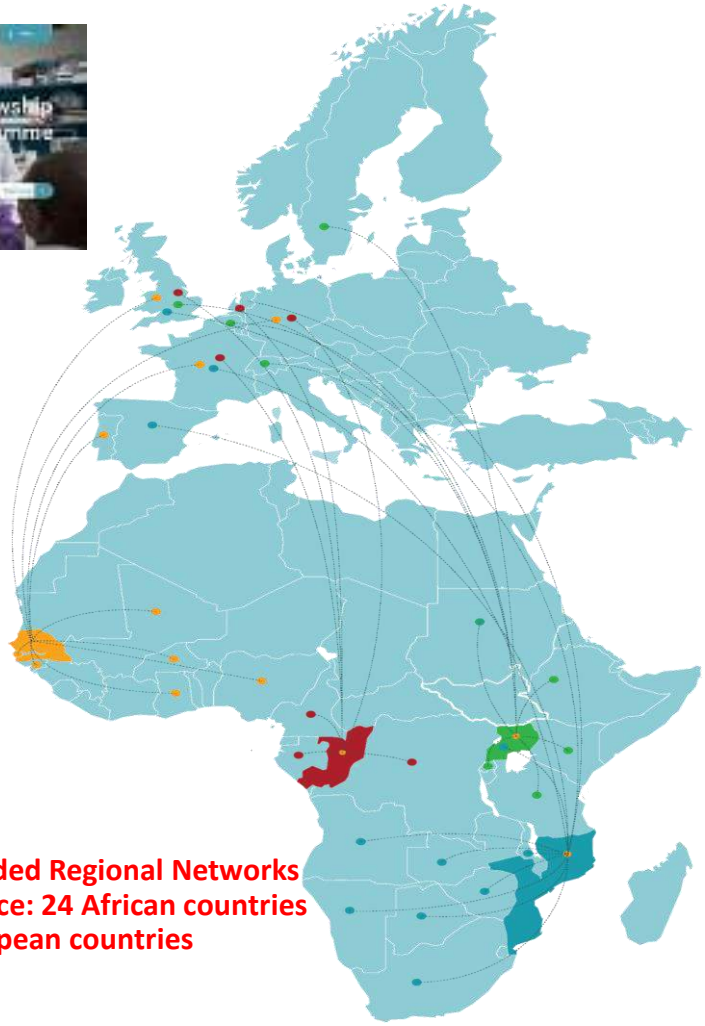
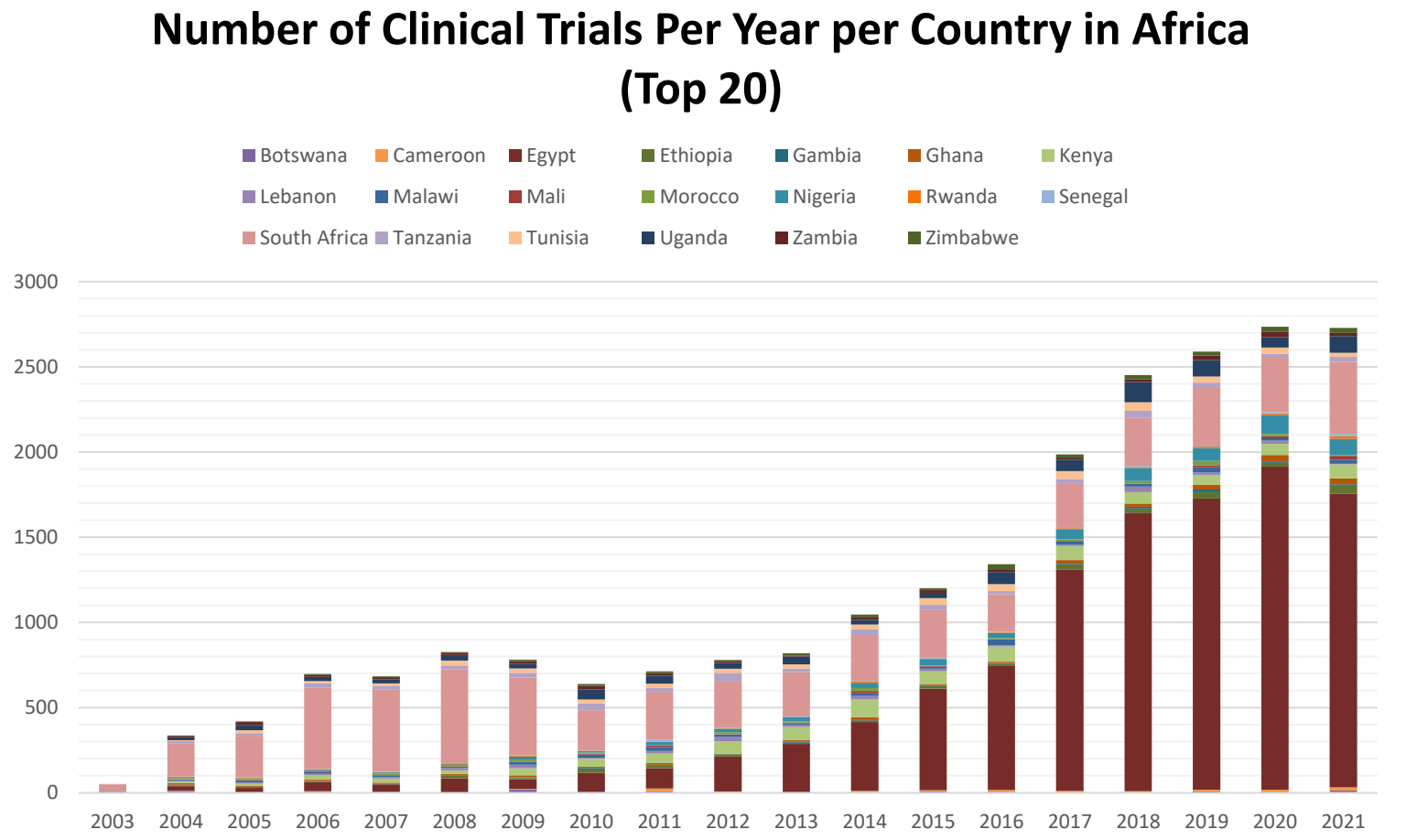
EDCTP 401 Fellowship training and retention programme



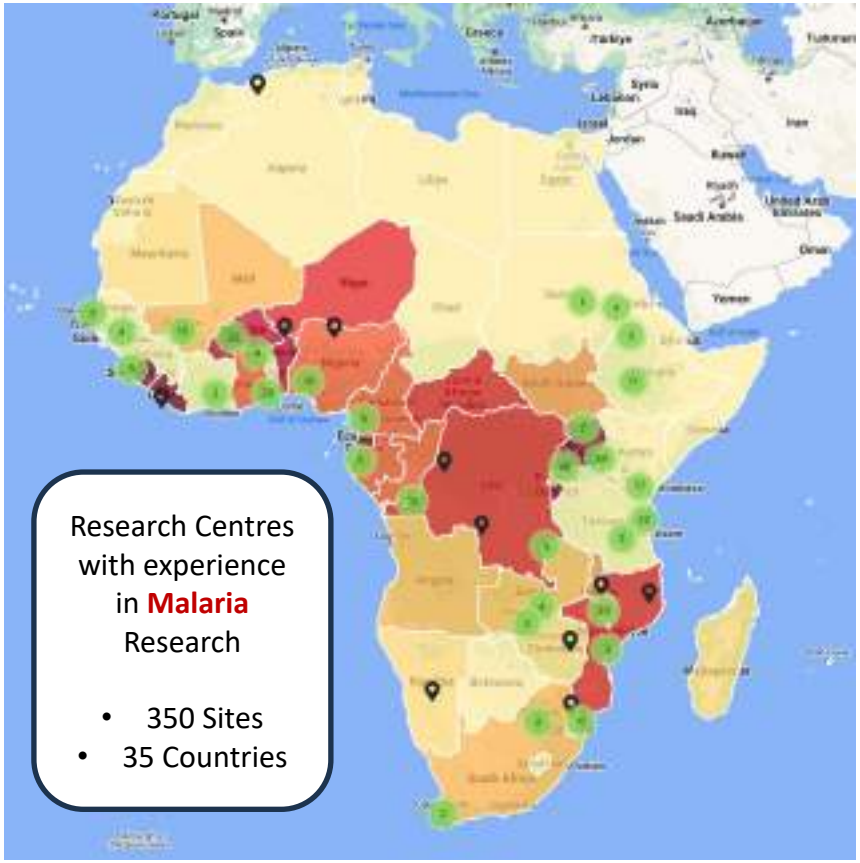
EDCTP funded Regional Networks of Excellence: 24 African countries and 7 European countries

Encouraging trend of clinical trials in Africa



Encouraging trend of clinical trials in Africa

Experience in Africa: TB & Malaria Research



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

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

The current status of the clinical trials ecosystem in Bangladesh, India, and in southeast areas

Dr. Firdausi Qadri & Prof. Jacob John

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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 3by mid 2024 (Partially performs essential regulatory functions)
Maturity level 1: some elements of regulatory systems exist

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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**

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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

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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.**

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Priority actions in Bangladesh

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

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

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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

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Priority actions

[*Perspectives from academic research in India*]

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

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. Infra-structure, 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

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Thank you

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

Clinical Trials Strategy in Singapore

Li Yang HSU
National University of Singapore

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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

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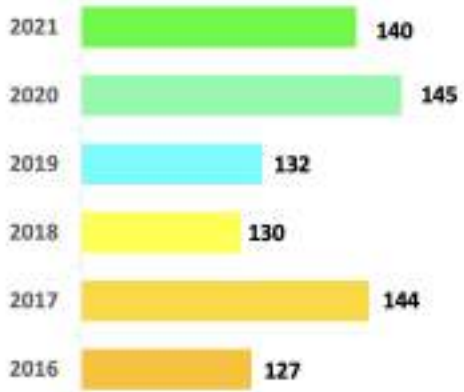
DEMOGRAPHICS OF CLINICAL TRIALS IN SINGAPORE (2016–2021)

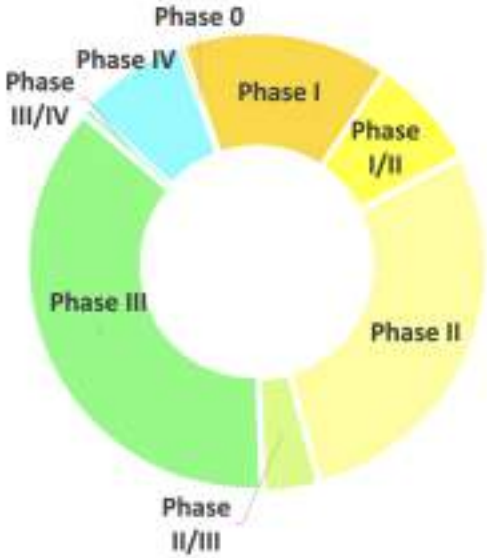
Number of Trials



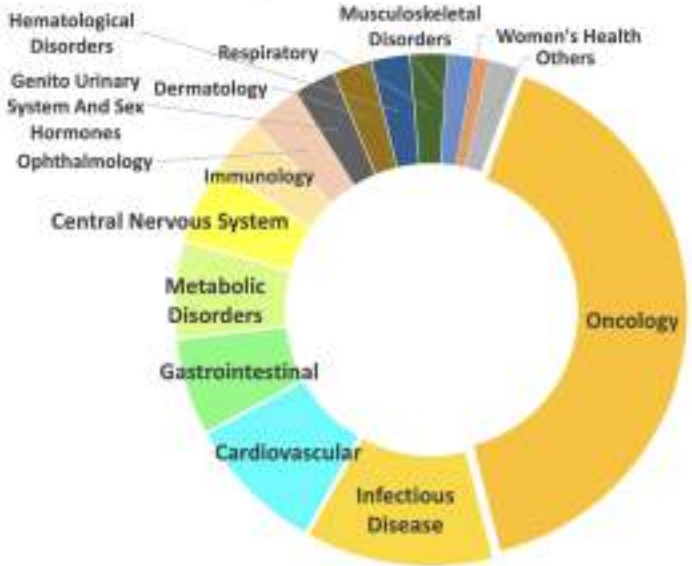
Sponsor Type

Trial Types

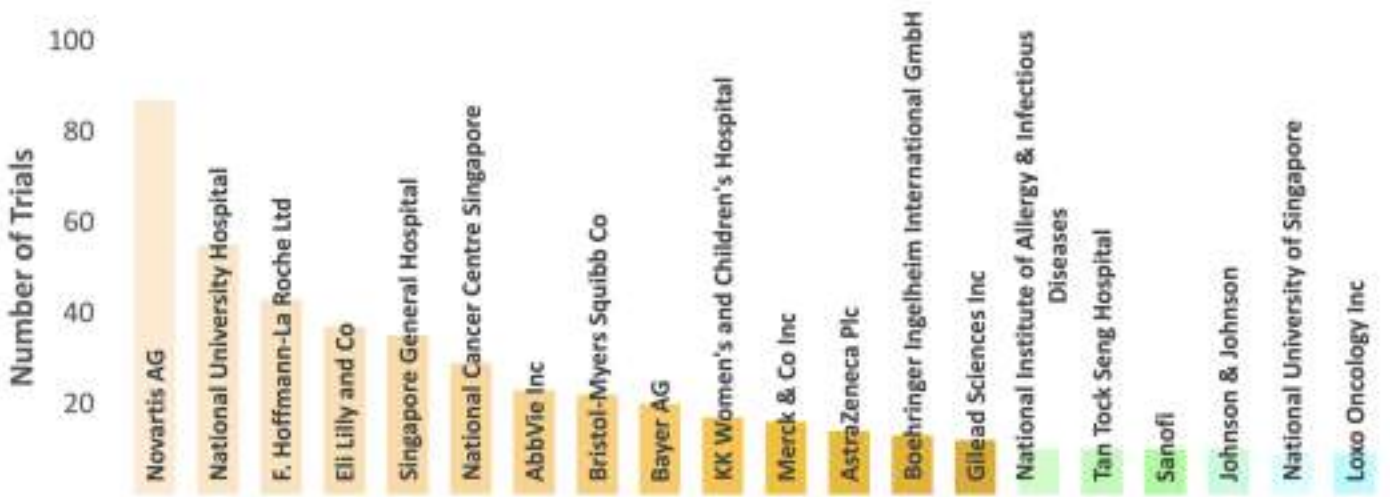
Trial Phases



Therapeutic Areas

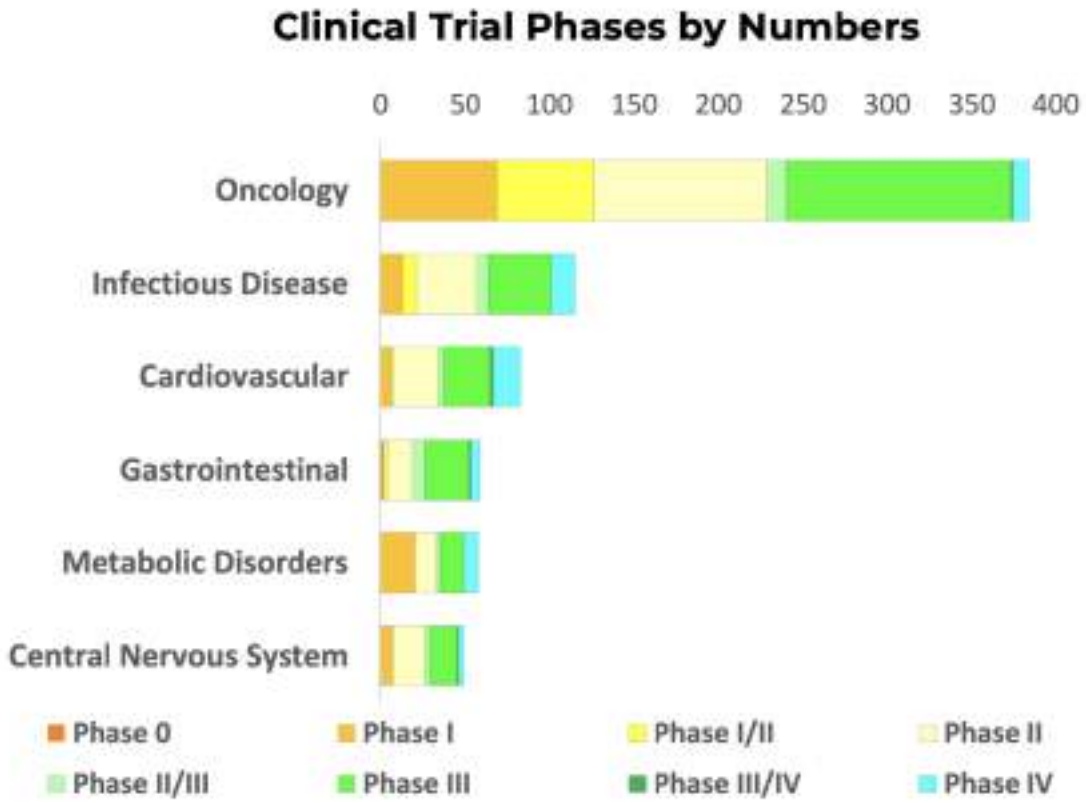


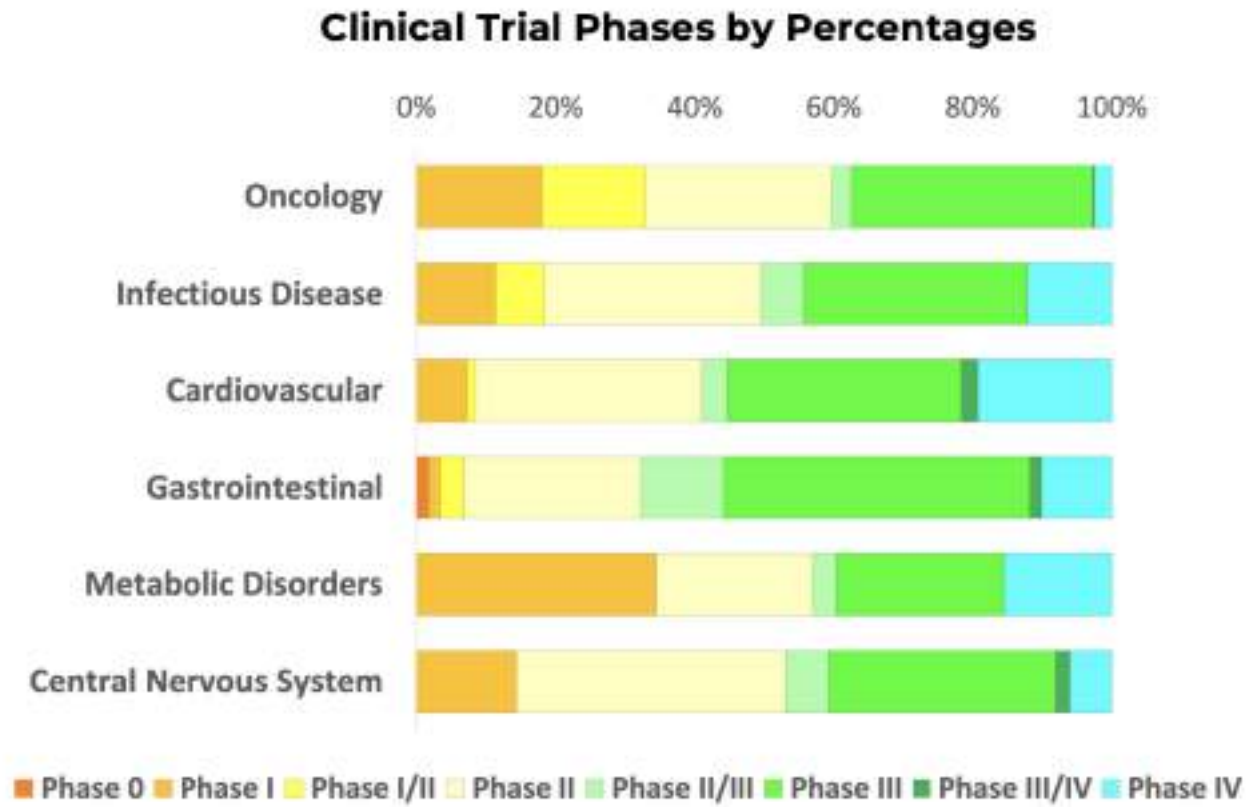
Top 20 Trial Sponsors



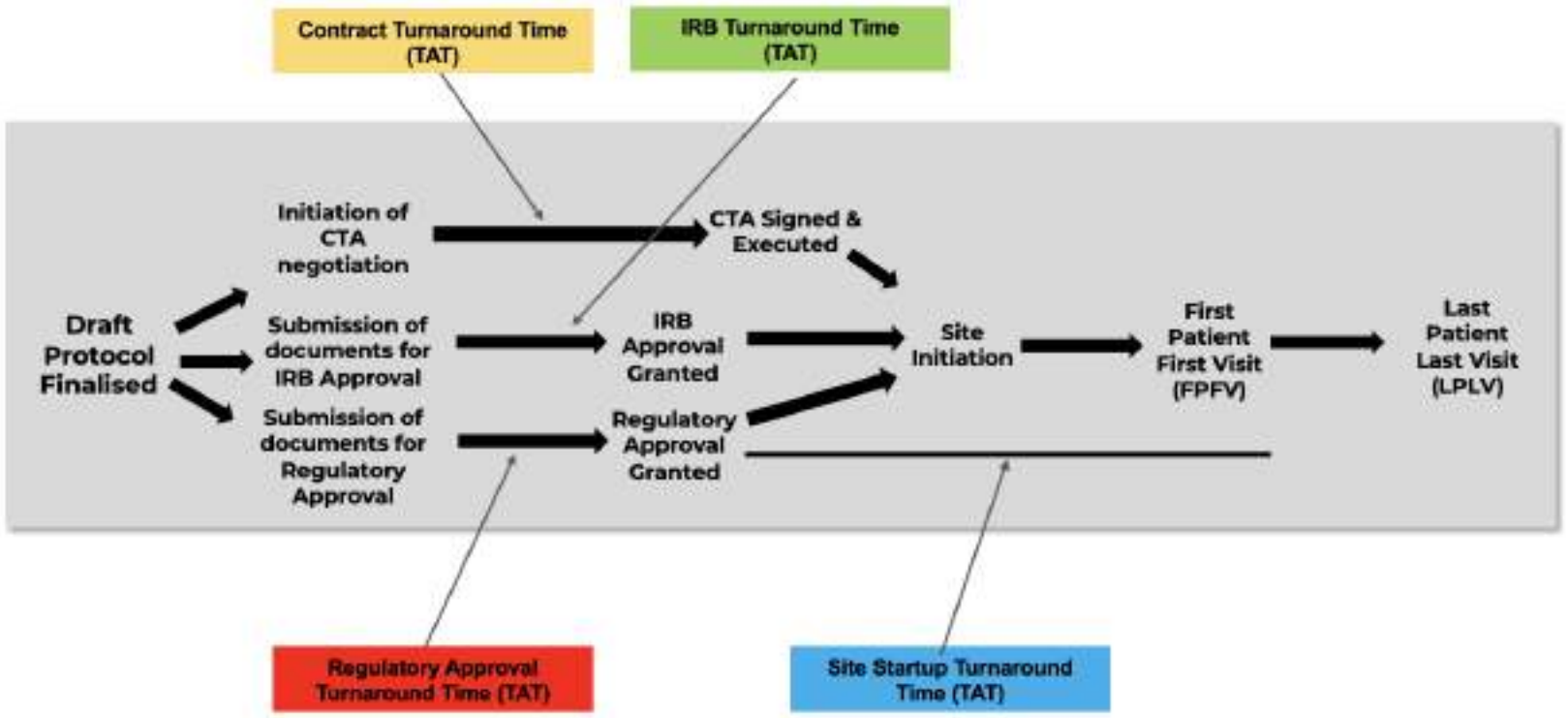
TOP 6 THERAPEUTIC AREAS OF CLINICAL TRIALS CONDUCTED IN SINGAPORE (2016 – 2021)

Clinical Trial Phases



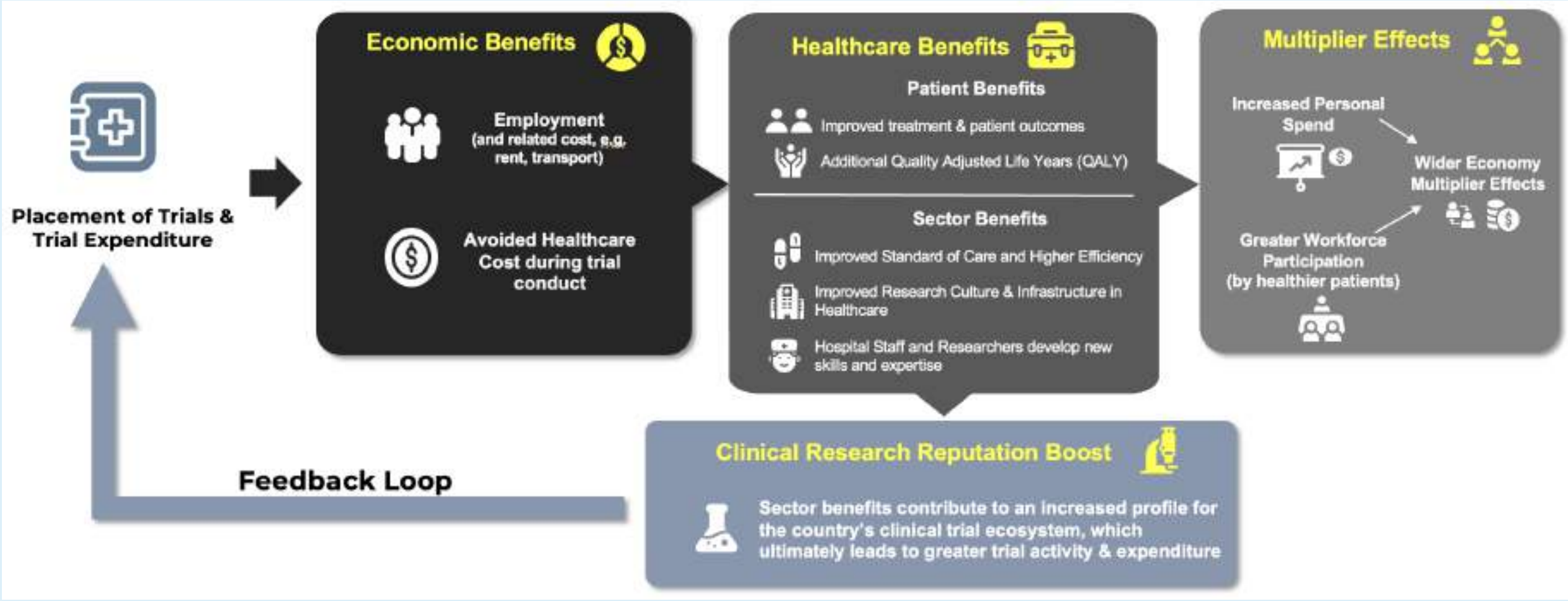


Barriers Experienced in Singapore



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

World Health Organization



- Support investigator-initiated trials to improve the healthcare system
- Enhance the clinical trials ecosystem in Singapore
- Attract more industry-sponsored trials to Singapore

World Health Organization

SINGAPORE CLINICAL RESEARCH INSTITUTE

Project Management	Data Management	Research Informatics	Research Monitoring	Biostatistics	Epidemiology
• Managing Budget, Scope, Quality and Resources of Projects • Regulatory and Ethics Submissions • Investigator and Stakeholders Management	• Database Selection • CRF/Data Design • Data Cleaning Strategy • Study Progress Reports	• Study Database Setup and Support • System Backup and Maintenance • Application Troubleshooting	• Site Monitoring Visits • Monitoring Severe Adverse Events • Training for Site Clinical Research Coordinators	• Study Design Support • Patient Randomisation Applications • Bio-statistical Analysis of Trial Data	• Efficiency and Cost Effectiveness of Healthcare systems Evaluation • Healthcare Intervention Effectiveness Evaluation • Real Word Data Analysis

Master Clinical Trials Agreement (2022)

World Health Organization

PRE-AGREED CLAUSES

- 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.

UTILIZATION

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

ADAPTABILITY

- 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

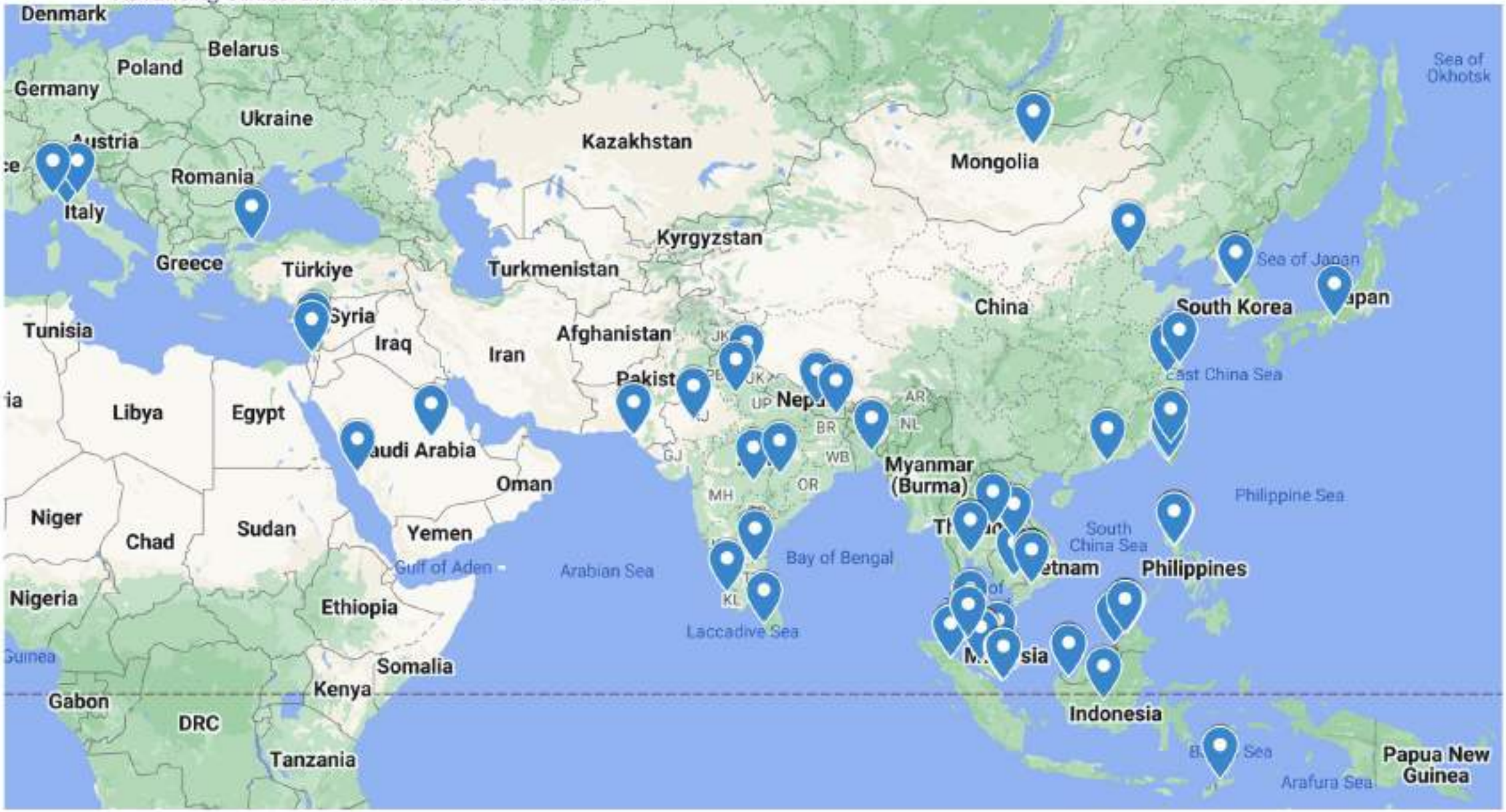
- Hurdles:
  - Funding of networks and trials
  - Contracting and capacity building

World Health Organization

advanceid.

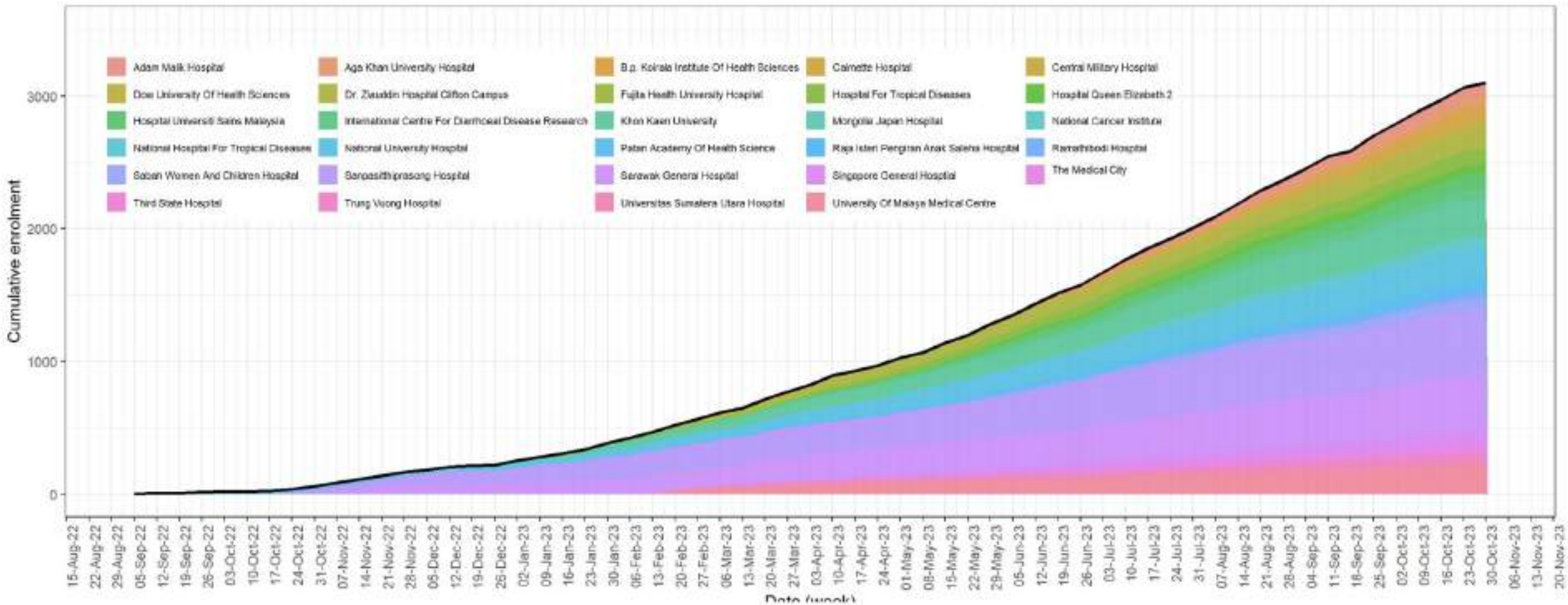
Advancing Clinical Evidence in Infectious Diseases

Collaborating Institutions



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.

World Health Organization

World Health Organization

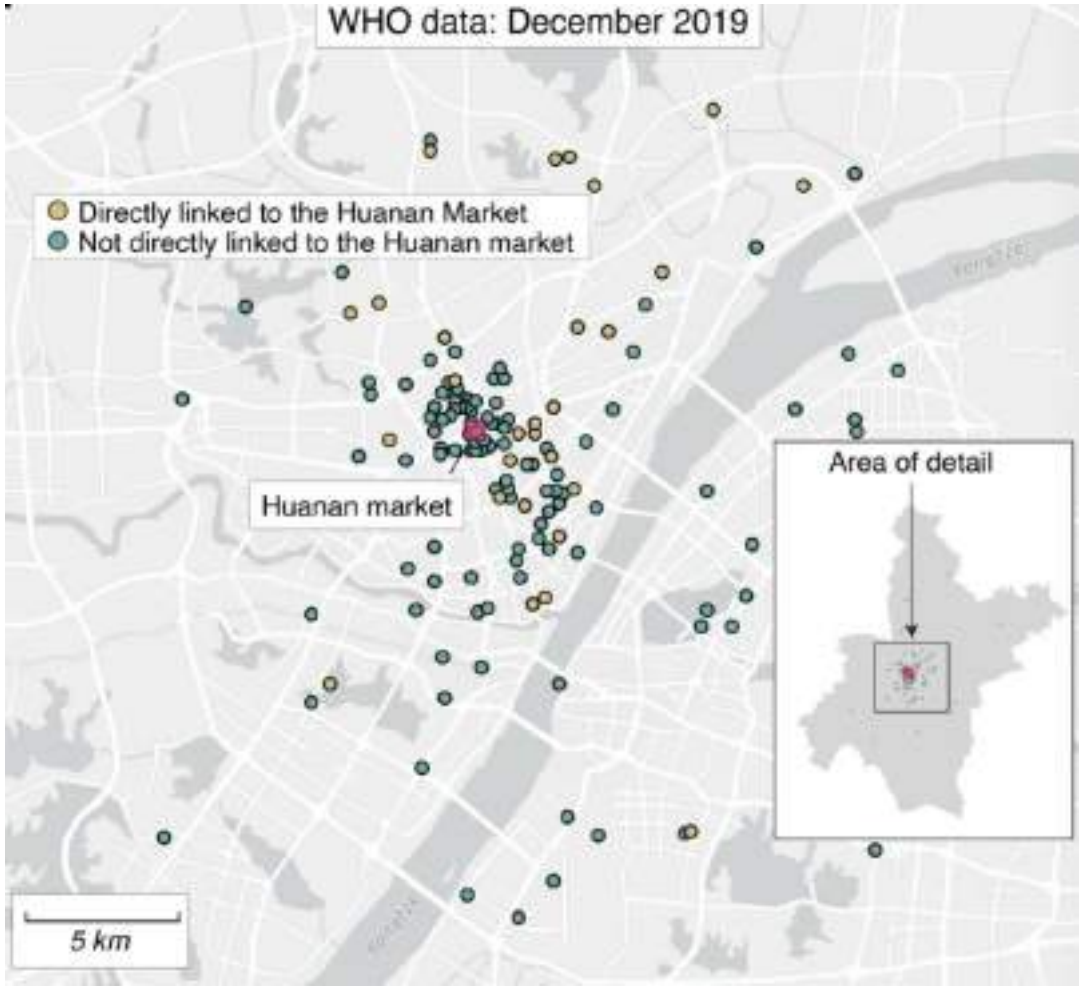
Global Clinical Trials Forum, 20-21 November 2023
WHO, Geneva, Switzerland

Preparing for the next pandemic: what we do in China

Dr Bin Cao
China-Japan Friendship Hospital, Beijing, China

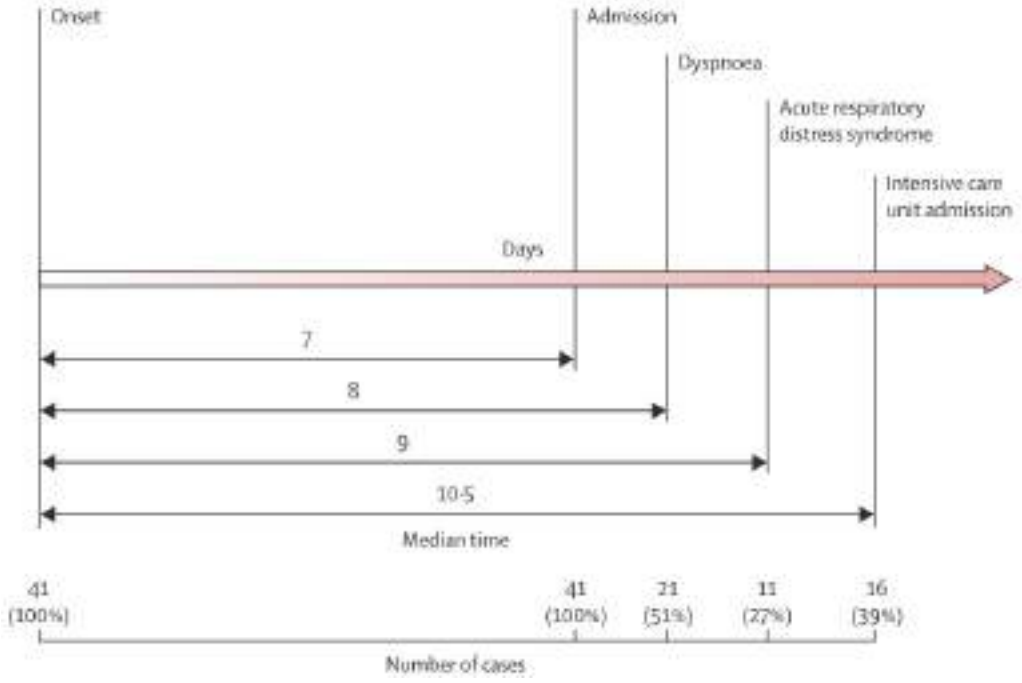
World Health Organization

Outbreak of COVID-19

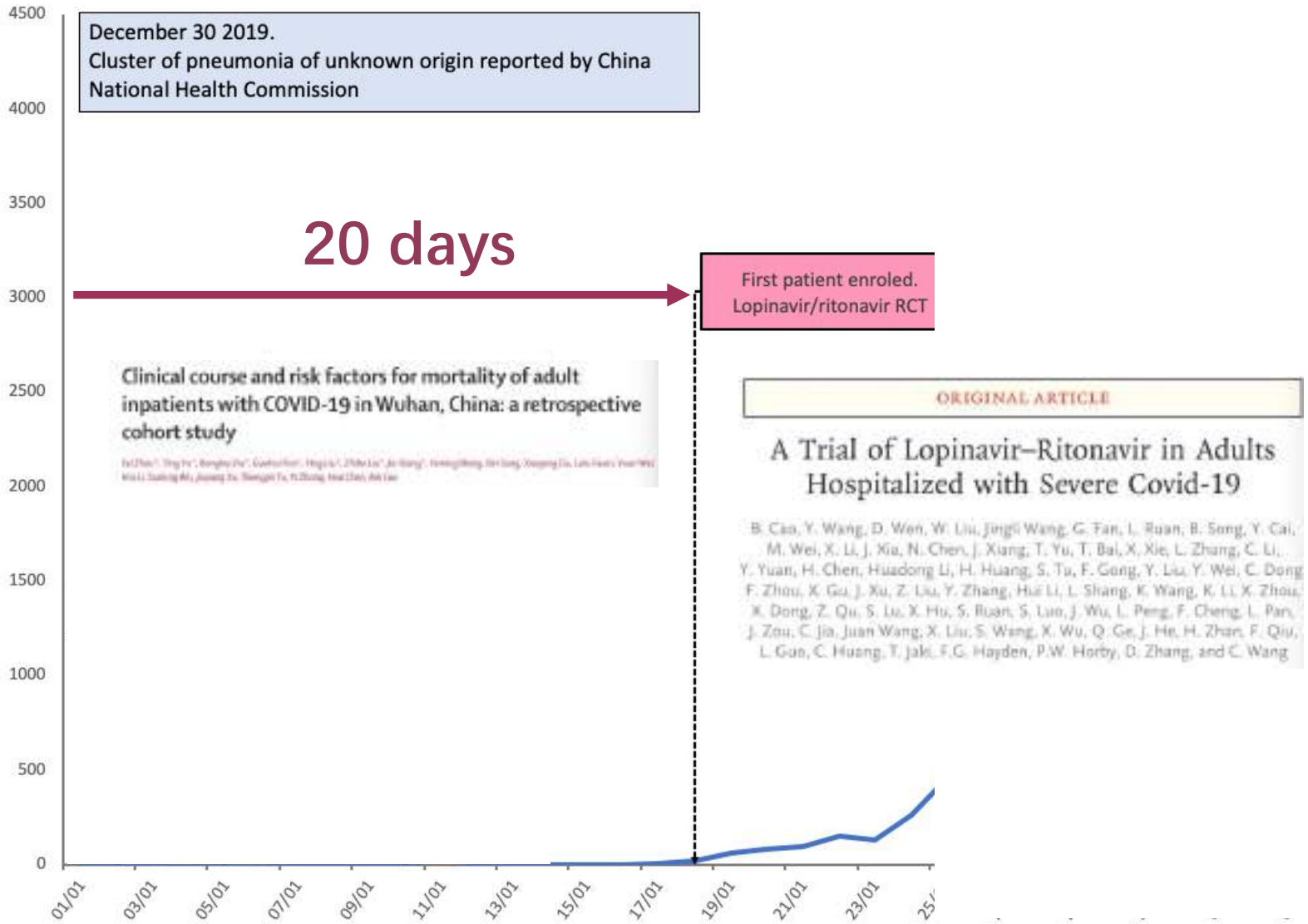


Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Chaolin Huang, Yeming Wang*, Xingwang Li*, Lili Ren*, Jianping Zhao*, Yi Hu*, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu, Zhenshun Cheng, Ting Yu, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie, Guangfa Wang, Rongmeng Jiang, Zhancheng Gao, Qi Jin, Jianwei Wang†, Bin Cao†*



Early COVID trials – Jan 2020



Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

ORIGINAL ARTICLE

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

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

courtesy to peter

Current COVID trials – 2022-2023

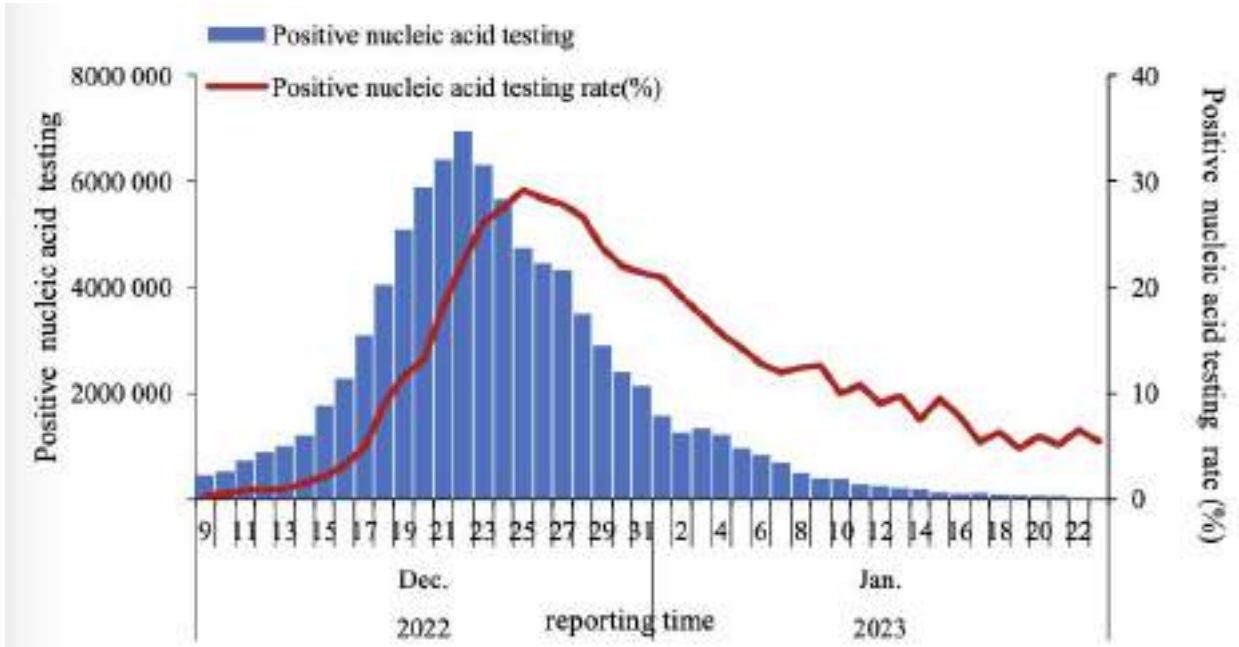


Figure 1-1 Daily number of positive nucleic acid testing and rate in Chinese mainland.

(Dec. 9, 2022 - Jan. 23, 2023)

https://en.chinacdc.cn/research/achievements/202307/t20230720_267982.html

The NEW ENGLAND JOURNAL of MEDICINE

Please review the Supplemental Files folder to review documents not compiled in the PDF.

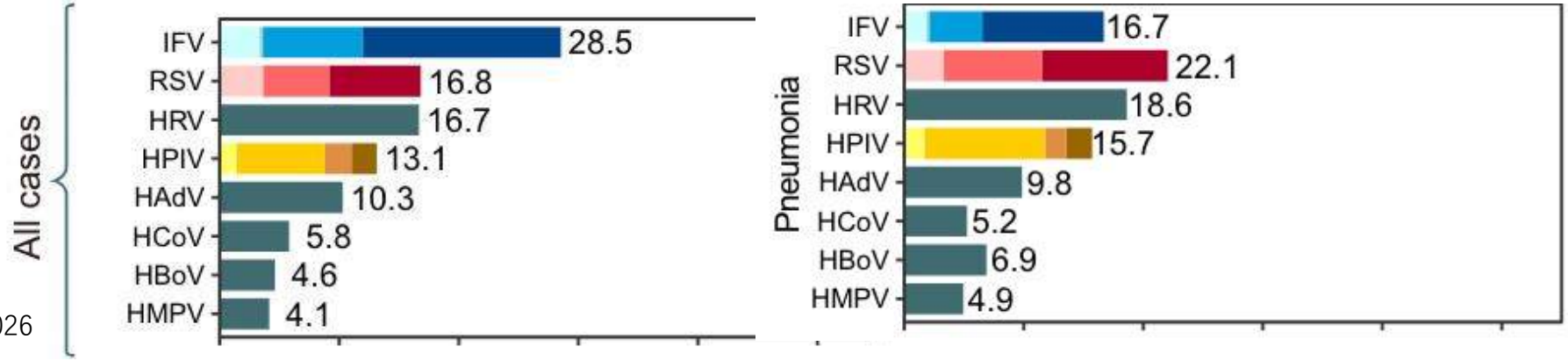
Oral simnotrelvir for adult patients with mild-to-moderate COVID-19

Journal:	*New England Journal of Medicine*
Manuscript ID	23-01425.R2

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

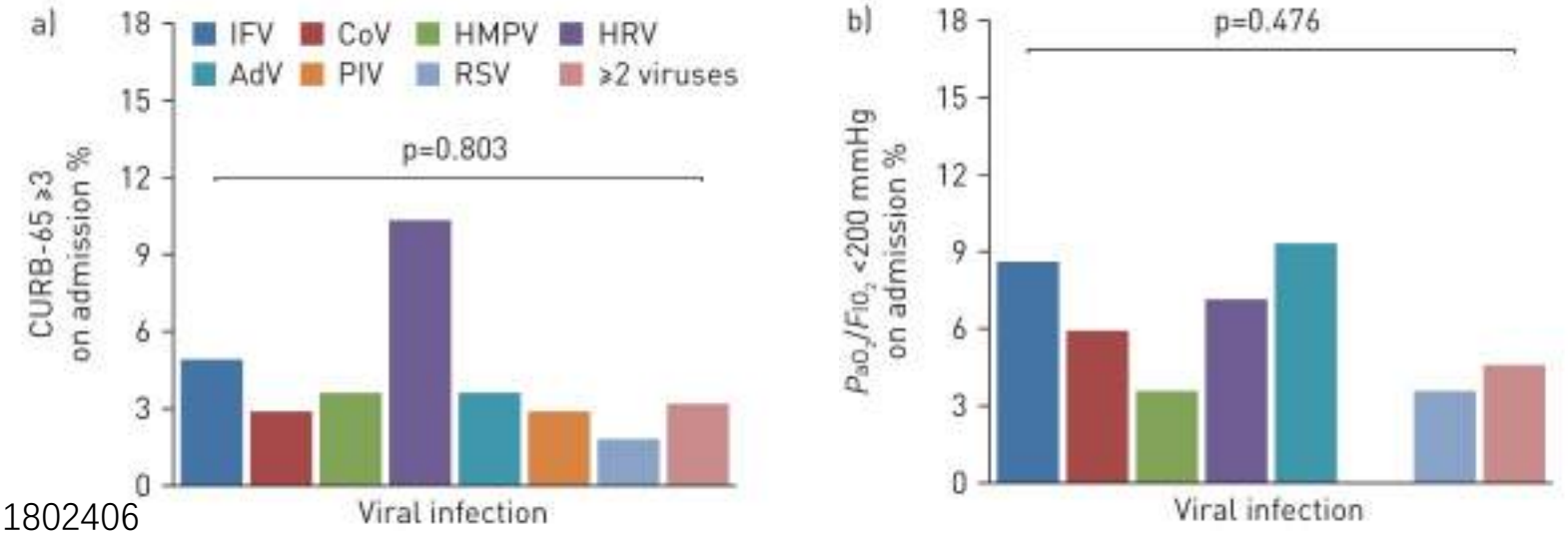
Preparing for our next threatening

2009-2019
China CDC



Nat Commun. 2021;12(1):5026

2015-2017
CAP-China



Eur Respir J. 2019;54(2):1802406

World Health Organization

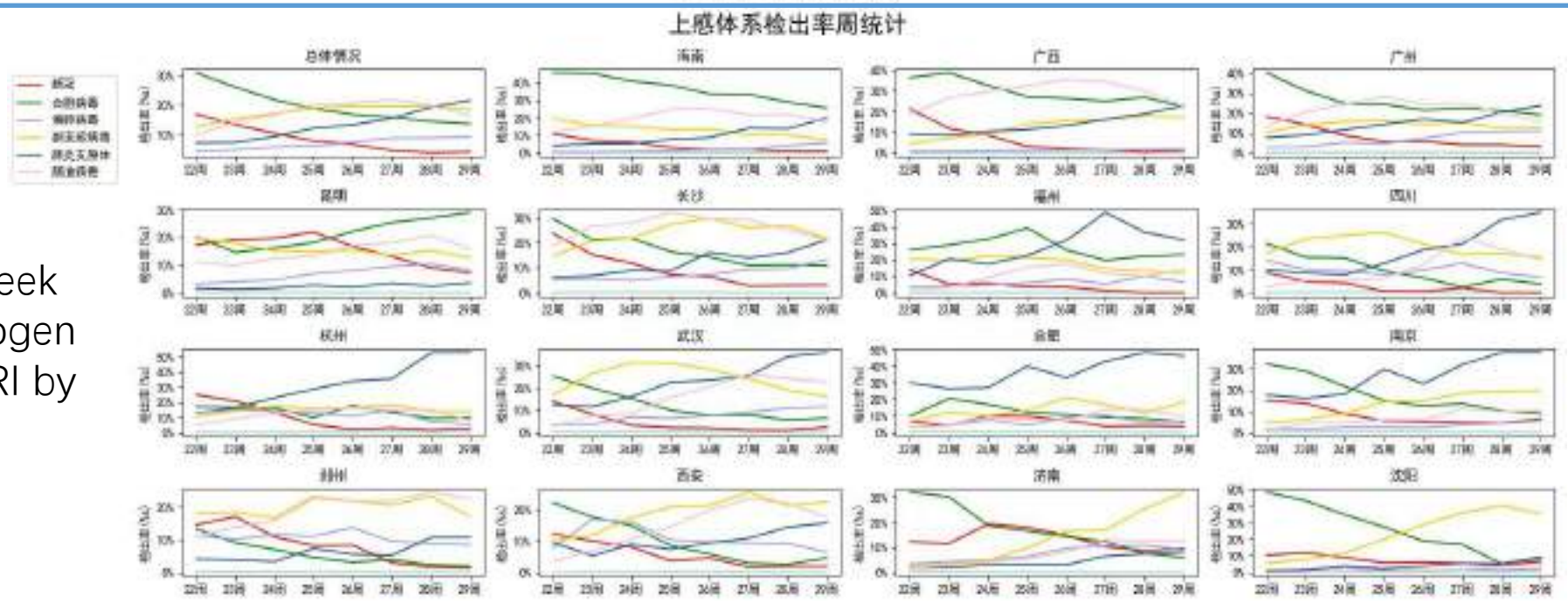
SEVENTY-FIFTH WORLD HEALTH ASSEMBLY
Agenda item 16.2

WHA75.8
27 May 2022

Strengthening clinical trials[1] to provide high-quality evidence on health interventions and to improve research quality and coordination

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

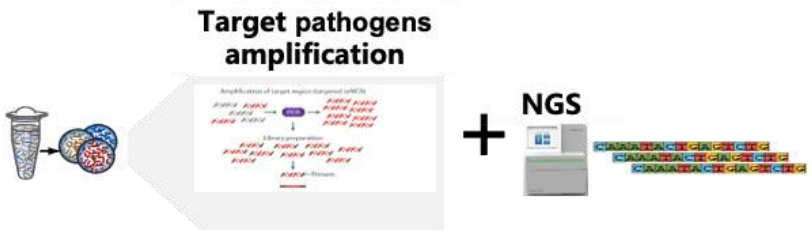
CAP-China network 1.0 (**2019**)
Only report viral pathogens in CAP


EUROPEAN RESPIRATORY *journal*

Disease severity and clinical outcomes of community-acquired pneumonia caused by non-influenza respiratory viruses in adults: a multicentre prospective registry study from the CAP-China Network

Cross-section

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



China surveillance

CAP-China network 3.0 (**2030**)
Surveillance + trial

Flu, rsv, hcov, hmpv et al

Patient characters

Platform plus basket trial

Acknowledgement

中国医学科学院
北京协和医学院

National Natural Science
Foundation of China
国家自然科学基金

昌平实验室
CHANGPING LABORATORY

新基石科学实验室
NEW CORNERSTONE
SCIENCE LABORATORY

Organisation mondiale de la Santé
BUREAU RÉGIONAL DE LA Méditerranée orientale

World Health Organization
REGIONAL OFFICE FOR THE Eastern Mediterranean

منظمة الصحة العالمية
المكتب الإقليمي لشرق المتوسط

First WHO Global Clinical Trials Forum

EMRO

Faiez Zannad

Emeritus Professor Cardiology and Therapeutics

Clincial Scientist and Clinical Trialist

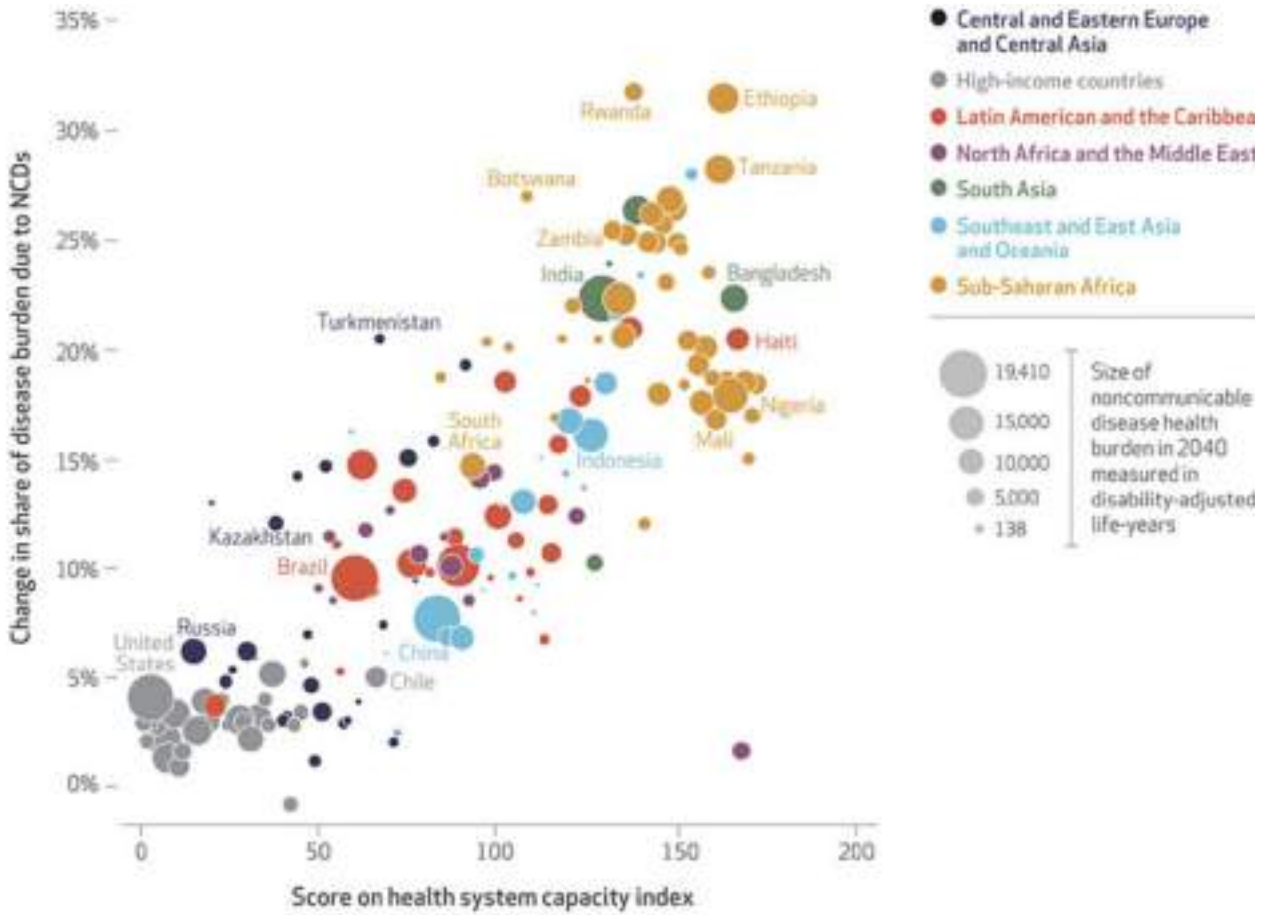
Inserm, Université de Lorraine.

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 AFFAIRSVOL. 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

Latin America

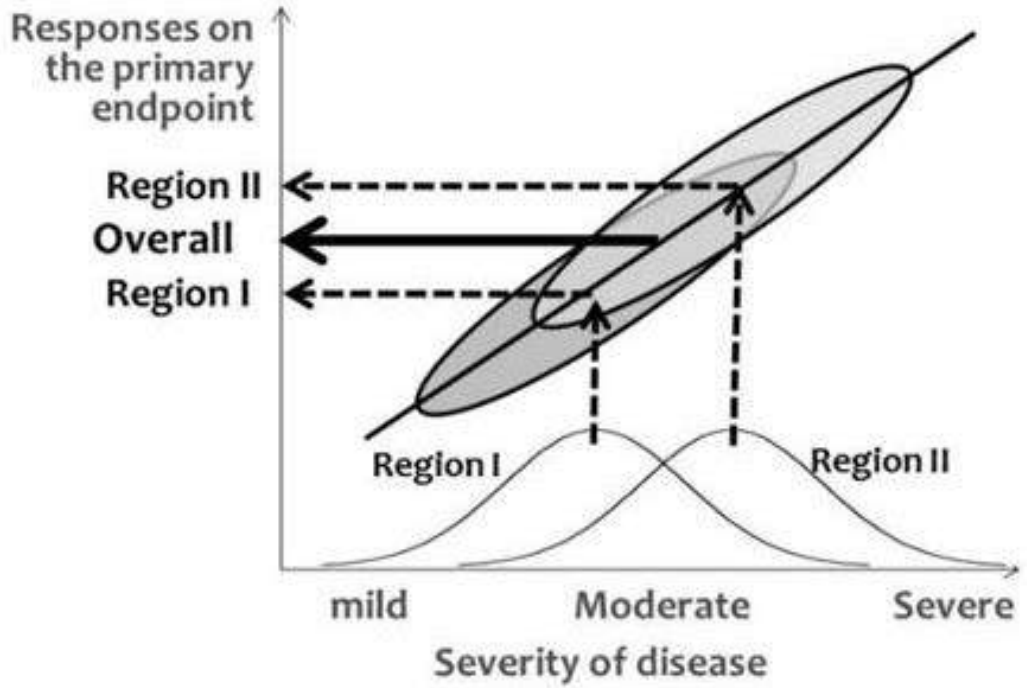
Argentina	297
Brazil	520

Asia-Pacific

China	237
India	237
Japan	343
Taiwan	141
Vietnam	138

Results in HICs are not necessarily generalizable to LMICs

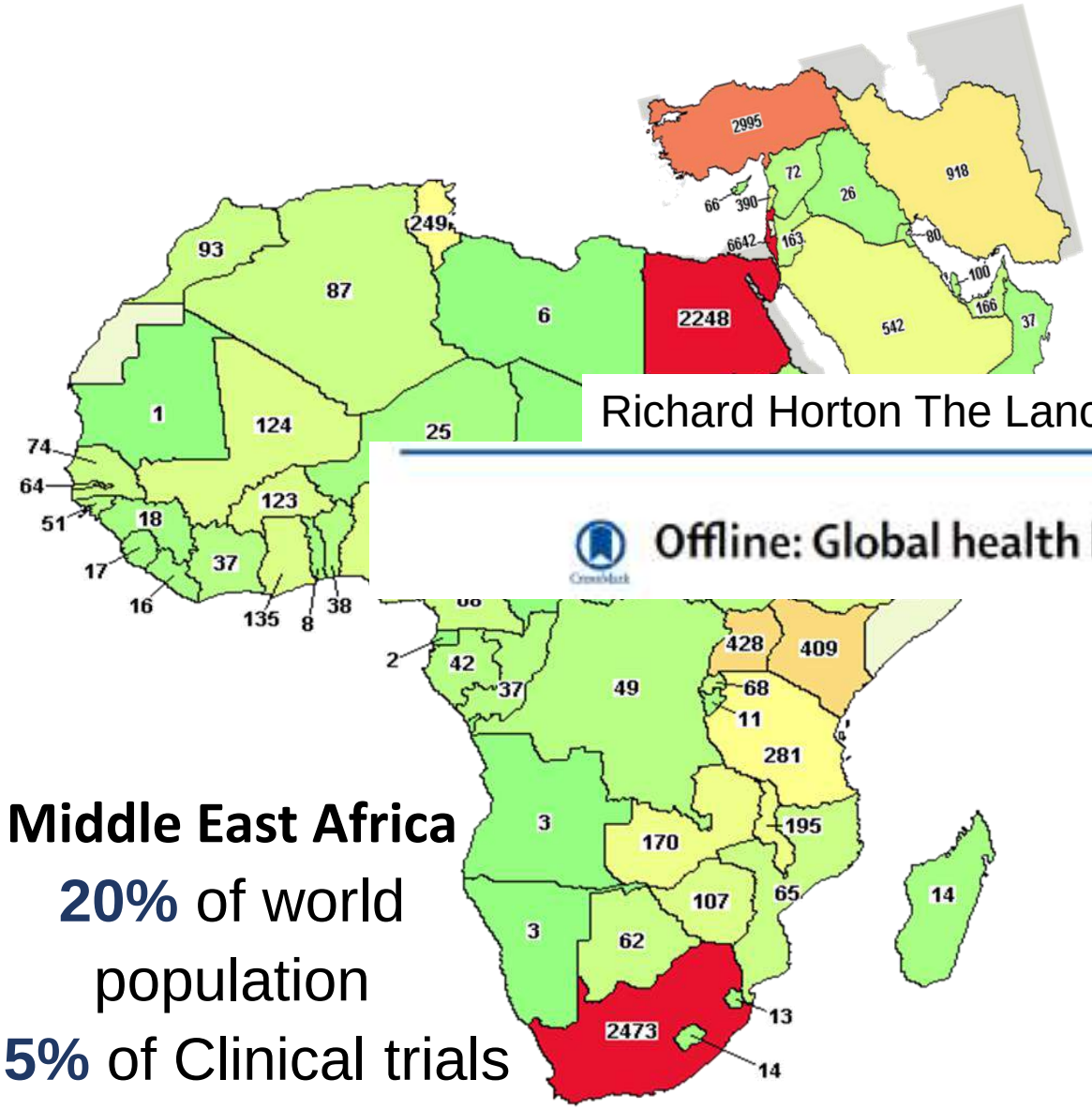
	Hospitalizations[a] per total person-years	Age- and sex-standardized hospitalization rate per 100 person-years (95% CI)	Deaths per total person-years	Age- and sex-standardized mortality rate per 100 person-years (95% CI)	Relative risk of death, model 1[b] HR (95% CI)
Low-income countries	434/3682	11.7 (10.5-12.9)	716/4092	19.1 (17.6-20.7)	2.49 (2.25-2.68)
Lower-middle-income countries	2177/12 954	17.3 (16.5-18.1)	2205/15 847	15.7 (15.0-16.4)	1.98 (1.85-2.11)
Upper-middle-income countries	2238/9784	22.6 (21.7-23.6)	1188/12 638	9.3 (8.8-9.9)	1.09 (1.01-1.17)
High-income countries	4429/14 340	29.9 (28.9-30.8)	1926/21 511	7.8 (7.5-8.2)	1 [Reference]



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

Yusuf S et al. JAMA. 2023;329(19):1650-1661

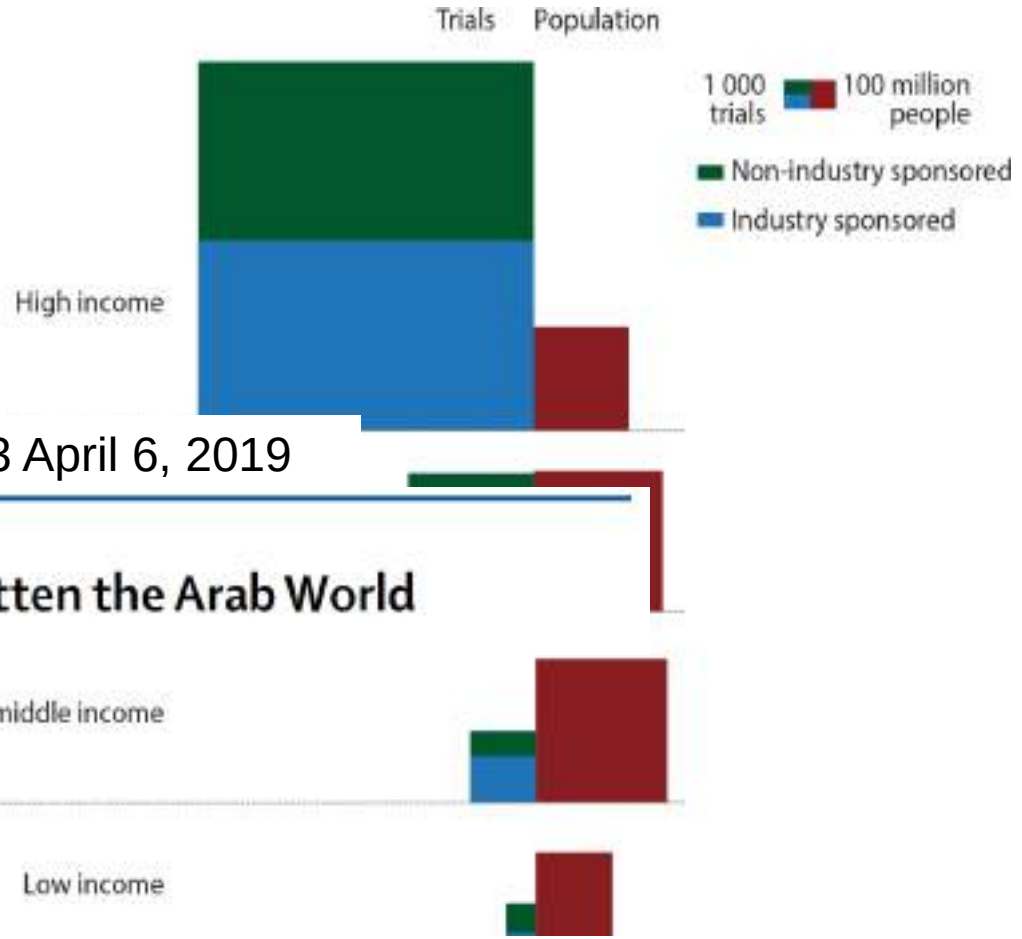
More people live in Middle East + Africa, but fewer trials contributed



Middle East Africa

20% of world population

6,5% of Clinical trials



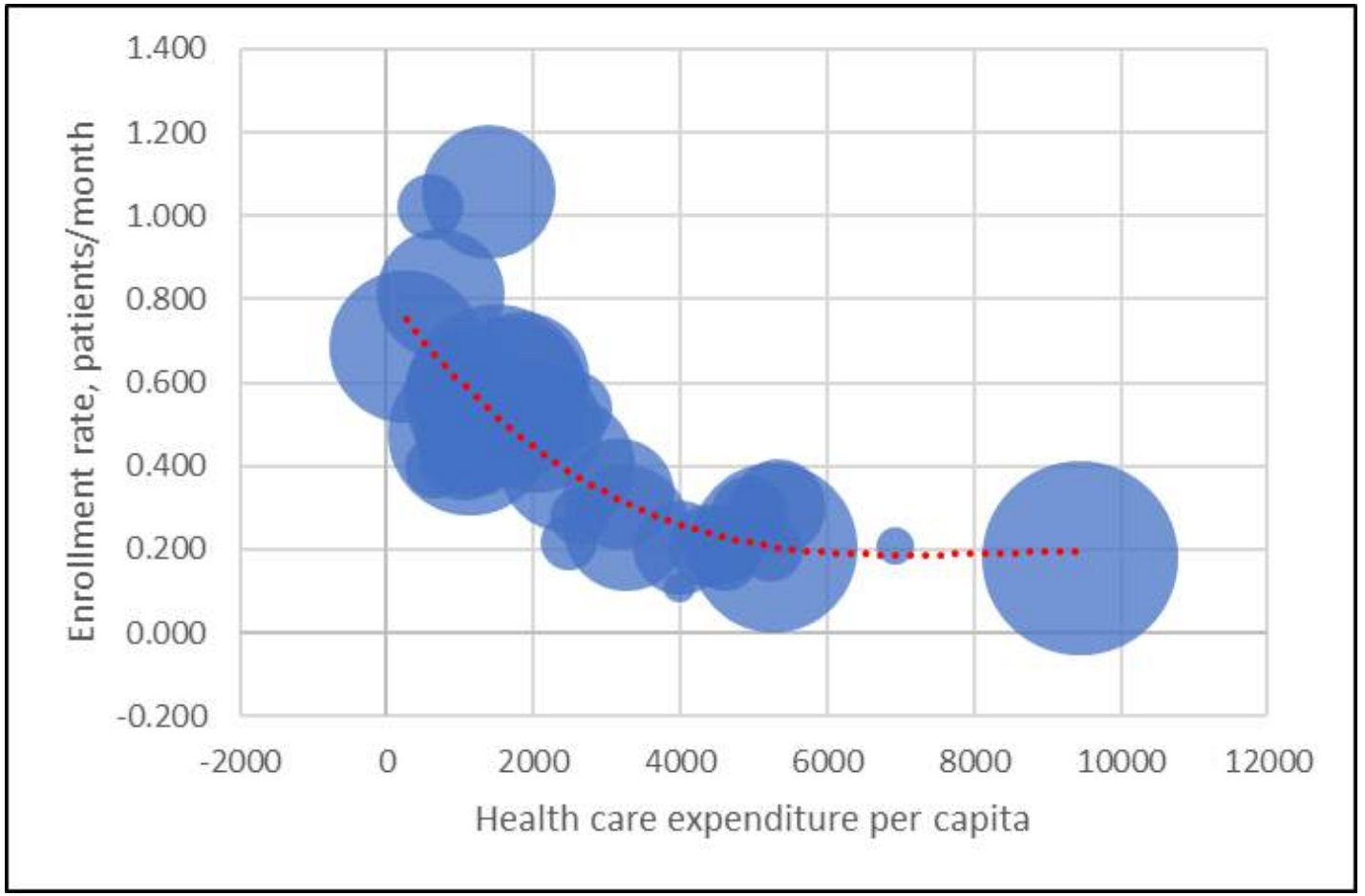
Richard Horton The Lancet Vol 393 April 6, 2019

Offline: Global health has forgotten the Arab World

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)



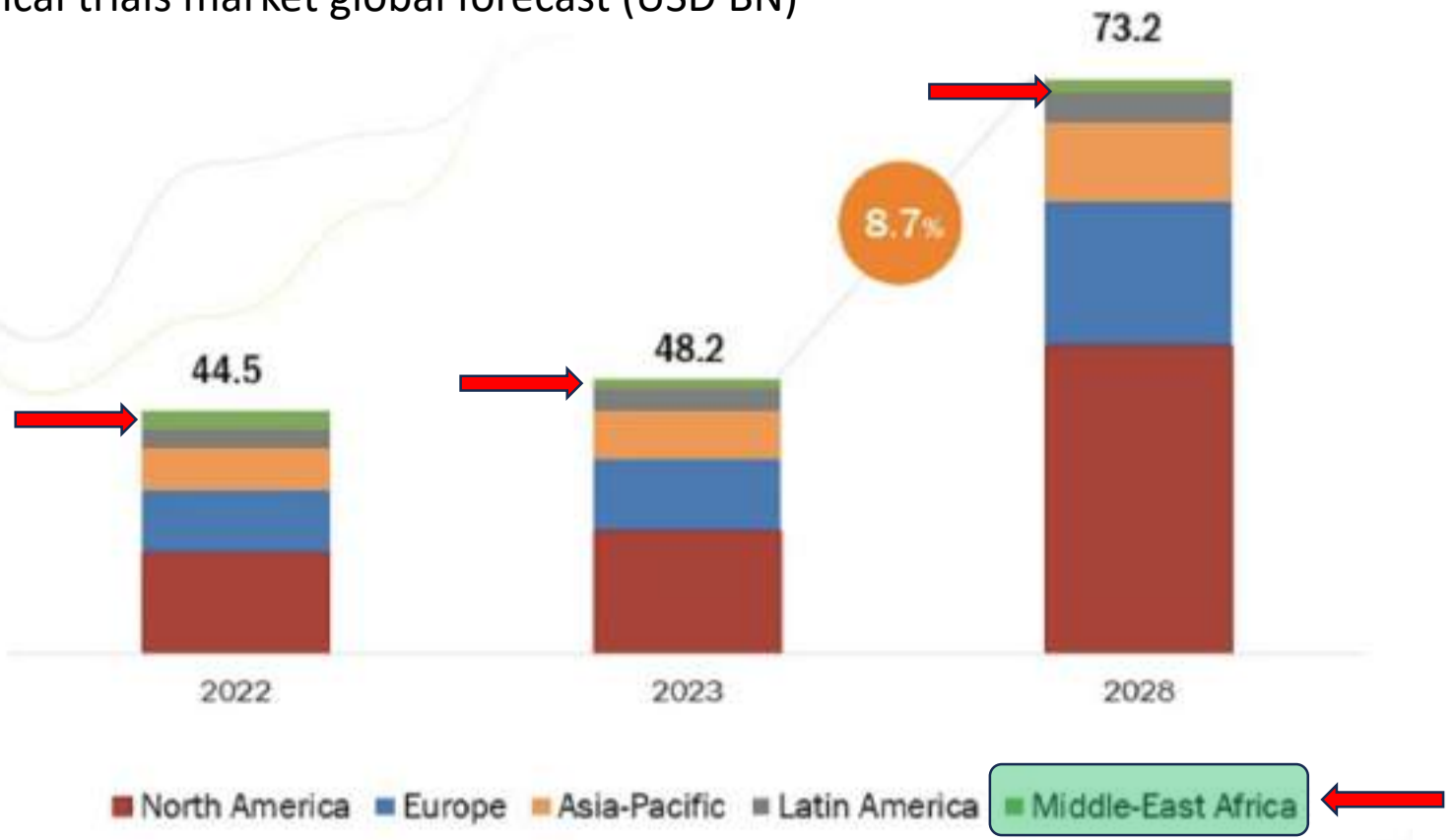
The depressingly stagnant growth of clinical trials in Middle East - Africa

CAGR OF

8.7%

The global clinical trials market is expected to be worth USD 73.2 billion by 2028, growing at a CAGR of 8.7% during the forecast period.

Clinical trials market global forecast (USD BN)



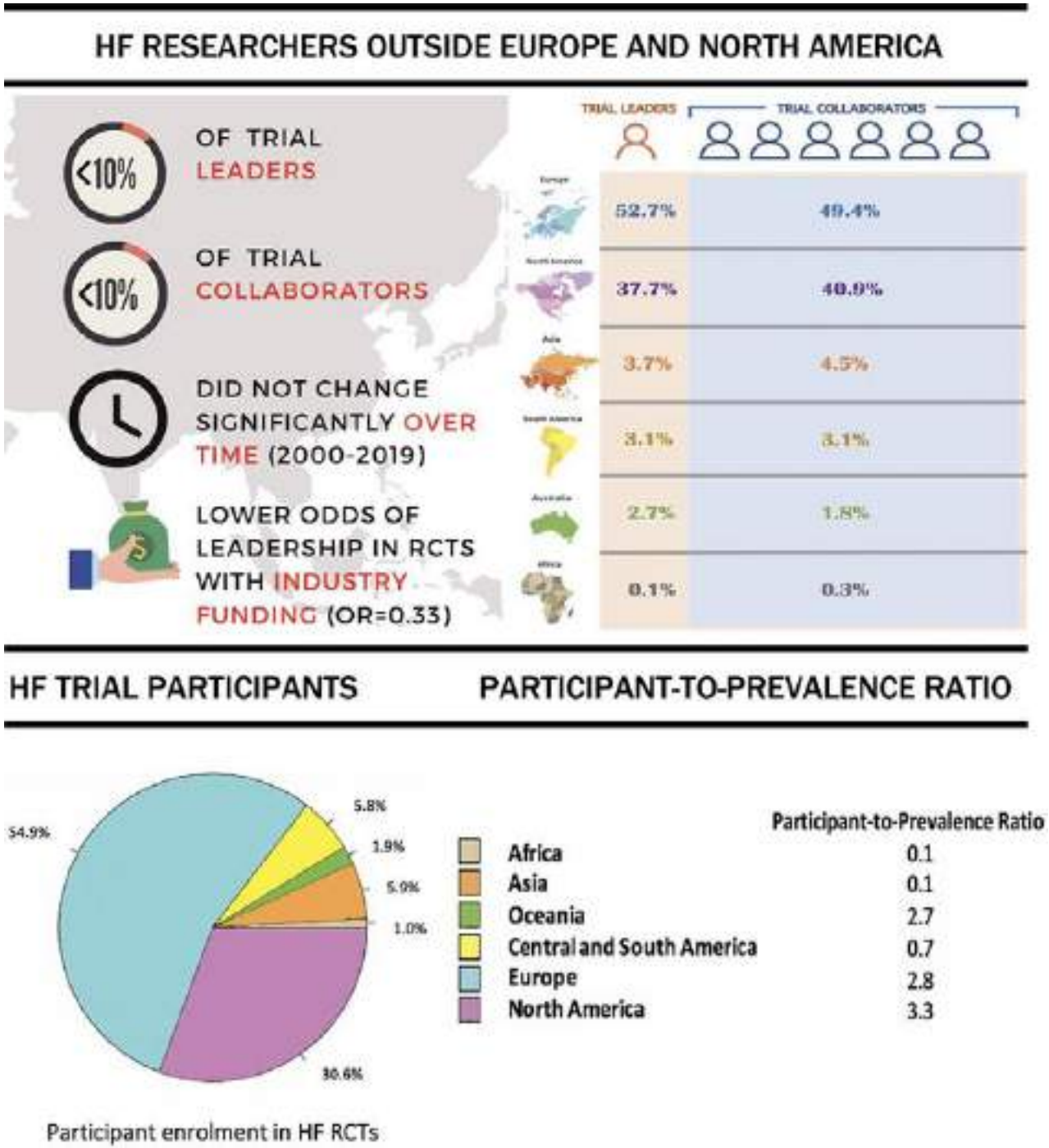
ESC European Society of Cardiology
European Heart Journal - Quality of Care and Clinical Outcomes (2021) 0, 1–11
https://doi.org/10.1093/ehjqcco/qcab058
ORIGINAL ARTICLE

Global representation of heart failure clinical trial leaders, collaborators, and enrolled participants: a bibliometric review 2000–20

Jie Wei Zhu[1], NhatChinh Le[1,†], Sunny Wei[1,†], Liesl Zühlke[2], Renato D. Lopes[3], Faiez Zannad[4] and Harriette G.C. Van Spall[1,5,6,*]

MOW
ROW

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

Faiez Zannad[1], Mohamed Sobhy[2], Wael Almahmeed[3], Mohamed Balghith[4], Javed Butler[5], Souad Dziri[6], Sahar Ebrahim[7], Ashraf El Fiky[8], Ahmed Elshal[9], Ines Fradi[10], Ziyad Ghazzal[11], Chokri Jeribi[12], Zainab Samad[13], Maciej Kostrubiec[14], Manal Milhem[15], Mossad Morsi[16], Ali Oto[17], Hany Ragy[18], Georges Saade[19], Rana Malkawi[20], Azza Saleh[21], Dina Shokri[21], Karen Sliwa[22], Habib Gamra[23], for the CVCT Regulatory summit Think Tank*

[1]Université de Lorraine, Inserm CRCT, CHU, Nancy, France
[2]University of Alexandria, Egyp
[3]Heart and Vascular Institute, Abu Dhabi, United Arab Emira
[4]King Saud Bin Abdulaziz Univ Sciences, Riyadh, Kingdom of
[5]University of Mississippi, Jack USA
[6]Eshmoun, Tunis, Tunisia

Journal of Global Health Reports. 2019;3:e2019082.

Interventions should be systemic and coordinated interventions, including[32]:

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.

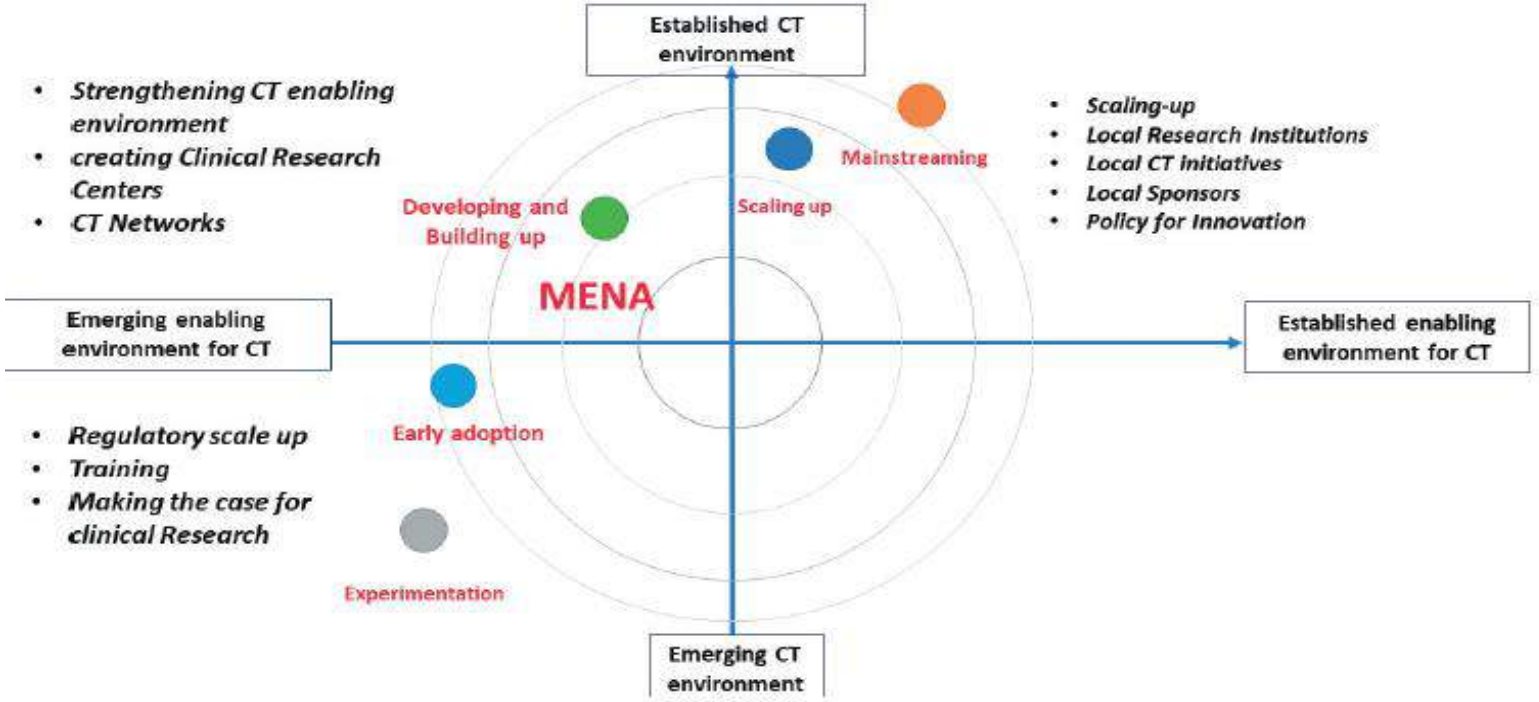
7. Incentivising investments, from international pharmaceutical and biotech companies that would feed into the clinical research culture and infrastructure.

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.

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%

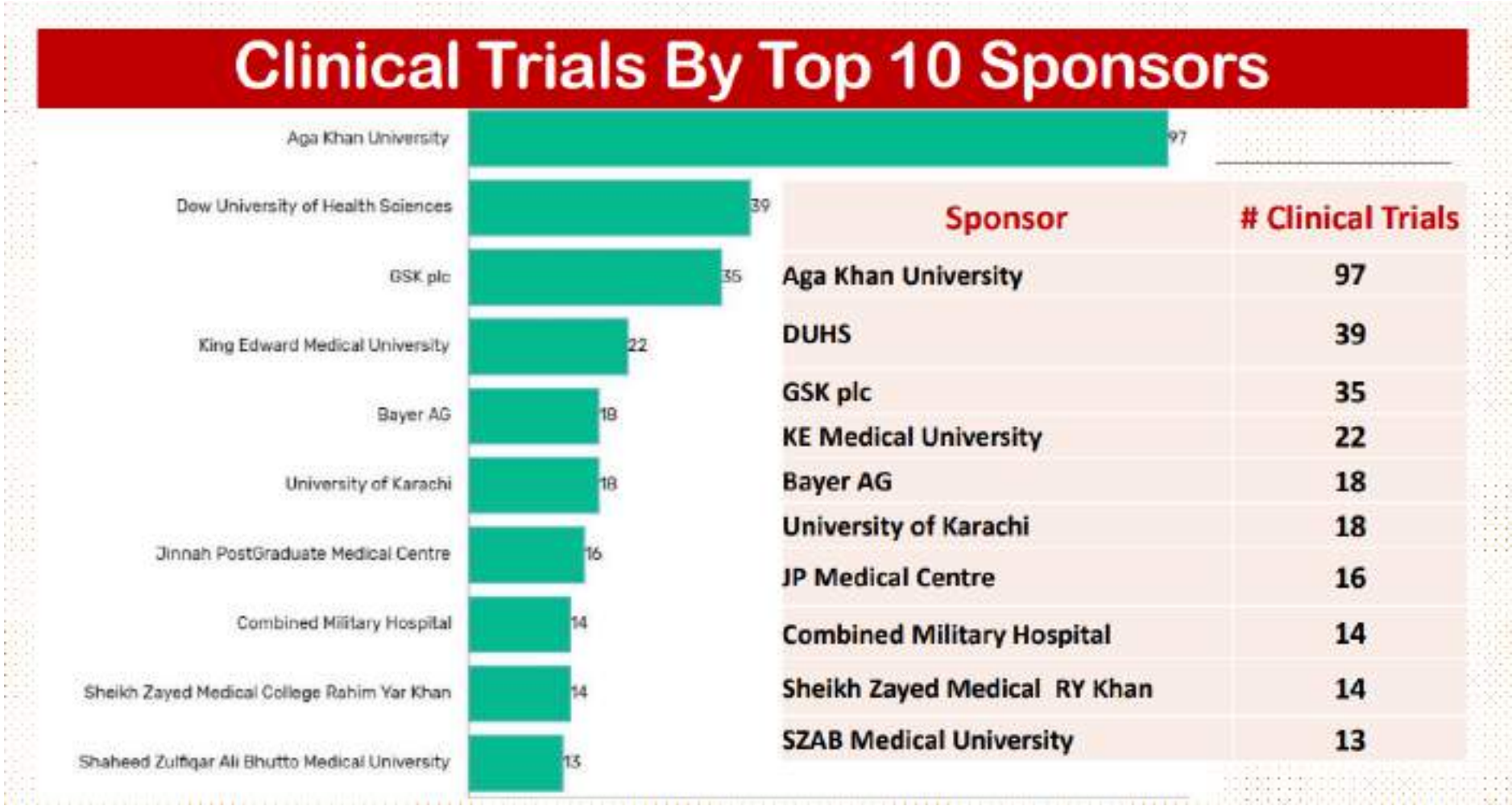
Diabetes- 30% of pop.

Hepatitis C- 7% of pop

Pakistan- Focus Therapy areas

Therapy Area	# Clinical Trials
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

Pakistan- Top clinical Trial sites/sponsors



Sponsor	# Clinical Trials
Aga Khan University	97
DUHS	39
GSK plc	35
KE Medical University	22
Bayer AG	18
University of Karachi	18
JP Medical Centre	16
Combined Military Hospital	14
Sheikh Zayed Medical RY Khan	14
SZAB Medical University	13

Human Clinical Research Central Administrative Portal-

آغا خان یونیورسٹی
THE AGA KHAN UNIVERSITY

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

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 through-put 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

STUDY NAME WHO	SPONSOR	PI	Sample size	Year	STATUS
CanSino	Beijing Institute of Biotechnology	Dr Faisal Mahmood	3000	2020	Final follow up
Livzon Trial	Livzon Mabpharm Inc China	Dr Faisal Mahmood	800	2021	Follow up
COPCOV Trial	Oxford University, UK	Dr Asim Beg	650	2020	Follow up completed
WHO Solidarity	WHO	Dr Nosheen Nasir	60	2020	Closing phase
ACT	PHRI Canada	Dr Aysha Almas	50	2021	Follow up completed
Meplazumab Trial	Jiangsu Pacific Meinuoke Biopharma	Dr Nosheen Nasir	8	2021	Second phase

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

Trials Pipeline

Year	Study Title	Sponsor
2023	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)	Alvotech Swiss AG - Switzerland
2023	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	Shionogi & Co., Ltd.
2023	A Multicenter, Double-blind, Randomized, Placebo-Controlled, Phase II/III Study to Evaluate the Efficacy, Safety and Pharmacokinetics of JT001 (VV116) for the Early Treatment of Coronavirus Disease 2019 (COVID-19) in Participants with Mild to Moderate COVID-19.	Shanghai JunTop Biosciences Co.
2022	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	EVEREST MEDICINES (HK) LIMITED
2023	Effectiveness Of novel approaches to Radical cure with Tafenoquine and primaquine (EFFORT)- A randomized controlled trial in P. vivax patients	Menzies School of Health Research, Australia
2022	Finding Treatments of COVID 19: A phase 2 multi centre adaptive platform trial to assess antiviral pharmacodynamics in early symptomatic COVID-19 (PLATCOV).	The University of Oxford

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

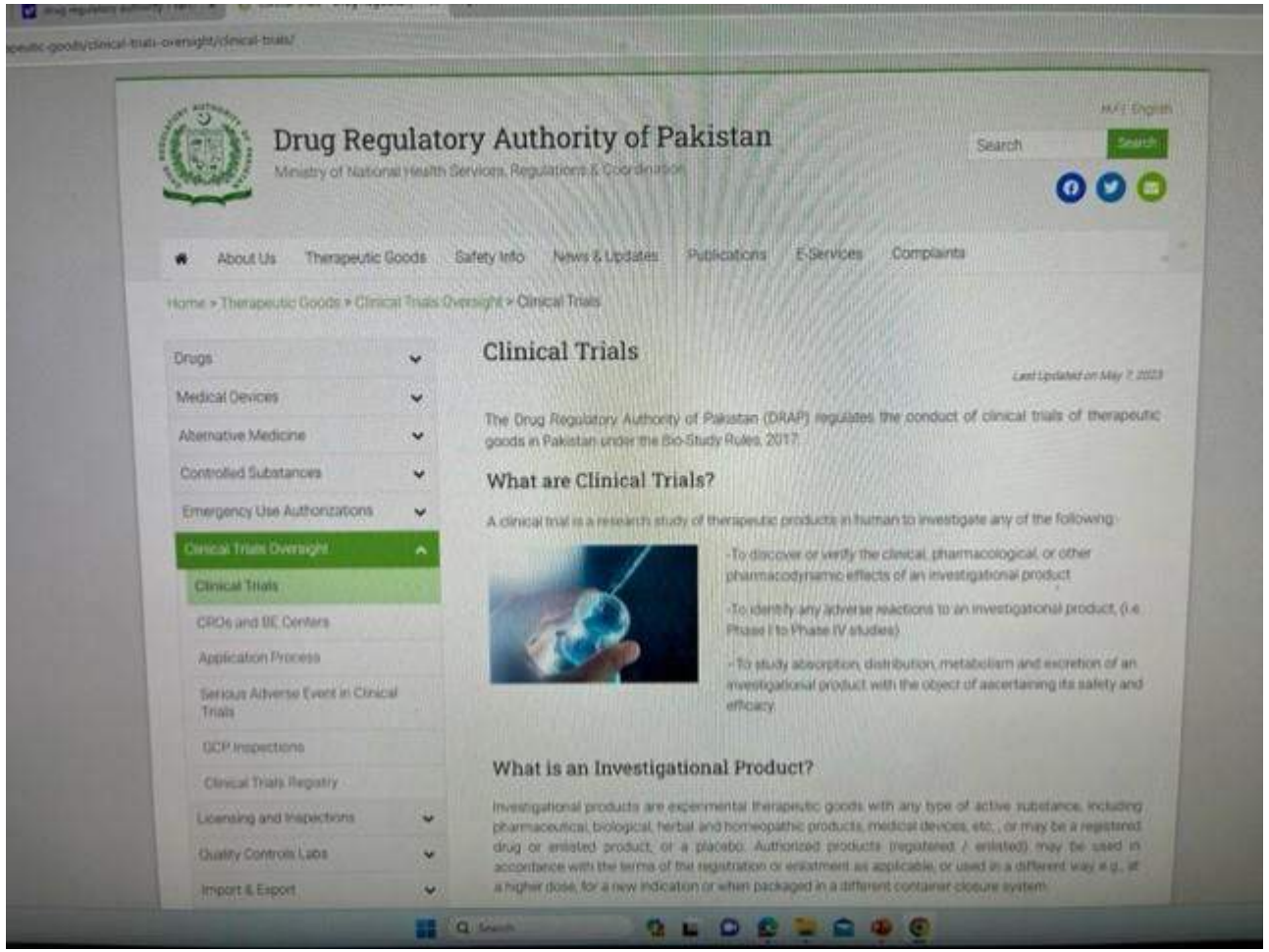
Mobile and Internet penetration

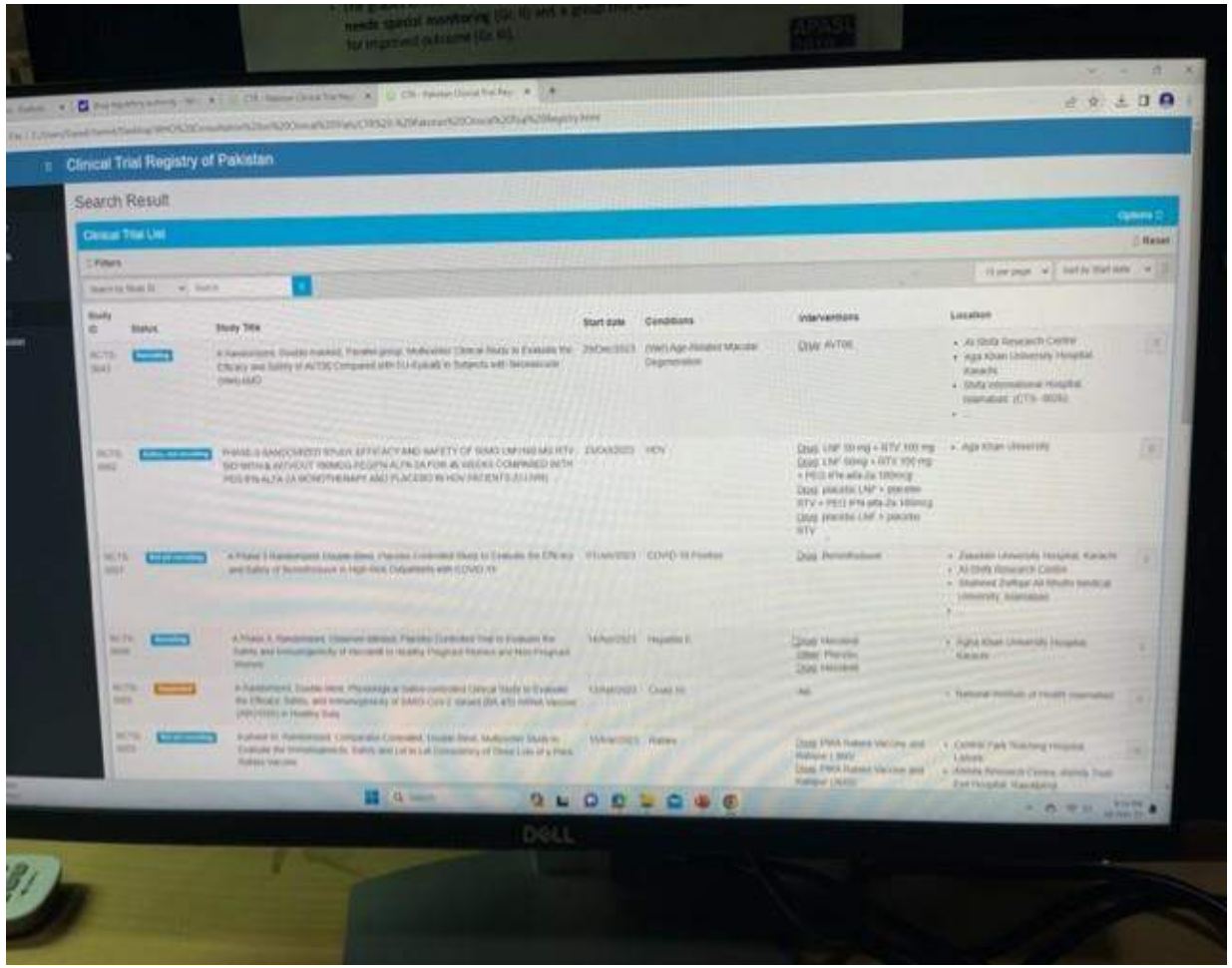
Rising adoption of electronic health records (EHRs)

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






AKU Karachi Campus

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

Regional Experience in Clinical Trials - PAHO

Carlos Alvarez-Moreno – Colombia
Evandro Lupatini - Brazil

World Health Organization

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.

World Health Organization

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.

World Health Organization

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.

World Health Organization

Priority actions

Action	Rationale	Outcome
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.

World Health Organization

Priority actions

Action	Rationale	Outcome
4. Stimulate the training of health professionals in clinical research.	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.)	• Increase in courses, diplomas, and master's degrees in clinical research; • Robust clinical ecosystem in each country and region.
5. Creation of large-scale national and international research networks on diseases or geographic areas with gaps, with effective coordination mechanisms.	The formation of networks of clinical research centers will allow clinical studies to be conducted more efficiently.	• Optimize the implementation, conduct, and monitoring of clinical trials;
6. Establish a network of national and regional ethics committees facilitating the research protocol review and approval process.	The harmonization of regulatory processes in different countries will facilitate the formation of networks of ethics committees and health agencies.	• Optimize approval times and development of multicenter and multi-country clinical studies.

World Health Organization

Roles and responsibilities

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

World Health Organization

Summary of discussion

Discussions

Regional Workshop – PAHO

1. Conducting high-impact clinical trials.
2. Research capabilities.
3. Clinical trial networks.
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.

World Health Organization

PANDEMIC SCIENCES INSTITUTE

OXFORD POPULATION HEALTH

UNIVERSITY OF OXFORD

Lessons from a large-scale, pragmatic, adaptive platform trial

Peter Horby on behalf of RECOVERY team

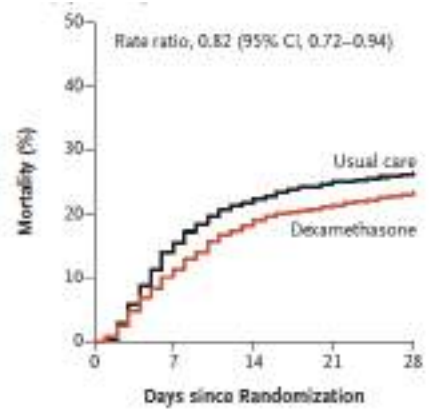
WHO, Geneva, 20-21 November 2023

RECOVERY

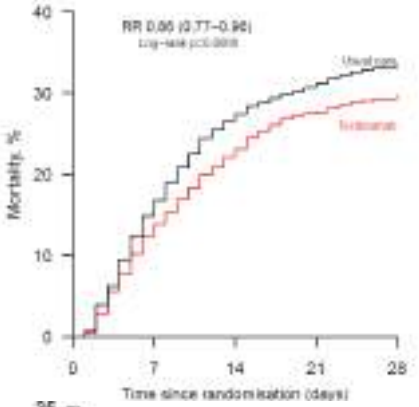
Randomised Evaluation of COVID-19 Therapy

Four effective treatments for high-risk patients

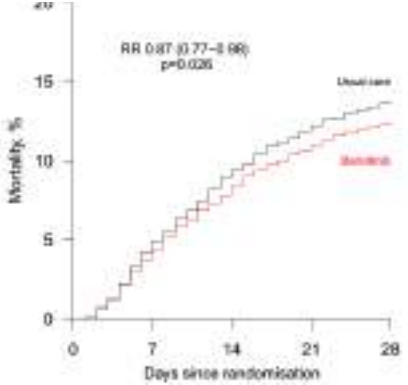
Dexamethasone



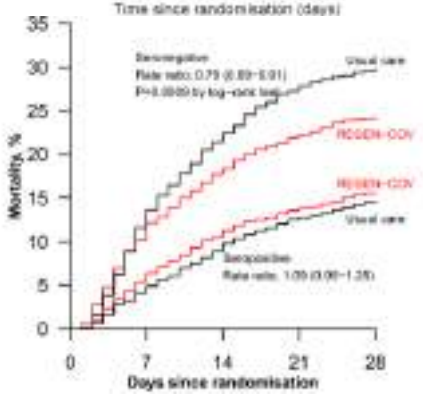
Tocilizumab



Baricitinib

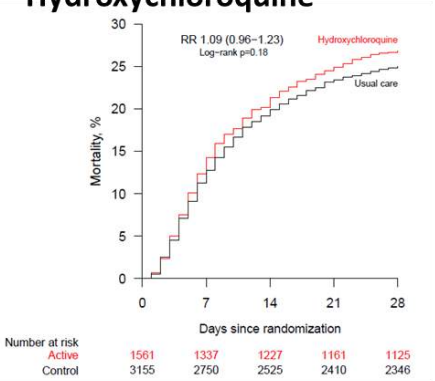


Ronapreve
(casirivimab+
imdevimab)

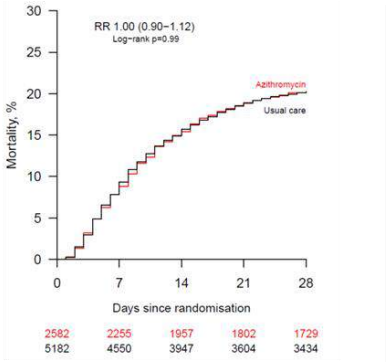


Eight ineffective drugs

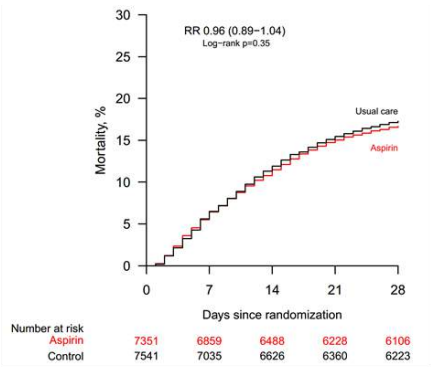
Hydroxychloroquine



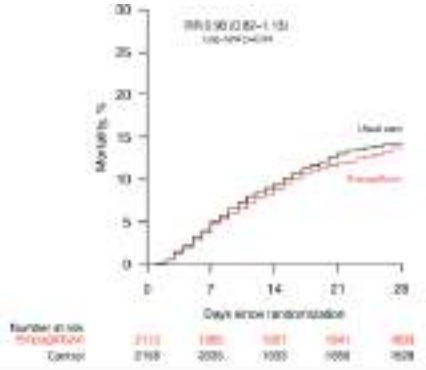
Azithromycin



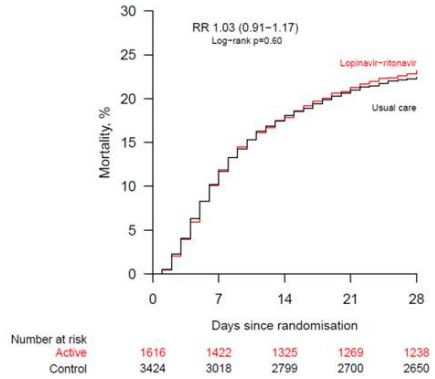
Aspirin



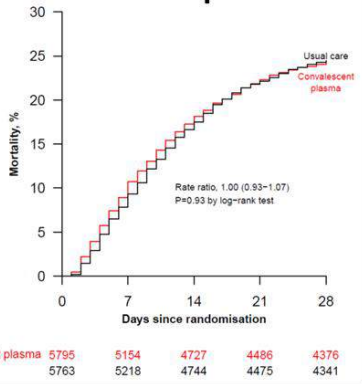
Empagliflozin



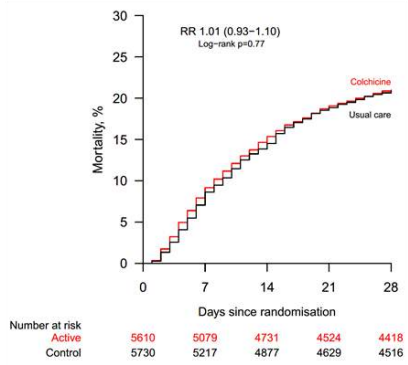
Lopinavir-ritonavir



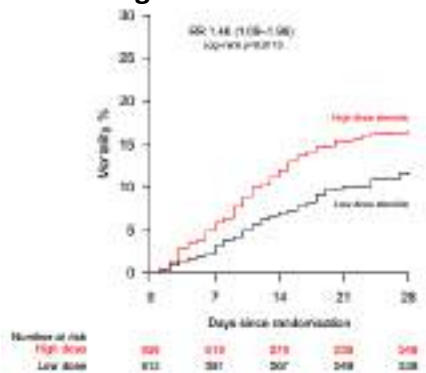
Convalescent plasma



Colchicine



Higher dose steroids



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

One page case record form

Eight minutes to randomise

N	[Min, Max]	Mean (SD)	Median [IQR]
48595	[0, 89]	8.30 (5.39)	7 [5, 10]

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

Application	Purpose	Submission date	MHRA	REC	Live	Submission to live
Initial		13 March	17 March	17 March	19 March	**6 days**
Subst. amend. 1	Add hydroxychloroquine	23 March	25 March	24 March	25 March	**2 days**
Subst. amend. 2	Add azithromycin	7 April	8 April	8 April	8 April	**1 day**
Subst. amend. 3	Add tocilizumab	14 April	16 April	16 April	23 April	**9 days**
Subst. amend. 4	Include children	27 April	5 May	30 April	9 May	**12 days**

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

	Tocilizumab (n=2022)	Usual care (n=2094)	RR (95% CI)
Mortality at 28 days			
eCRF only	583 (29%)	697 (33%)	0.83 (0.75–0.93)
Linkage only	610 (30%)	722 (34%)	0.84 (0.75–0.94)
Combined	621 (31%)	729 (35%)	0.85 (0.76–0.94)
Invasive mechanical ventilation or death*			
eCRF only	565/1754 (32%)	709/1800 (39%)	0.83 (0.76–0.91)
Linkage only	610/1754 (35%)	739/1800 (41%)	0.85 (0.78–0.92)
Combined	619/1754 (35%)	754/1800 (42%)	0.84 (0.77–0.92)

0.75 1 1.5

Tocilizumab better | Usual care better

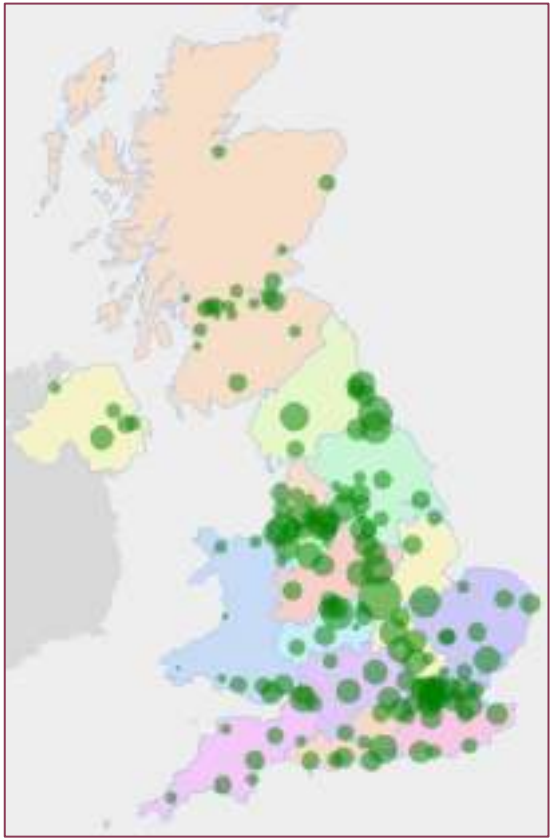
*Analyses exclude only those on no ventilation support or non-invasive ventilation at second randomisation

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.'*

Comprehensive uptake

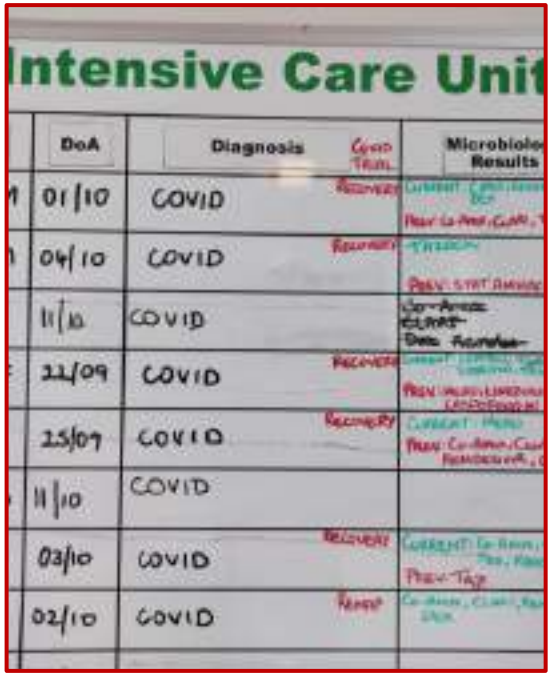


5. Point-of-care trial

At peak
500 enrolments per day

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



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

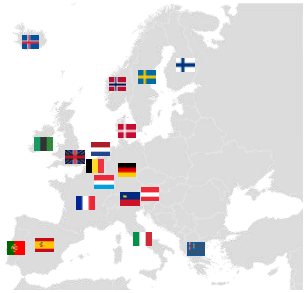
Problem statement

- 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 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

See ACT EU website 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
Telephone +31 (0)88 781 6000
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

World Health Organization

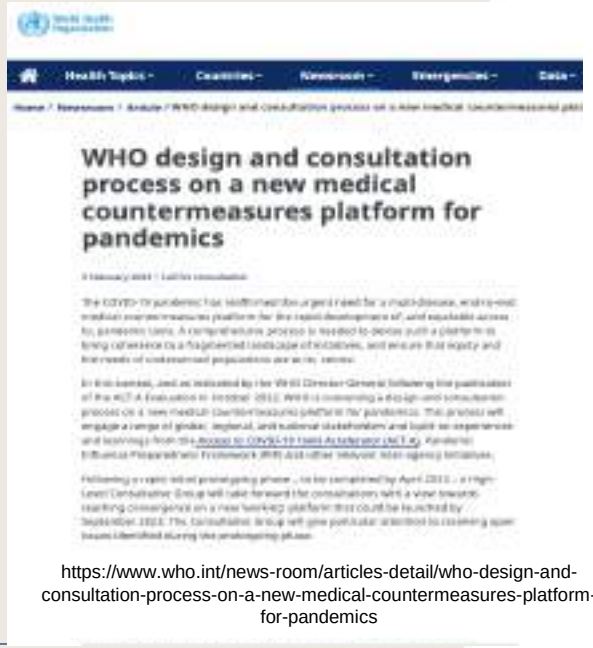
HEALTH EMERGENCIES programme

R&DBlueprint
Powering research to prevent epidemics

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"

..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

World Health Organization

HEALTH EMERGENCIES programme

R&DBlueprint
Powering research to prevent epidemics

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** 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

2 Availability

Agreement on availability and access to candidate vaccines and therapeutics

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.

3 Clinical trials

CORE protocols and platforms to promptly initiate trials with equitable access to research

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

4 Agreements

Prior agreement on legal collaboration, insurance, indemnity and liability

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.

5 Funding

Access to readily available funding through committed financing mechanism

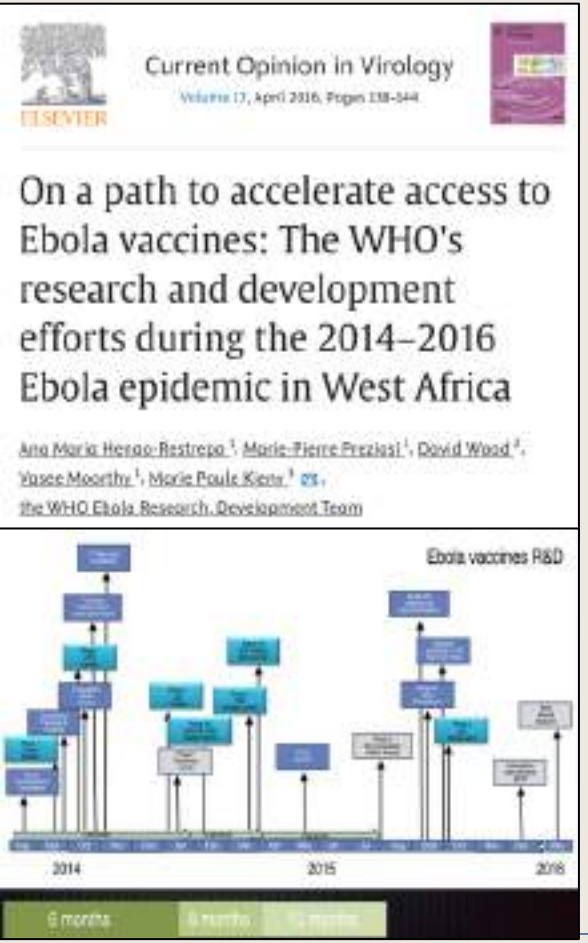
Signed agreements with contributors; aimed at a simple approval process for releasing of funds and simplifying financial reporting.

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

R&DBlueprint
Powering research to prevent epidemics



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

World Health Organization

HEALTH EMERGENCIES programme

R&D Blueprint
Powering research to prevent epidemics

With the support of hundreds of experts worldwide WHO has discussed trial designs and developed protocols that get adjusted in every epidemic

Pathogen	R&D Roadmap	Vaccines					Therapeutics					Diagnostics					Research priorities for other areas of research and innovation.
		Landscape Candidate Vaccines	TPP Vaccines	Trial design Vaccines	Simple protocol available	Regulatory pathway consultations	Landscape Candidate Therapeutics	TPP Therapeutics	Trial design Therapeutics	Simple protocol available	Regulatory pathway consultations	Landscape Candidate Diagnostics	TPP Diagnostics	Trial design Diagnostics	Simple protocol available	Regulatory consultations	
COVID-19	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
MERS-CoV	✓	✓	✓	✓		✓	✓		✓			✓	✓				✓
Zika	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓		✓	✓
Nipah	✓	✓	✓	✓					✓	✓							✓
Lassa fever	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓		✓	✓
Ebola ZEBOV	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓
Ebola SUDV	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓
Marburg	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓
Crimean–Congo hemorrhagic fever	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓			✓	✓
Rift Valley fever	✓	✓	✓	✓		✓	✓		✓		✓	✓	✓				✓
Chikungunya	✓	✓	✓	✓			✓		✓								✓
Plague	✓	✓	✓	✓		✓	✓		✓		✓					✓	
Monkeypox	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓
Pathogen X	✓			✓					✓								

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Powering research to prevent epidemics

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	**Randomized clinical trials**	**Open-label randomized trials**	**Observational studies**
Animal Rule Immunobridging Comparisons using immunomarkers	Placebo controlled trials Simple large randomized trials	Randomization during deployment	

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

SUDAN ebolavirus Therapeutics

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 dexamethasone for all participants.

Table 2. Summary of Proposed Trial Design Options

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

MARBURG Vaccines & Therapeutics

Seamless progression from phase 1 to Phase 3

During the inter-epidemic period		*During the outbreak*	
Phases 1 and 2 Individual randomization among vaccines (no placebo) For candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends	→	**Phase 1 and 2** Cluster-randomized (immediate versus delayed) For candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends in order to collect additional safety information before unduly many volunteers are recruited.	**Phase 3** Cluster-randomized (immediate versus delayed) For candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends.
1. **Phase 1**. Enrolment of first 100 (including HCWs/FLWs in affected areas and contacts of previous cases) 2. **Phase 2**. Enrolment of up to 1000 HCWs/FLWs in affected areas.		1. **Phase 1**-Enrolment of up to 200 (100 per arm) participants (contacts of MAVD cases including HCWs/FLWs) 2. Safety analysis of Phase 1 data by DSMC (7 and 14 days post-vaccination) with formal recommendation on whether to continue to recruit. 3. **Phase 2** - Enrolment continues (up to 1000 contacts) 4. These participants will also be included in Phase 3 analyses	1. Enrolment of participants (contacts of MAVD cases including HCWs/FLWs) 2. Analysis as defined in the Statistical Analysis plan

Factorial design

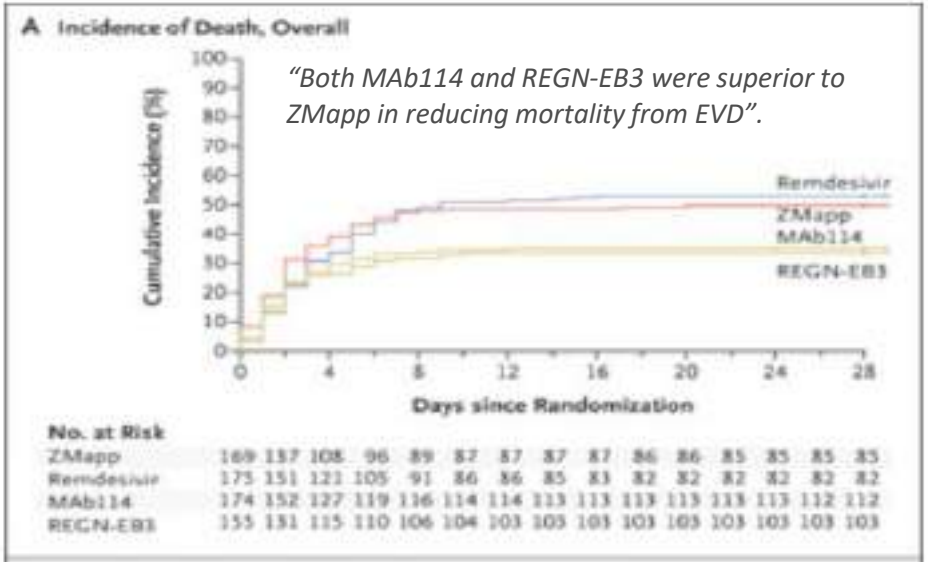
	MARV	SUDV	EBOV and emerging strains
Randomisation 1	Monoclonal antibody vs no additional treatment (1:1)	Monoclonal antibody vs no additional treatment (1:1)	Emergent therapy vs no additional treatment (1:1)
Randomisation 2	Antiviral vs no additional treatment (1:1)		
Randomisation 3	Low-dose corticosteroids vs no additional treatment (1:1)		

Selection of candidates based on WHO expert working group recommendations

https://cdn.who.int/media/docs/default-source/blue-print/sudan-therapeutics-prioritization-and-trial-design-committee-summary-nov-15-2022_final-web.pdf?sfvrsn=3d04f6b6_4

Finally, some good news about Ebola: Two new treatments dramatically lower the death rate in a trial

The therapies, both monoclonal antibody preparations, will now be used to treat all patients



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

https://www.nejm.org/doi/full/10.1056/nejmoa1910993

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WHO R&D Blueprint – Ad-hoc Expert Consultation on clinical trials for Ebola Therapeutics

Deliberations on design options for randomized controlled clinical trials to assess the safety and efficacy of investigational therapeutics for the treatment of patients with Ebola virus disease

11 October 2018 - Geneva, Switzerland

Main conclusions

Following the above deliberations, it was agreed that an amendment to the INRB and NIH protocol would be made to include an additional experimental therapeutic (i.e. Regeneron) as soon as possible after the publication of this report and additional secondary objectives would be added to the protocol also as soon as possible. The protocol would also add a mention about the limitations of the current design and the need for flexibility and adaptation to account for emerging evidence and products.

Introducing amendments to the NIH proposed protocol

The NIH team will proceed with the preparations for the initiation of the proposed trial in DRC during the current outbreak, with the commitment that in parallel they will submit asap amendments to the pertinent IRBs and NRAs as described above (i.e. a four way RCT, adding agreed additional secondary objectives, modifying the Statistical Analysis Plan and lastly, clearly indicating the potential to include further adaptations to the design as noted above).

https://cdn.who.int/media/docs/default-source/blue-print/note-for-record-study-design-evd-26-may-2018.pdf?sfvrsn=28da84d2_4&download=true

https://www.who.int/publications/m/item/who-r-d-blueprint-ad-hoc-expert-consultation-on-clinical-trials-for-ebola-therapeutics

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

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

N Engl J Med 2021; 385:179-186

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)

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

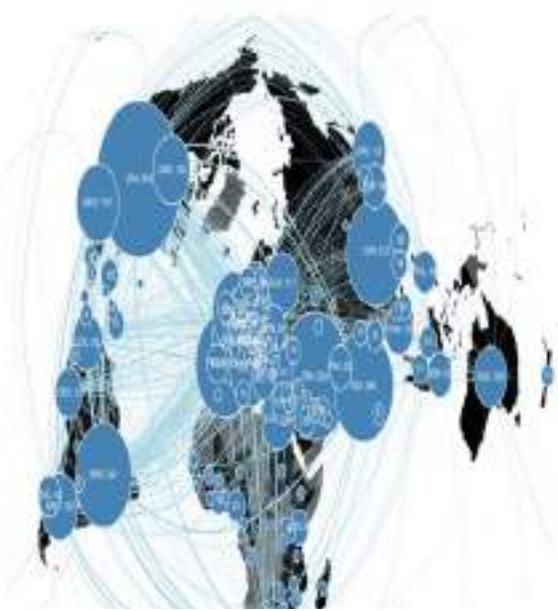
- **INTEGRATING** trials as part of the epidemic response
- **DESIGNING IN ADVANCE** CORE protocols
- **ENROLLING SUFFICIENT** numbers needed to assess effects on **SEVERE** disease
  - **SMALLER** numbers are needed to assess effects on overall disease incidence, and **SMALLER STILL** for assessing 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

Country	N sites
Colombia	6
Kenya	5
Mali	14
The Philippines	10
Sierra Leone	3
Total	**38**

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-trial-of-covid-19-vaccines

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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

	Outside epidemics	In the context of epidemics
Teams involved in design and implementation	Specialized research teams national and international	Research centers designated by the MOH, **epidemic response teams and clinicians in affected countries** as part of an international collaboration
Questions to be answered	As part of an individual product R&D plan	Design to address key uncertainties to inform **public health decisions**
Selection of interventions	As part of an individual product R&D plan	Ideally as part of a **transparent global process** using defined criteria and data available at the time of the epidemic
Time for preparation	Months to years	**CORE protocols** discussed during the inter-epidemic period 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

	Outside epidemics	In the context of epidemics
Process for the study implementation	Mostly aiming to fulfil international guidelines	Committed to fulfil international guidelines **with a clear sense of what is feasible** and community engagement
Logistics	Defined by infrastructure of specialized research center and defined SOPs	**Adjusted to the epidemic response team**, while complying with defined SOPs
Quality assurance	Use of CROs and audits Variable percentage of verification of records	Use of CROs and audits **100% verification of records**
Trust	Relies on regulatory processes	Relies on regulatory processes **Careful community engagement** and transparency are very important

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

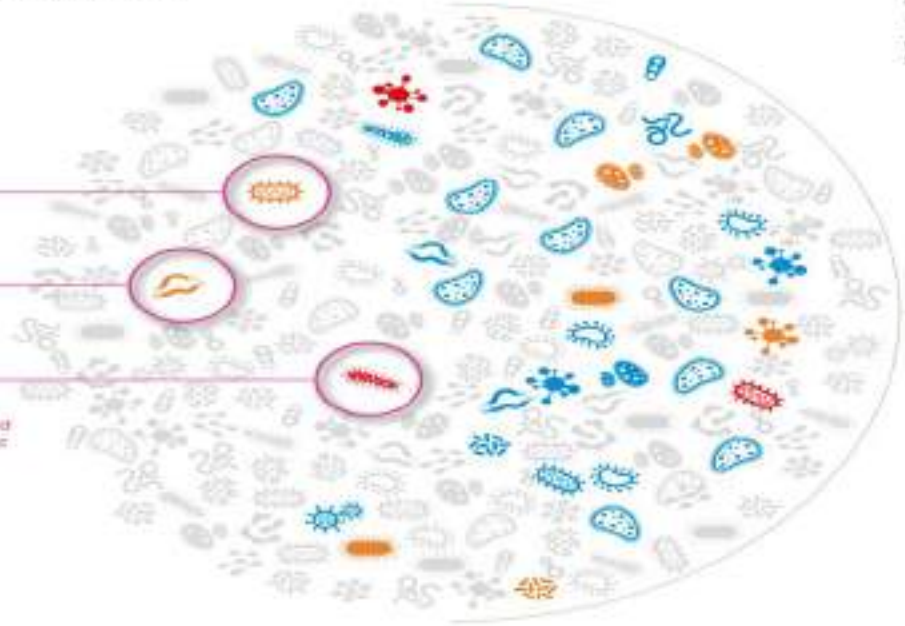
30 — **Viral families** are being studied to ensure all viruses that can infect humans are reviewed for any pathogen X

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

Pathogen X — **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?



The final shortlist of priority pathogens

The list is expected in early 2024 and will shortlist priority viral families, the highest threat pathogens, the prototype pathogens for research and any Pathogen X.

The list will be used to guide investments into researching safe and effective vaccines and treatments.

Pathogen 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 not 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.

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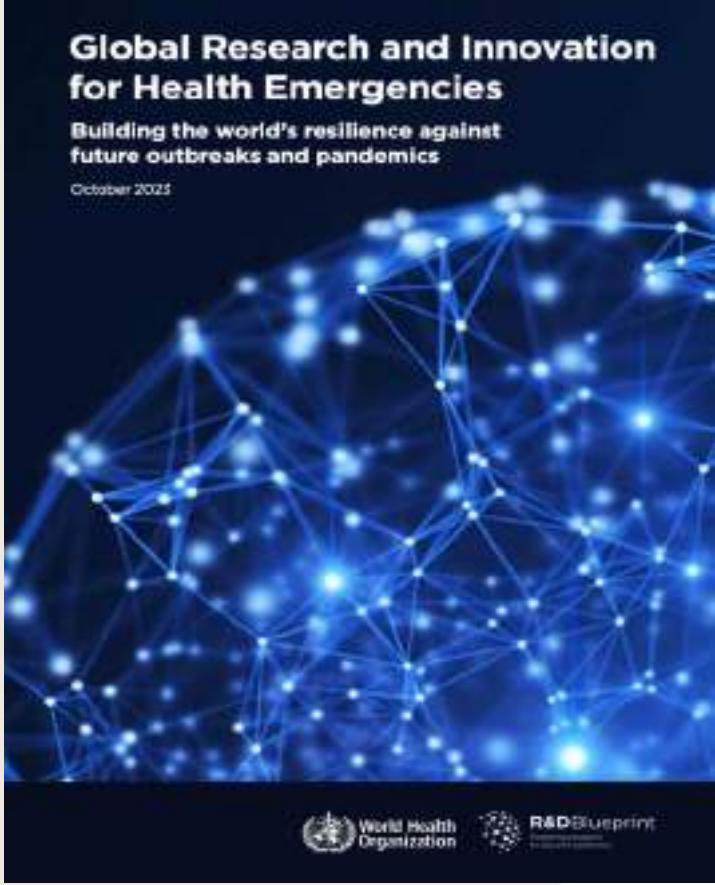
https://www.who.int/teams/blueprint/who-r-and-d-blueprint-for-epidemics
WHO R&D Blueprint for Epidemics
World Health Organizationhttps://cdn.who.int › default-source › blue-print

R&D Blueprint
Powering research to prevent epidemics

To be prepared to integrate research during epidemic[20]

- **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 vral 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.



XXXXX

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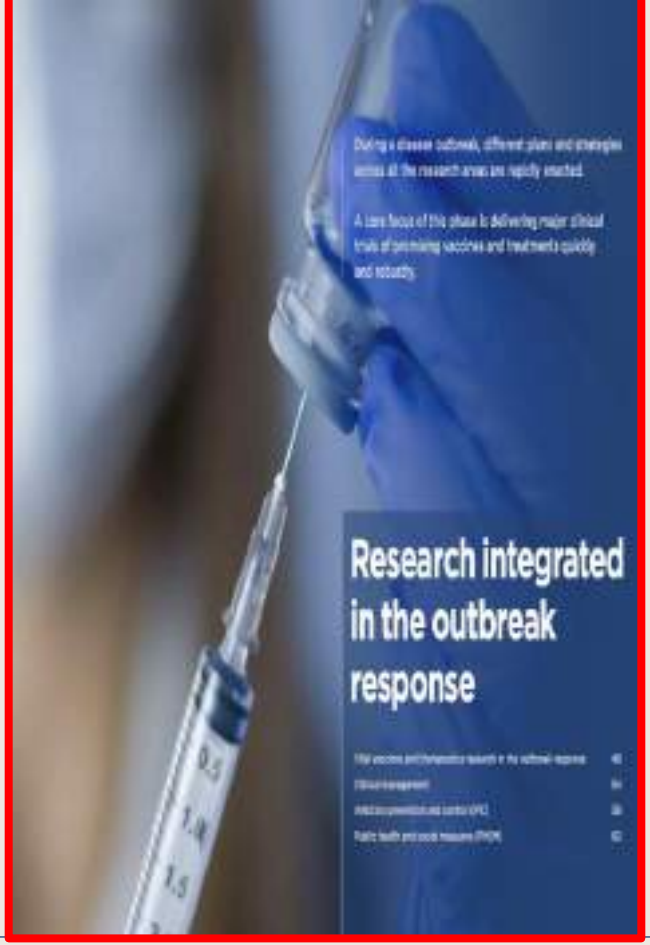
Extra slides

Improving vaccine effectiveness studies:
a vital step before the next pandemic

https://www.who.int/news-room/events/detail/2023/09/14/default-calendar/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.



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https://www.who.int/news-room/events/detail/2023/10/23/default-calendar/global-research-and-innovations-forum--building-the-world-s-resilience-against-future-outbreaks-and-pandemics

R&DBlueprint
Powering research to prevent epidemics

Some sources of information

Search for documents/material	
Disease	Webpage
COVID-19	https://www.who.int/teams/blueprint/covid-19
Monkeypox	https://www.who.int/teams/blueprint/monkeypox
Ebola/Marburg	https://www.who.int/teams/blueprint/ebolavirus
Lassa Fever	https://www.who.int/teams/health-emergencies-preparedness-and-response/blueprint/lassa-fever
MERS-Cov & SARS	https://www.who.int/teams/blueprint/mers-cov
Nipah & Henipaviruses	https://www.who.int/teams/blueprint/nipah
Zika	https://www.who.int/teams/blueprint/zika
Plague	https://www.who.int/teams/blueprint/plague
Disease prioritisation	Prioritizing diseases for research and development in emergency contexts (who.int)

Some sources of information

MAIN LINK	https://www.who.int/teams/blueprint/monkeypox	
Document	Type	Link
WHO Monkeypox Research - What study designs can be used to address the remaining knowledge gaps for monkeypox vaccines?	Consulation	https://www.who.int/news-room/events/detail/2022/08/02/default-calendar/who-monkeypox-research---what-study-designs-can-be-used-to-address-the-remaining-knowledge-gaps-for-monkeypox-vaccines
Towards the development of a global CORE protocol for evaluation of treatments for MPX Leveraging the Congolese Experience	Consulation	https://www.who.int/news-room/events/detail/2022/07/10/default-calendar/towards-the-development-of-a-global-core-protocol-for--evaluation-of-treatments-for-mpx-leveraging-the-congolese-experience
WHO monkeypox research: What are the knowledge gaps and priority research questions?	Consulation	https://www.who.int/news-room/events/detail/2022/06/02/default-calendar/who-monkeypox-research--what-are-the-knowledge-gaps-and-priority-research-questions
CORE PROTOCOL - An international adaptive multi-country randomized,placebo-controlled, double-blinded trial of the safety and efficacy of treatments for patients with monkeypox virus disease	Technical document	https://www.who.int/publications/m/item/core-protocol---an-international-adaptive-multi-country-randomized-placebo-controlled--double-blinded-trial-of-the-safety-and-efficacy-of-treatments-for-patients-with-monkeypox-virus-disease
WHO Target Product Profiles for Monkeypox Therapeutics	Technical document	https://www.who.int/publications/m/item/who-target-product-profiles-for-monkeypox-therapeutics
Landscape vaccines	Technical document	https://www.who.int/publications/m/item/mpox-vaccine-tracker---list-of-vaccine-candidates-in-research---development
Landscape therapeutics	Technical document	https://www.who.int/publications/m/item/mpox-therapeutics-tracker---list-of-therapeutics-candidates-in-research---development

Some sources of information

Document	Type	Link
Rift Valley Fever Research and Development Roadmap	roadmap	https://www.who.int/publications/m/item/rift-valley-fever-research-and-development-(r-d)-roadmap
TPP for RVF virus vaccine	TPP	https://www.who.int/docs/default-source/blue-print/call-for-comments/tpp-rift-valley-fever-vaccines-draft3-0pc.pdf?sfvrsn=f2f3b314_2
Efficacy trials of Rift Valley Fever vaccines and therapeutics - Guidance on clinical trial design	Meeting report, November 2019	https://www.who.int/docs/default-source/documents/r-d-blueprint-meetings/rvf/rvf-blueprint-meeting-report.pdf
Rift Valley fever Vaccines Target Product Profile 5 November 2019 Call for consultation Call for comments	call for comments	https://www.who.int/news-room/articles-detail/rift-valley-fever-vaccines-target-product-profile
WHO consultation on Rift Valley Fever therapeutics and vaccine evaluation 1 November 2019	Consultation	https://www.who.int/news-room/events/detail/2019/11/01/default-calendar/who-consultation-on-rift-valley-fever-therapeutics-and-vaccine-evaluation

Some sources of information

Document	Type	Link
Efficacy trials of Plague Vaccines: endpoints trial design, site selection	Meeting report, April 2018	https://cdn.who.int/media/docs/default-source/blue-print/plaguevxeval-finalmeetingreport.pdf?sfvrsn=c251bd35_2
Landscape of plague vaccines canidates	Landscape of vaccines	Landscape of Plague vaccine candidates (who.int)
WHO TPP for plague vaccines	Target product profile for vaccines	https://www.who.int/publications/m/item/who-target-product-profile-for-plague-vaccines

Some sources of information

Document	Type	Link
An R&D Blueprint for Action to Prevent Epidemics - Update 2017		https://www.who.int/publications/m/item/an-r-d-blueprint-for-action-to-prevent-epidemics---update-2017
An R&D Blueprint for Action to Prevent Epidemics - 15 May 2015		https://cdn.who.int/media/docs/default-source/blue-print/an-randd-blueprint-for-action-to-prevent-epidemics.pdf?sfvrsn=f890ab4e_1&download=true
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
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
1st WHO R&D Blueprint Consultation on Therapeutic Evaluation in Public Health Emergencies	meeting report, December 2017	https://www.who.int/docs/default-source/blue-print/1st-who-rd-blueprint-consultation-on-therapeutic-evaluation-in-public-health-emergencies.pdf?sfvrsn=9e7d5ae0_2
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
2018 Annual Review of Diseases Prioritized under the Research and Development Blueprint	meeting report, February 2018	https://www.who.int/docs/default-source/blue-print/2018-annual-review-of-diseases-prioritized-under-the-research-and-development-blueprint.pdf?sfvrsn=4c22e36_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
WHO Target Product Profiles, Preferred Product Characteristics, and Target Regimen Profiles: Standard Procedure	Generic TPP methodology	WHO Target Product Profiles_harmonized methodology_version1_03_07Dec2021.pdf

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

Funding models that best support both sustainable capacity and project deliverables

Tom Nyirenda - EDCTP

World Health Organization

Historical and colonial links laid the foundation of research in Africa

Critical role of European national institutes and universities

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

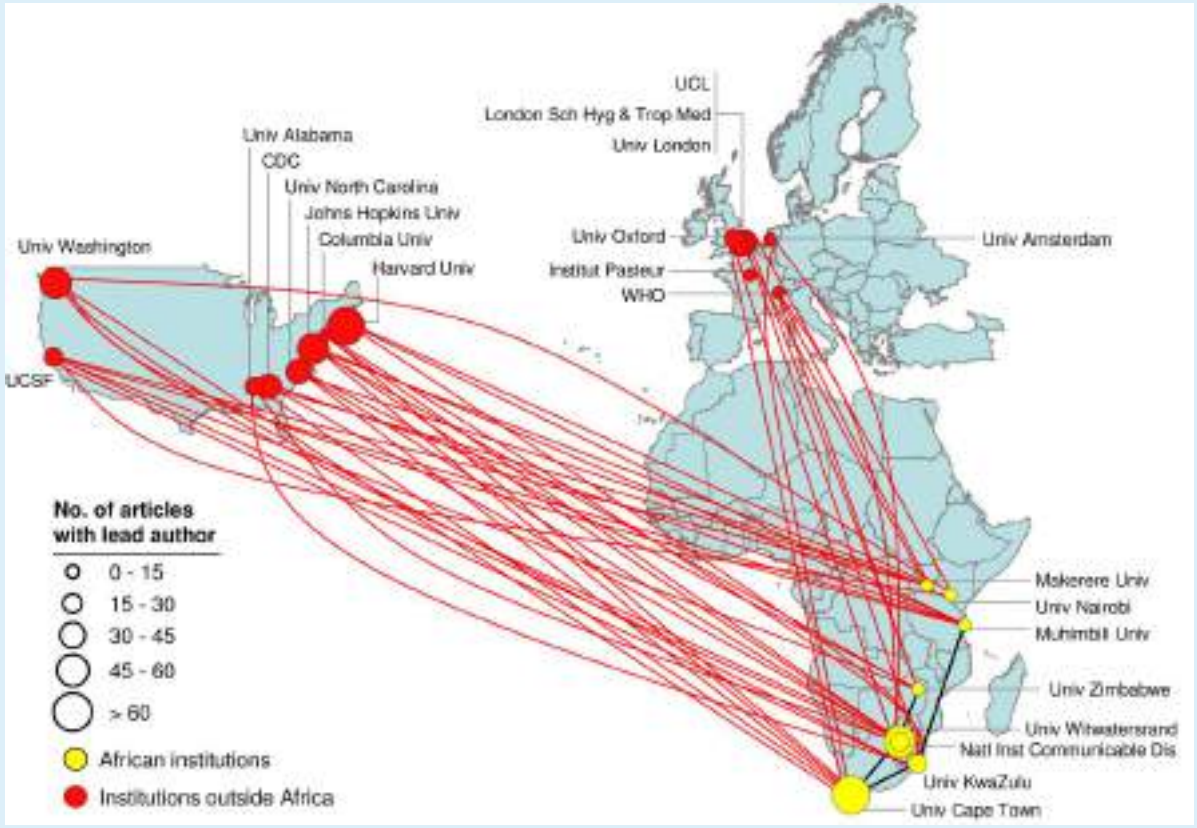
LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

INSTITUTE OF TROPICAL MEDICINE ANTWERP

World Health Organization

Consequences of historical approach

Fragmentation and marginalisation: HIV collaboration bias as of 2006 (Nwaka et al. Health in Action. June 2010)



Only 5% of publications had south-south linkages

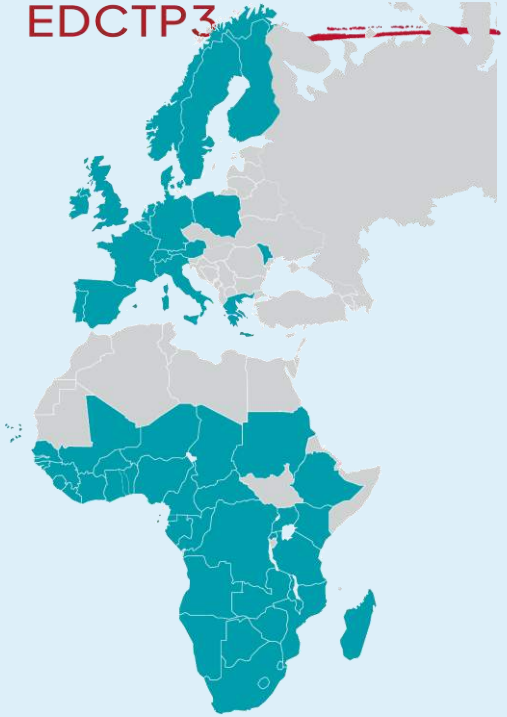
World Health Organization

From individualism to partnerships: 2006 and beyond

Good partnership principles and model funding models have emerged

Global Health EDCTP3

E D C T P



ESSENCE on Health Research

Effective research capacity strengthening:
A quick guide for funders

World Health Organization

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

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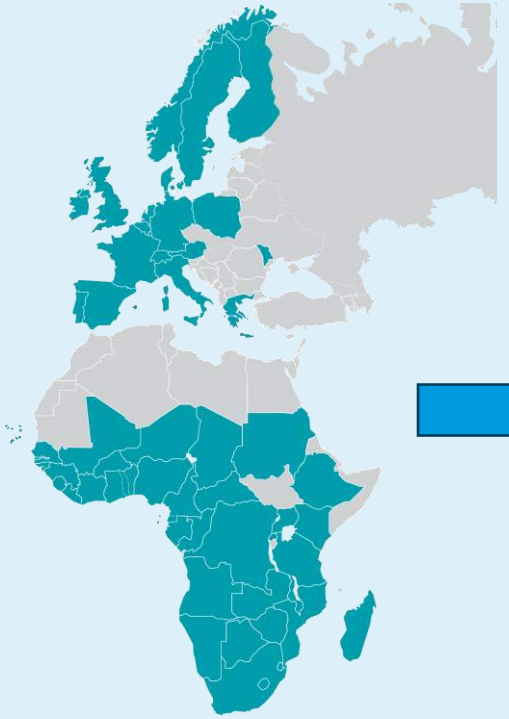
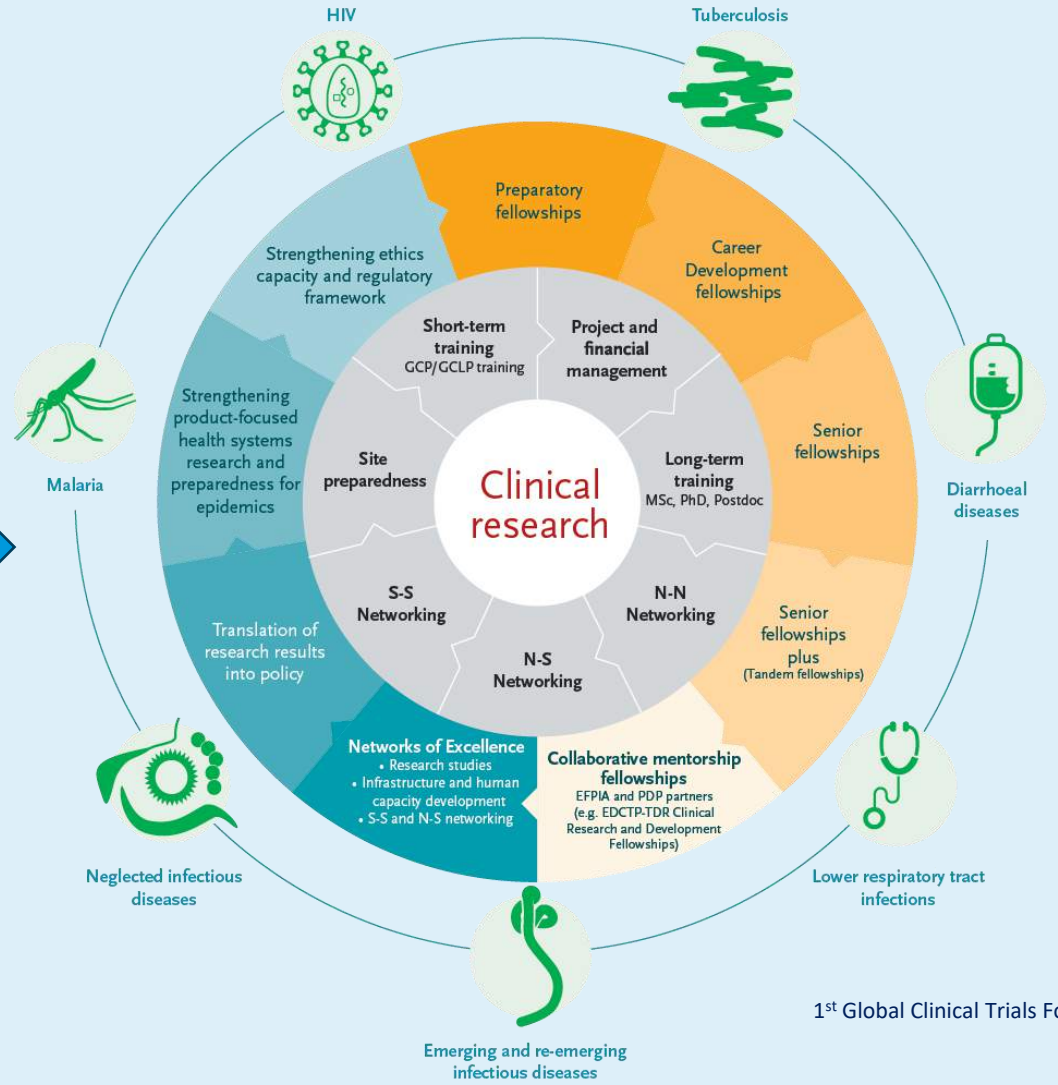
EDCTP example of layered programmes within a partnership

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

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Thank you

Those who shared views:-

- Dr Peter Kilmarx -NIH
- Dr Divya Shah -Wellcome
- Dr Mark Palmer –MRC UK
- Dr Garry Aslanyan -TDR

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Priority actions

Action	Rationale	Outcome
1.		
2.		
3.		
4.		
5.		
6.		

Roles and responsibilities

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

Stakeholders	Roles	Responsibilities
1.		
2.		
3.		
4.		
5.		
6.		

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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]

Discussions
Follow-up actions planned in the region

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

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

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VISION

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

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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*

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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.

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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.

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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

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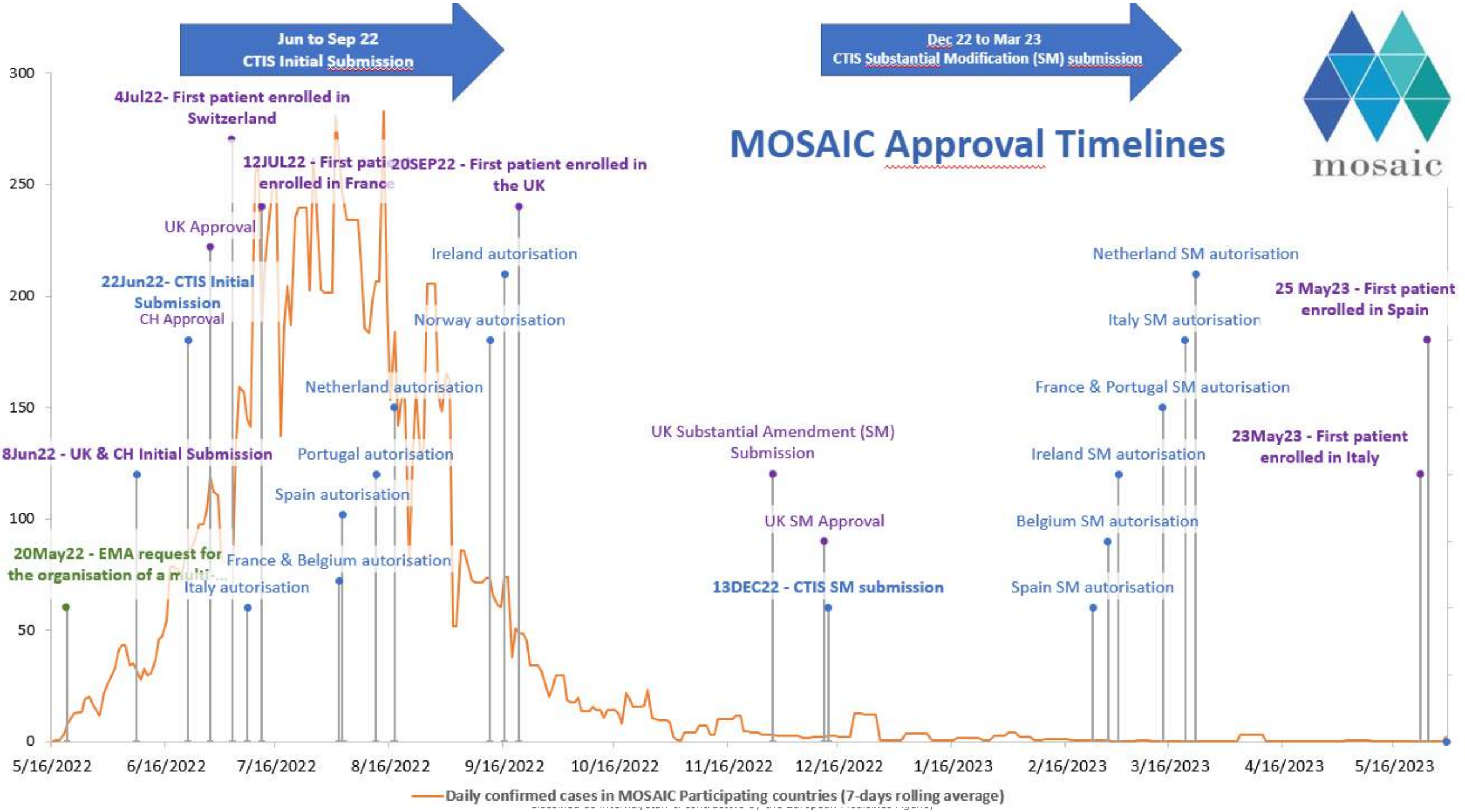
MOSAIC Approval Timelines



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)

Document amount – CTR Experiences

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?

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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

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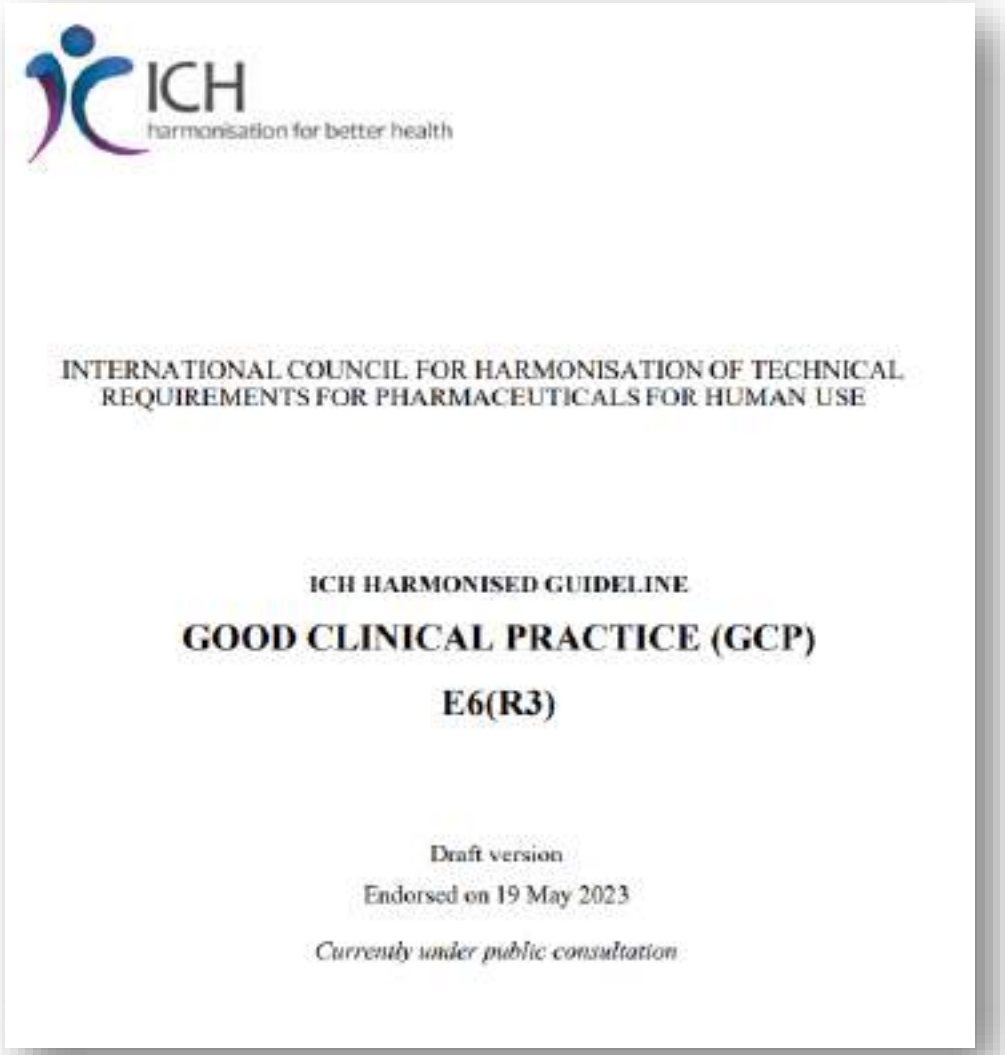
Modernizing The Conduct of Clinical Trials Harmonizing Good Clinical Practice Guidelines – ICH E6(R3) – GCP

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
  - **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
  - For example, no blanket training requirement and training should correspond to the role expected to be played in the trial


ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP)

E6(R3)

Draft version

Endorsed on 19 May 2023

Currently under public consultation

https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

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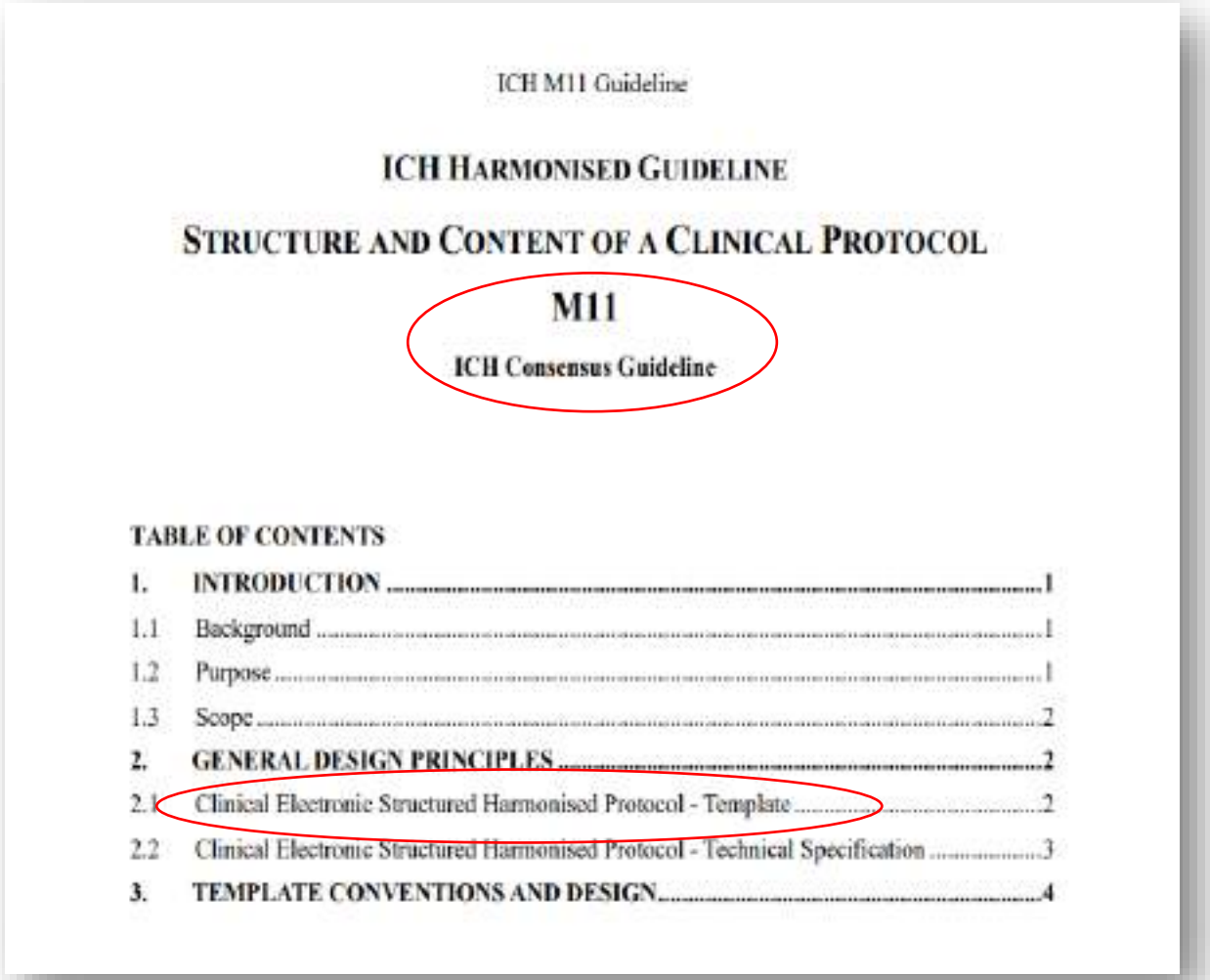
Potential Strategies for Efficient Regulatory Review



ICH M11 Guideline

ICH HARMONISED GUIDELINE

STRUCTURE AND CONTENT OF A CLINICAL PROTOCOL

M11

ICH Consensus Guideline

TABLE OF CONTENTS

- 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

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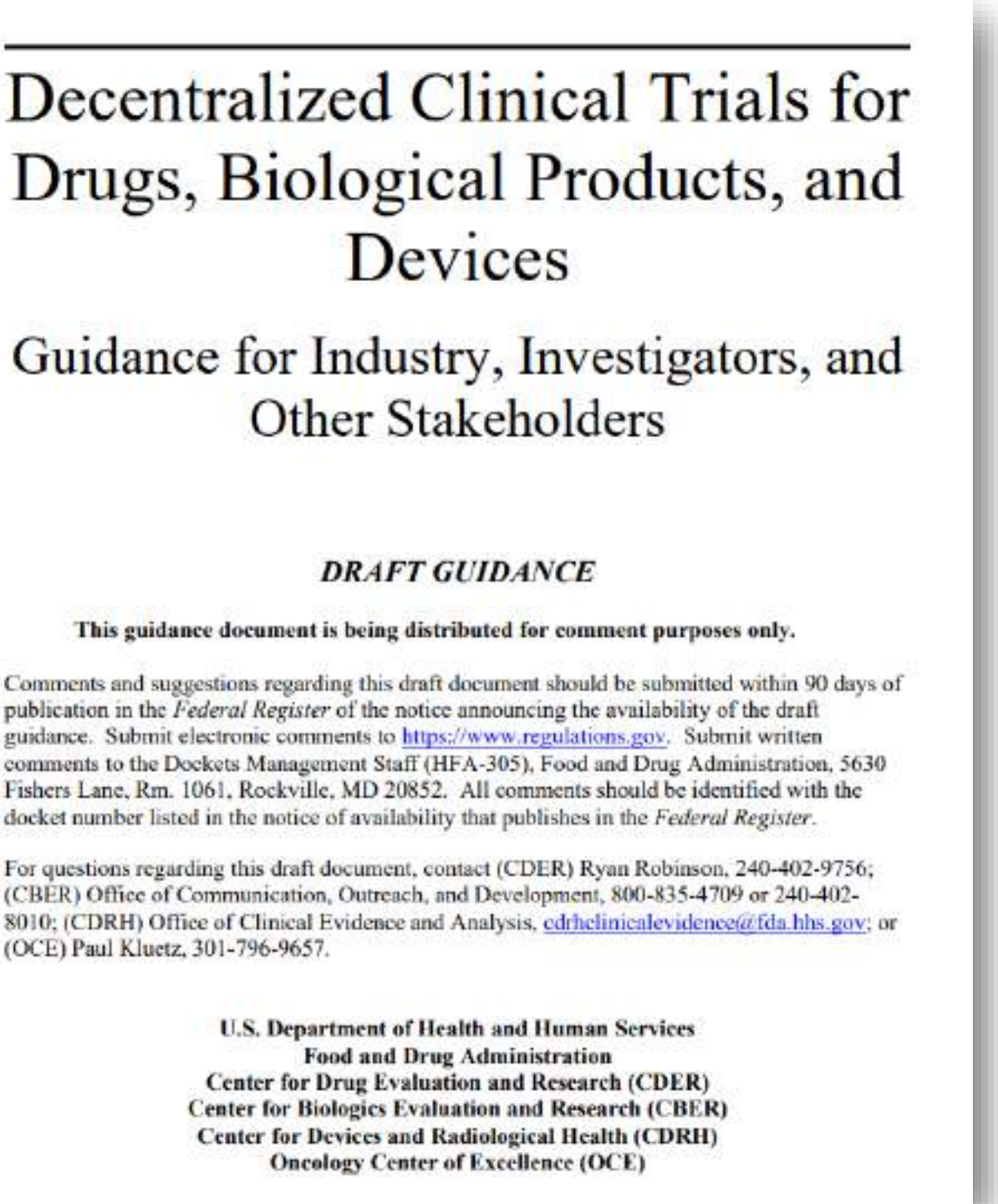
Regulatory elements to support multi-local trials

- Additional helpful elements may include incorporation of decentralized elements, such as remote informed consent, use of local providers for appropriate protocol elements



Decentralized Clinical Trials for Drugs, Biological Products, and Devices

Guidance for Industry, Investigators, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ryan Robinson, 240-402-9756; (CBER) Office of Communication, Outreach, and Development, 800-835-4709 or 240-402-8010; (CDRH) Office of Clinical Evidence and Analysis, cdrhclinicalevidence@fda.hhs.gov; or (OCE) Paul Kluetz, 301-796-9657.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

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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.

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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.

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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

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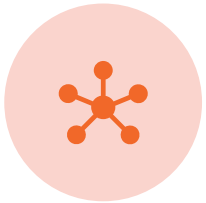
Summary: Bigger, better and faster clinical trials

We must seize the opportunity to get better medicines to patients faster



Need to leverage and sustain clinical trial networks all over the world

Coordination of approval process requires concerted regulatory and ethics processes to facilitate the implementation of impactful and ethical clinical research

Mechanisms for convergence among authorities across countries is of the essence

Coordination mechanisms and dialogue between regulators and the research community

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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

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

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)*

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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

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Priority actions

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

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Priority actions

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

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Roles and responsibilities

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

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Roles and responsibilities

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

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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

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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

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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.

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Thank You

ETHICS WORKING GROUP

World Health Organization

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

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)

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Objectives

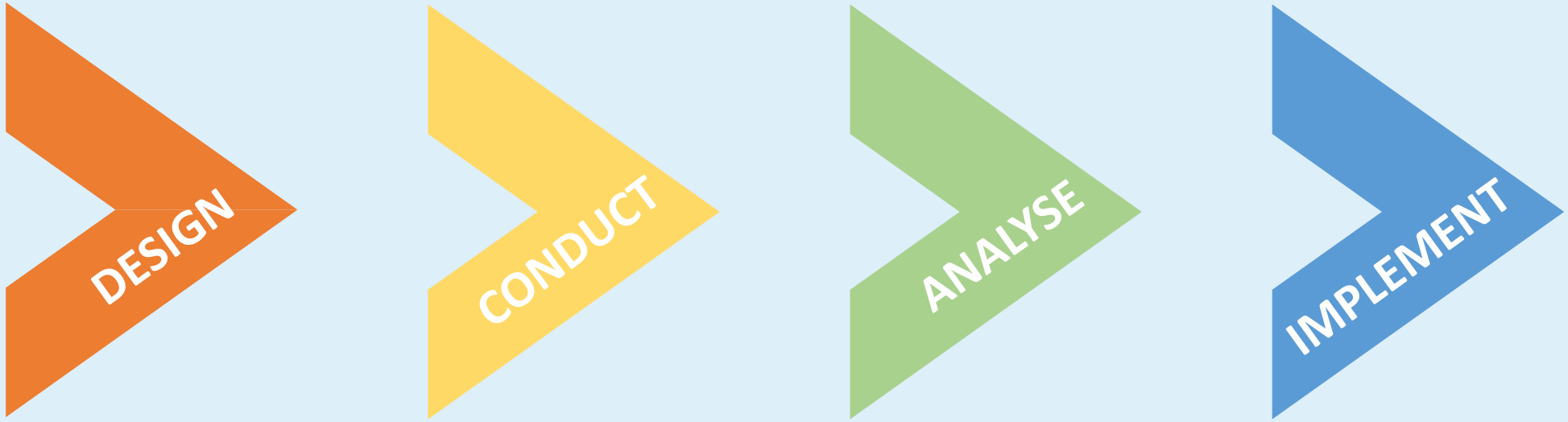
To identify key enabling factors and characteristics of informative and efficient clinical trials that lead to impact

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

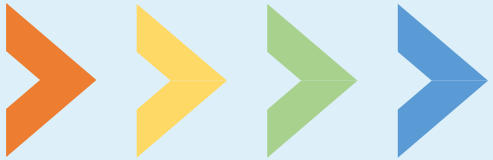
Combine evidence from primary research into systematic reviews of effectiveness; values and preferences; gender, equity and human rights; and resource use

Knowledge translation

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

Produce evidence

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



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

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

Implement evidence

Use evidence to inform policies and programme

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

Action	Rationale	Outcome
1. Knowledge and Capacity	Focus and prioritise clinical trial training (including clinical epidemiology and biostatistics) and regional mentoring to overcome knowledge and capacity deficits	Large-scale, adequately powered trials with credible event rate estimates and credible treatment effects led by investigators from LMIC
2. Enabling Environment	Streamline regulatory and ethics approval with mutual approval processes to reduce the time and administrative requirements at trial design stage	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
3. Tools and Technologies	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.	Fit-for-purpose accessible and scalable platforms for efficient recruitment, data management, analysis and monitoring; recognising limited connectivity in regions
4. Engagement and Partnership	Include public and communities in research prioritization and trial conduct to improve inclusivity and diversity of trial participation	Greater relevance, generalizability, and uptake, of results to all populations

Priority Actions

KNOWLEDGE & CAPACITY

TOOLS

ENABLING ENVIRONMENT

ENGAGEMENT & PARTNERSHIP

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

ENABLING ENVIRONMENT

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

DESIGN

TOOLS

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

ENGAGEMENT & PARTNERSHIP

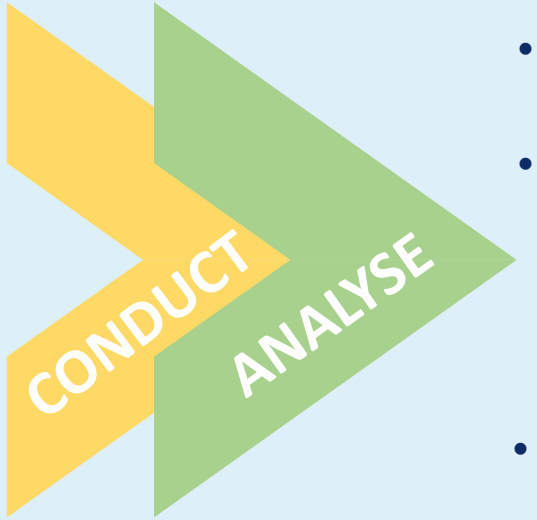
- Prioritization of questions to address unmet public health needs
- Design community-based trials
- Engaged Ethics Committees
- Ensure relevant audience perspectives included e.g. guidelines developers and national decision-makers

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

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

IMPLEMENT

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

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

1	Public and communities				
2	Trial participants				
3	Principal investigators				
4	Funding agencies				
5	Regulatory and ethics bodies				
6	Healthcare staff				

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Roles and responsibilities

Stakeholders	Roles	Responsibilities
1. Public and communities	• Engagement & Partnership • Enabling environment	Establish structures and networks and/or use existing networks to ensure public and community values and preferences are included. Create demand for trials and shape their questions and designs
2. Trial participants	• Engagement & Partnership	Participate in trials and potentially advise on trial design
3. Principal investigators	• Knowledge & Capacity • Tools and technologies	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
4. Funding agencies	• Enabling Environment • Tools and Technologies • Engagement & Partnership	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
5. Regulatory and ethics	• Enabling Environment	Collaborate and harmonise across regions
6. Healthcare staff	• Knowledge & capacity • Engagement and Partnership	Lead and conduct trials and ensure that all aspects of a trial are conducted according to standards

Comment

Translating evidence into global impact: lessons for HIV research and policy development from the AMBITION trial

Translating evidence into global impact: lessons for HIV research and policy development from the AMBITION trial

Jarvis JN, et al. Lancet Global Health. 2023;11(11):e1688-90.

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Synthesize evidence

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

Published in LGH and PLoS NTD, 2022

Knowledge translation

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

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

Evaluate and improve policy and practice

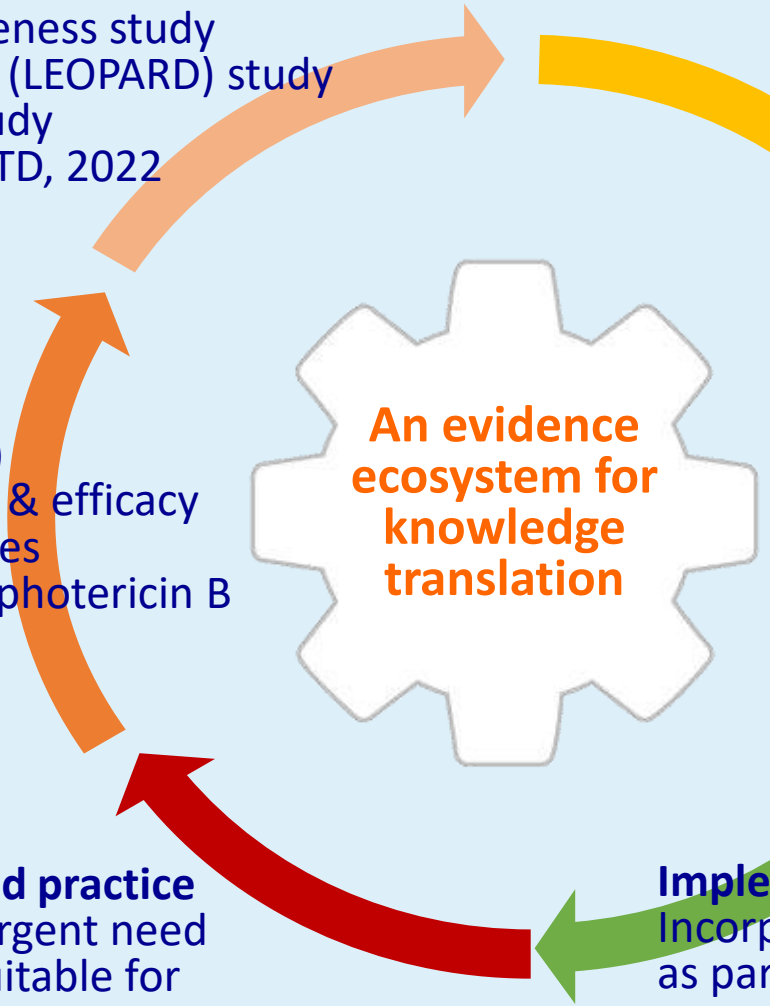
WHO 2018 clinical guidelines: urgent need for simple treatments for CM suitable for low-resource settings

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



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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

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

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

World Health Organization

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

World Health Organization

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)

World Health Organization

Sustainable Strong Continuous National Clinical Research Ecosystems

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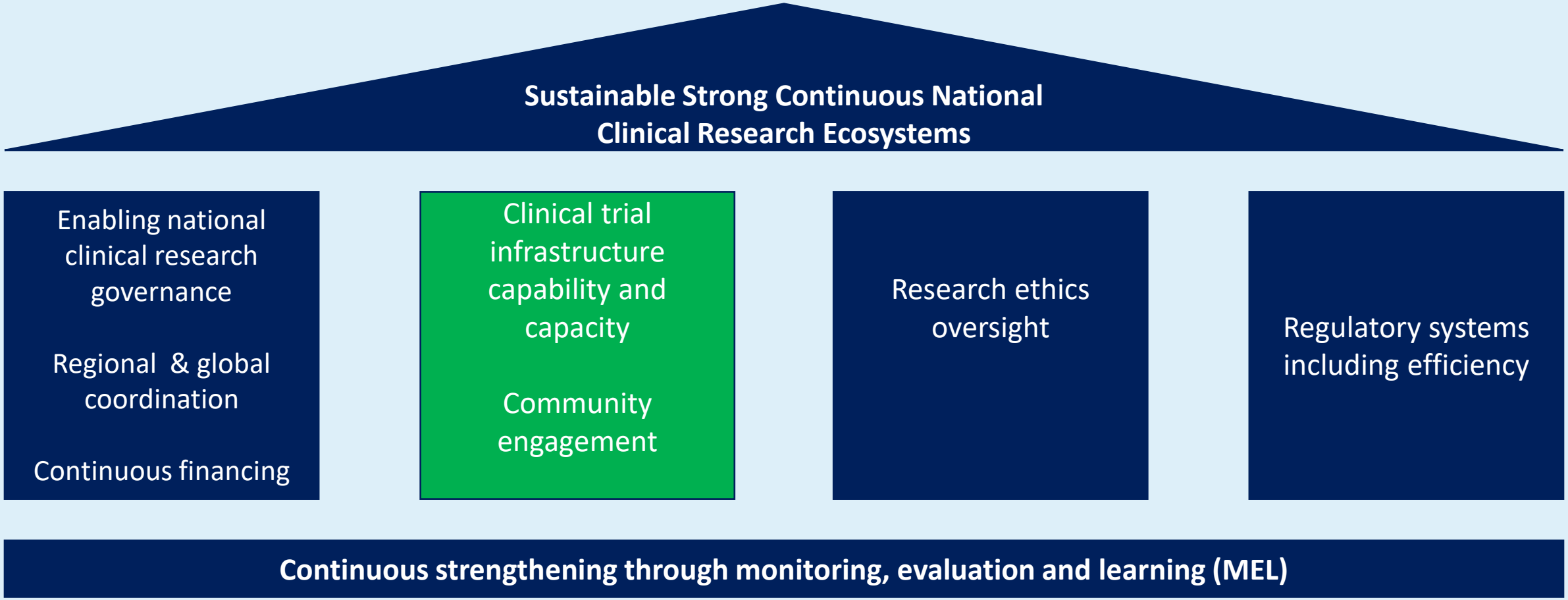

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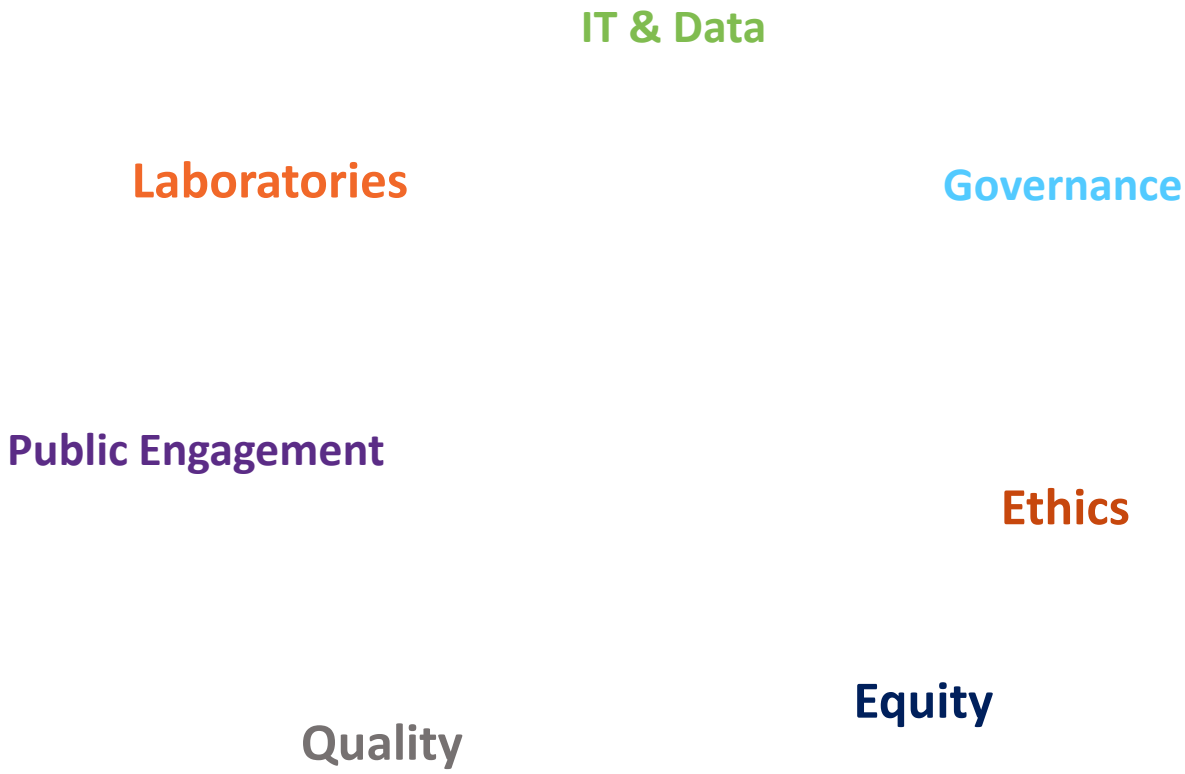
Clinical Trial Infrastructure Capability and Capacity Pillar: Space for a Maturity Framework

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?



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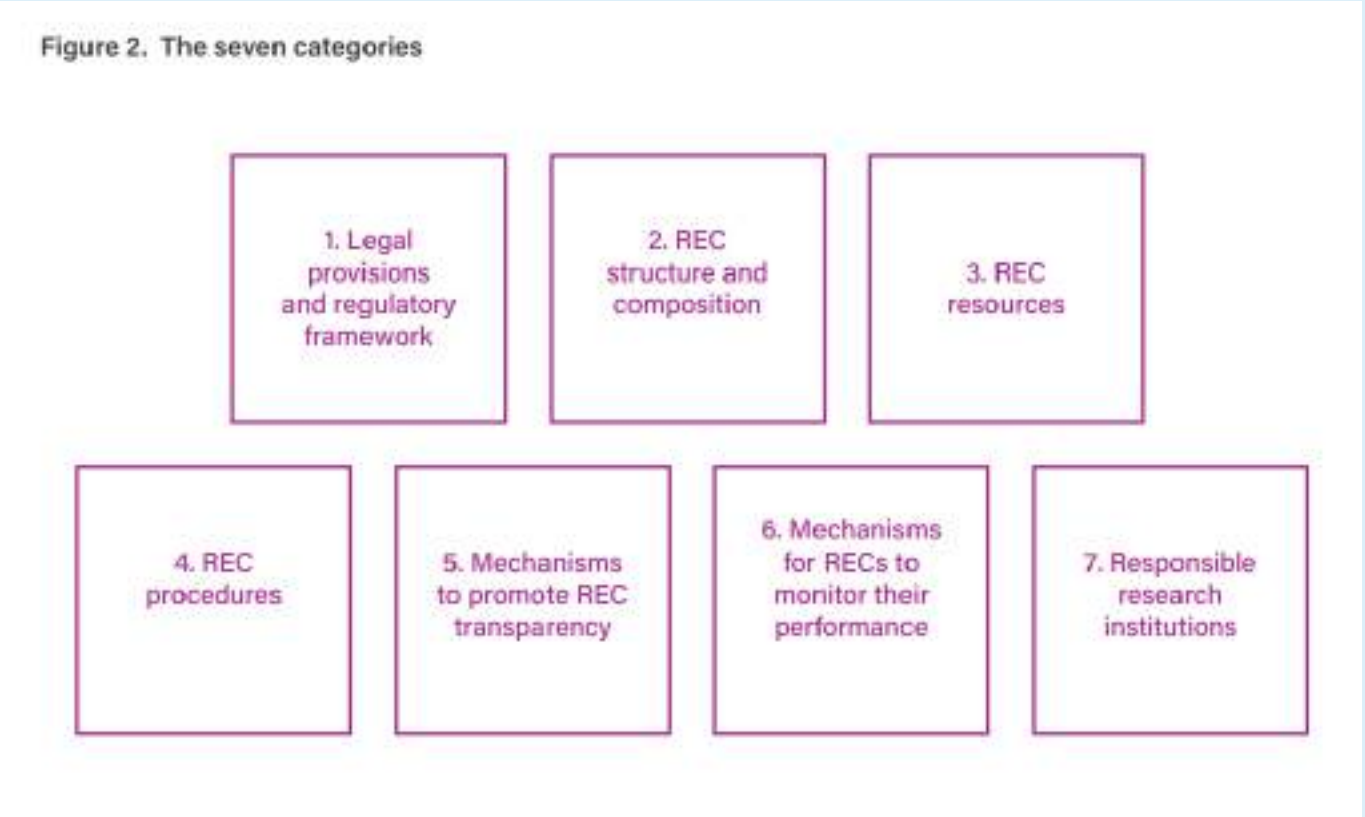
Global Benchmarking Tool for Research Ethics Committees

Figure 2. The seven categories



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Sustainable Strong Continuous National Clinical Research Ecosystems

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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

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Current levels of maturity of national regulatory systems

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

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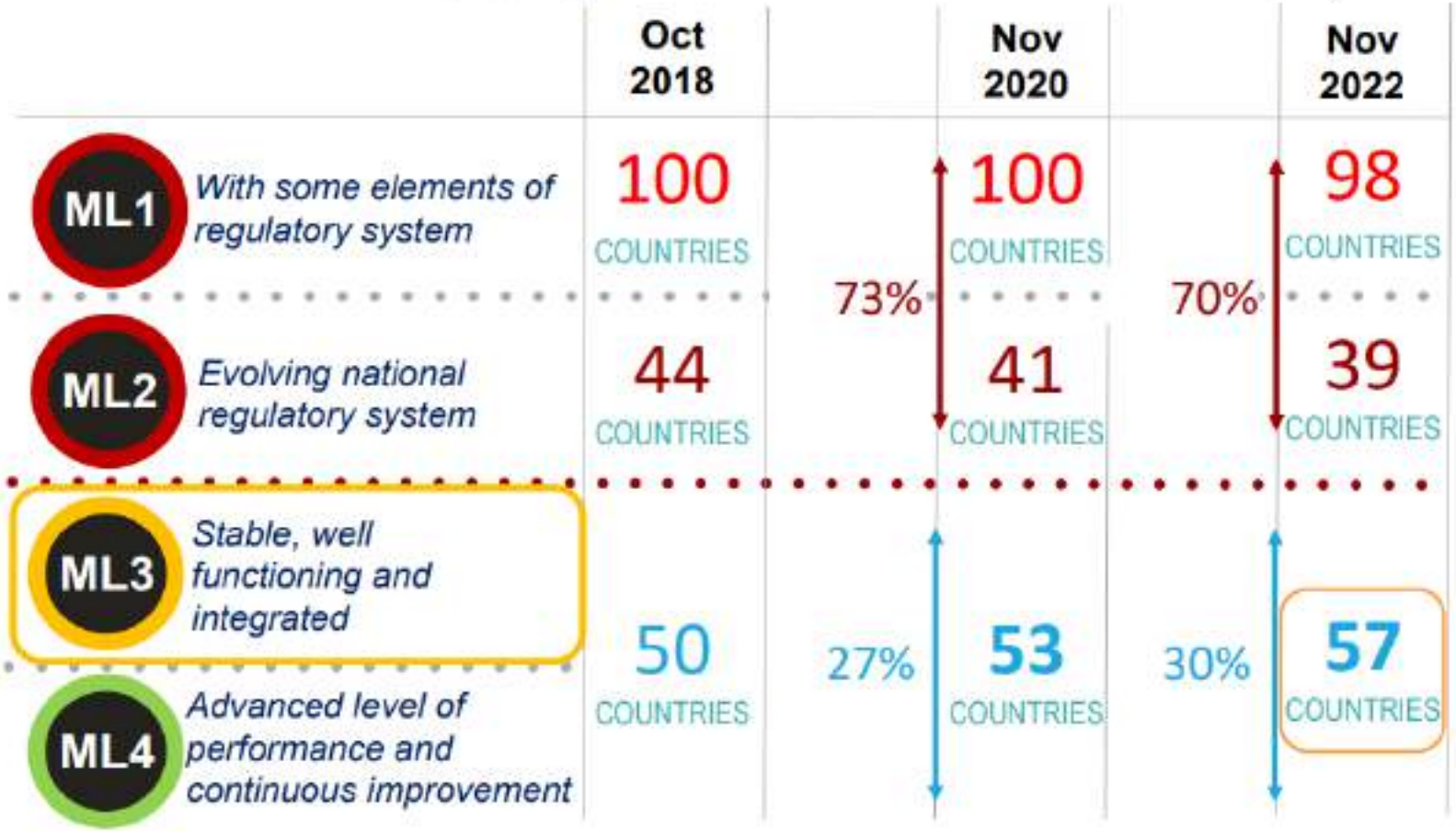

Vaccines developed in countries with weak regulatory systems, i.e., ML1/ML2, are not eligible for EUL or prequalification

ML3 GOAL of WHA Resolution 67.20

ML: *(regulatory system) maturity level*

- **Singapore** medicines regulatory system, 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)*

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

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Click to edit Master title style

Backup slides on initiatives identified

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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

World Health Organization

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

World Health Organization

Previous initiatives focused on governance of research institutions

CIOMS internationational 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

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Related initatives 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]

Action	Rationale	Outcome
1.		
2.		
3.		
4.		
5.		
6.		

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Roles and responsibilities

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

Stakeholders	Roles	Responsibilities
1.		
2.		
3.		
4.		
5.		
6.		

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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]

Discussions
Follow-up actions from the WG

World Health Organization

World Health Organization

Please feel free to choose title and close slides from the below alternatives

World Health Organization

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

[Please insert the focus area work of the WG]

[Please insert the names of the WG members]

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

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

[Please insert the names of the WG members]

World Health Organization

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

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

[Please insert the names of the WG members]

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Thank you

World Health Organization

Thank you

World Health Organization

Thank you

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WHO Science Division, Geneva, Switzerland

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

World Health Organization

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

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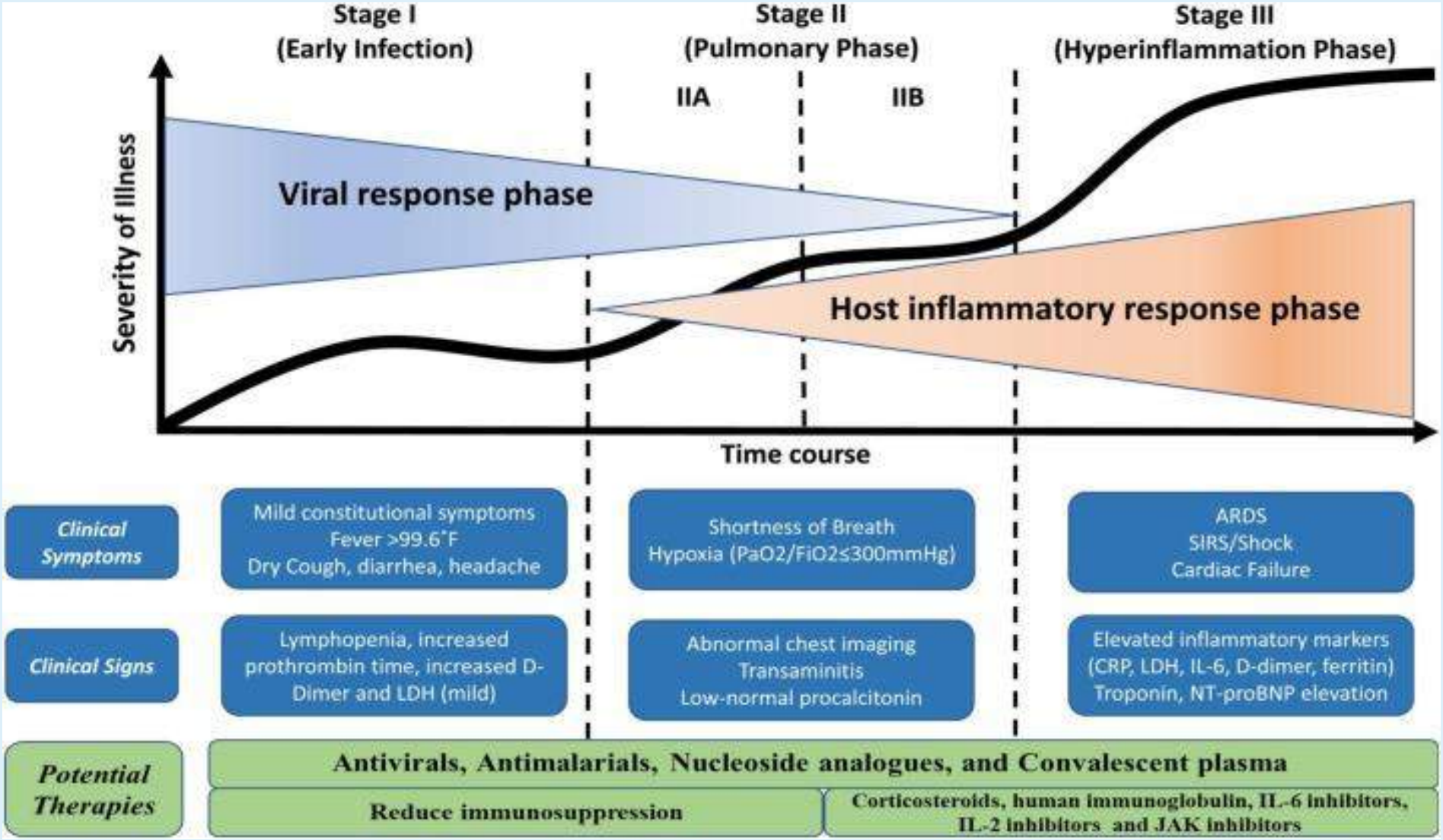
”Hand me down evidence” from hospitals particularly inappropriate in primary care



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The sickness iceberg, prevention and early intervention

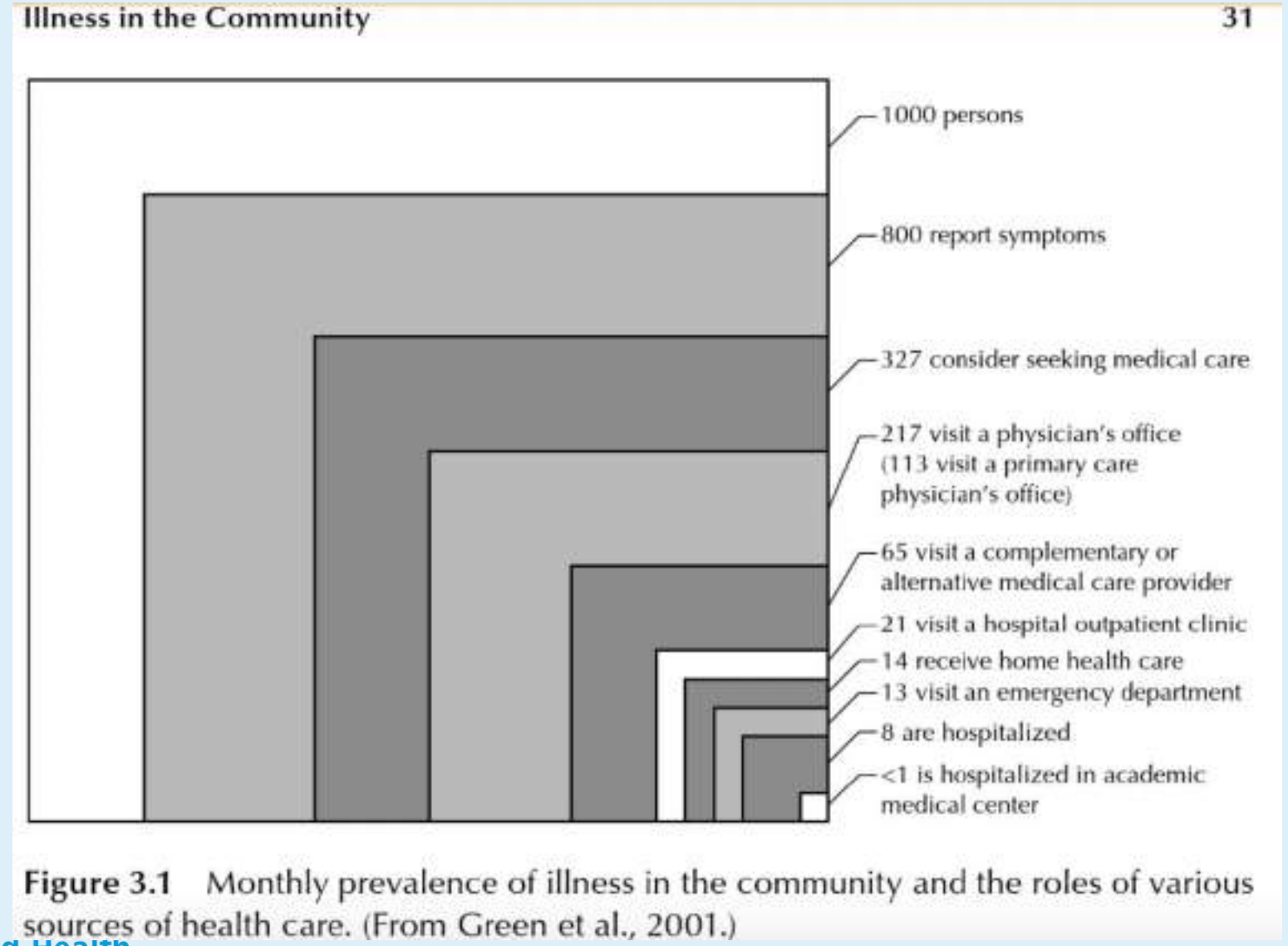
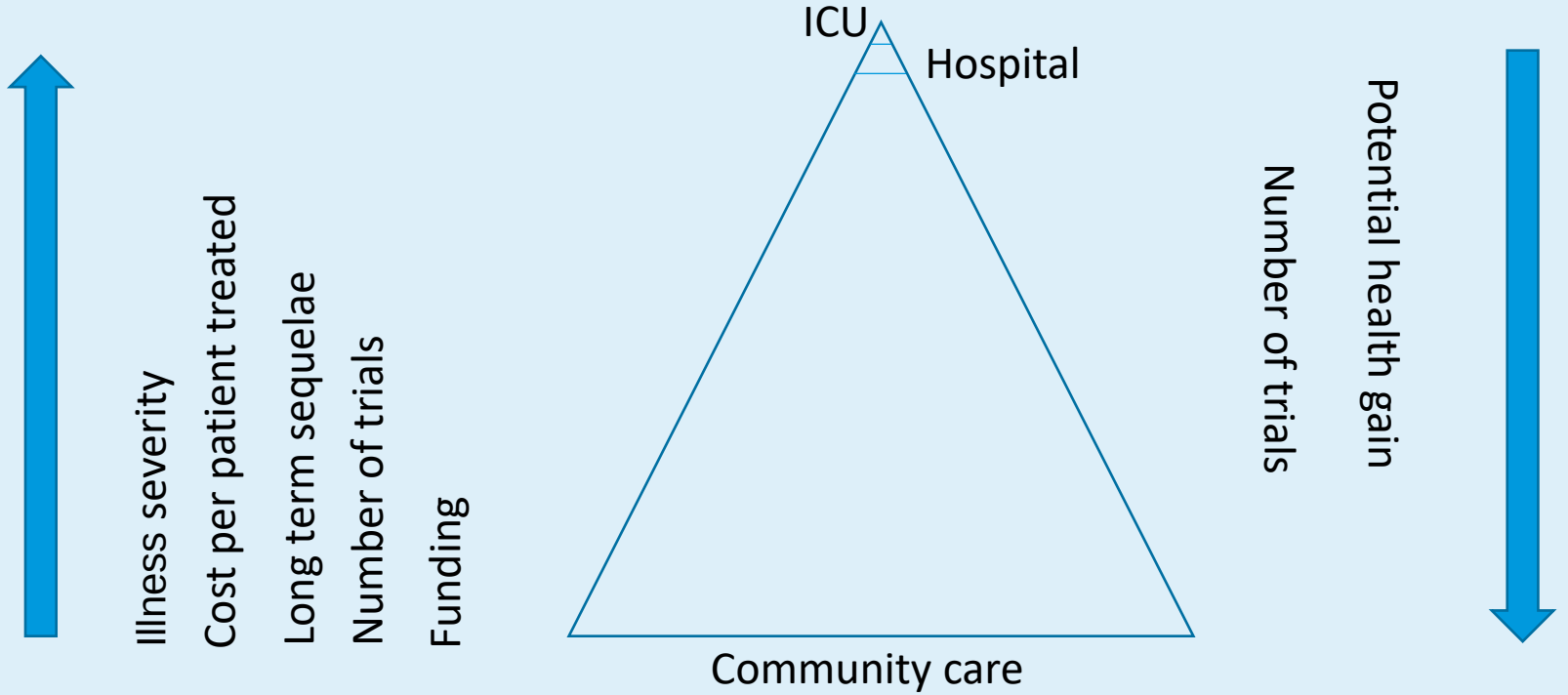


Figure 3.1 Monthly prevalence of illness in the community and the roles of various sources of health care. (From Green et al., 2001.)

Ian McWhiney
1926-2012

World Health Organization

Inverse funding and potential health gain law



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The Lancet · Saturday 27 February 1971

THE INVERSE CARE LAW

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

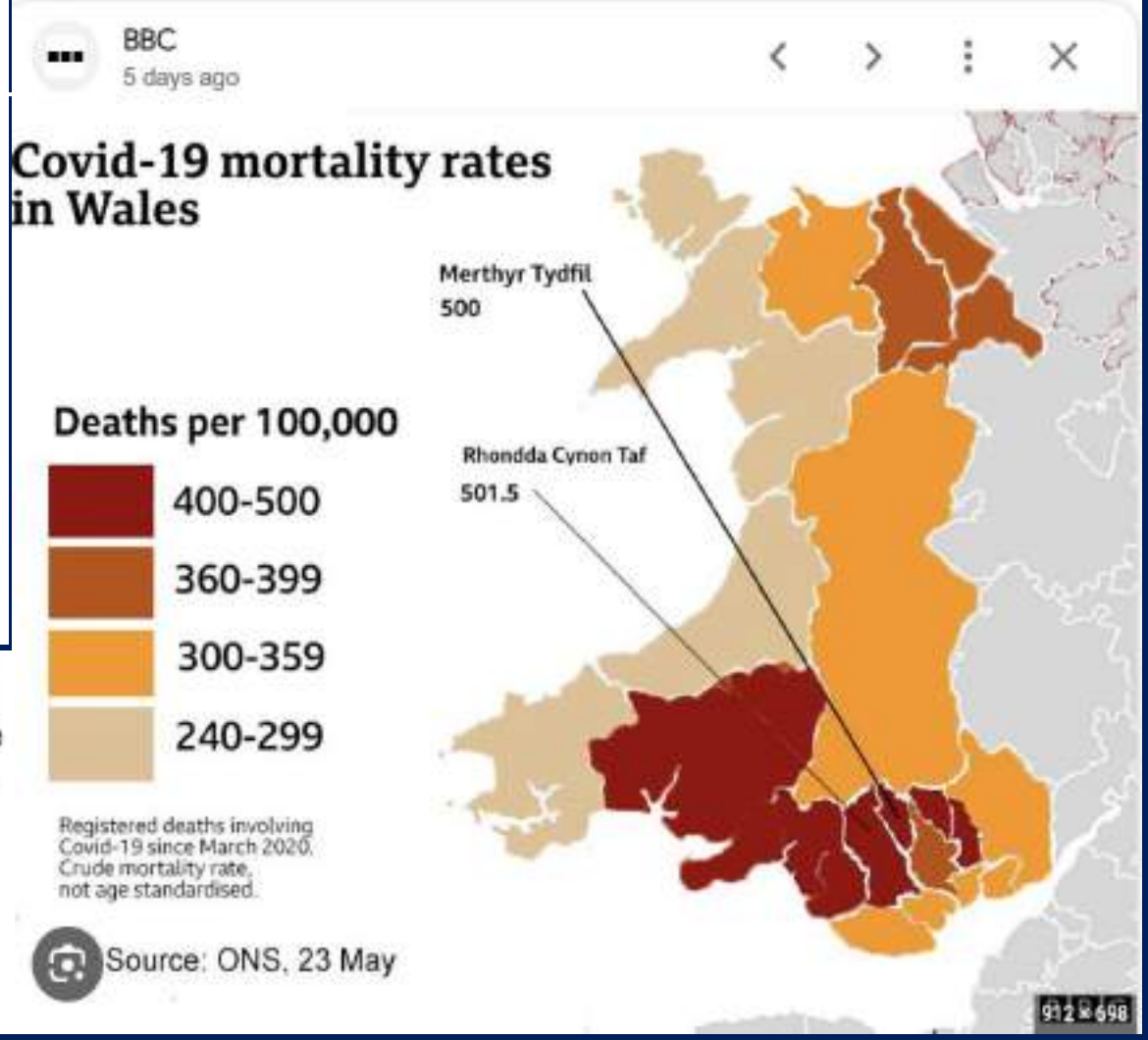
Summary The availability of good medical care tends to vary inversely with the need for it in the population served. This inverse care law operates more completely where medical care is most exposed to market forces, and less so where such exposure is reduced. The market distribution of medical care is a primitive and historically outdated social form, and any return to it would further exaggerate the maldistribution of medical resources.

World Health Organization

Health inequalities: Deprivation and poverty and COVID-19

The unequal impact of the coronavirus in our communities can be measured by rates of mortality among the most deprived. Deprivation underpins almost all inequalities.

Office for National Statistics (ONS) data shows that people who live in the most deprived areas of England and Wales are around twice as likely to die after contracting COVID-19. The data released in August 2020, when cases and mortality rates were relatively low reveal that in England, the age-standardised mortality rate for deaths involving COVID-19 in the most deprived areas in July 2020 was 3.1 deaths per 100,000 population; as seen in previous months, this was more than double the mortality rate in the least deprived areas (1.4 deaths per 100,000 population).



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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

World Health Organization

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

Barriers

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: E**thical, **A**dministrative, **R**egulatory, **L**egal 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

World Health Organization

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 Therapeutic**s 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**

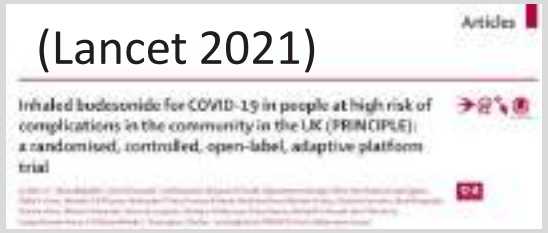
World Health Organization

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

World Health Organization

PRINCIPLE Trial of repurposed medicines



23 Jun 2021 — Ivermectin — 01 July

8 Apr 2021 — Favipiravir — 01 July

Colchicine: 4 Mar – 26 May

Inhaled Budesonide: 1 Dec – 31 March

Doxycycline: 24 Jul – 14 Dec

Azithromycin: 22 May – 30 Nov

Hydroxychloroquine: 2 Apr – 22 May

>10,500 participants

Usual Care

Apr 2020 | Jun | Aug | Oct | Dec | Feb 2021 | Apr | Jun | Aug | Oct | Dec | Feb 2022 | Apr | Jun | Aug

Identifying what does NOT work critical: Home rune for antimicrobial stewardship

Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

Christopher C Butler, Ly-Mee Yu, Jienchi Dorward, Oghenekome Gbinigie, Gail Hayw
Michelle A Detry, Christina Saunders, Mark Fitzgerald, Victoria Harris, Ratko Djuka
Emma Ogburn, Philip H Evans, Nicholas P B Thomas, Mahendra G Patel, F D Richa

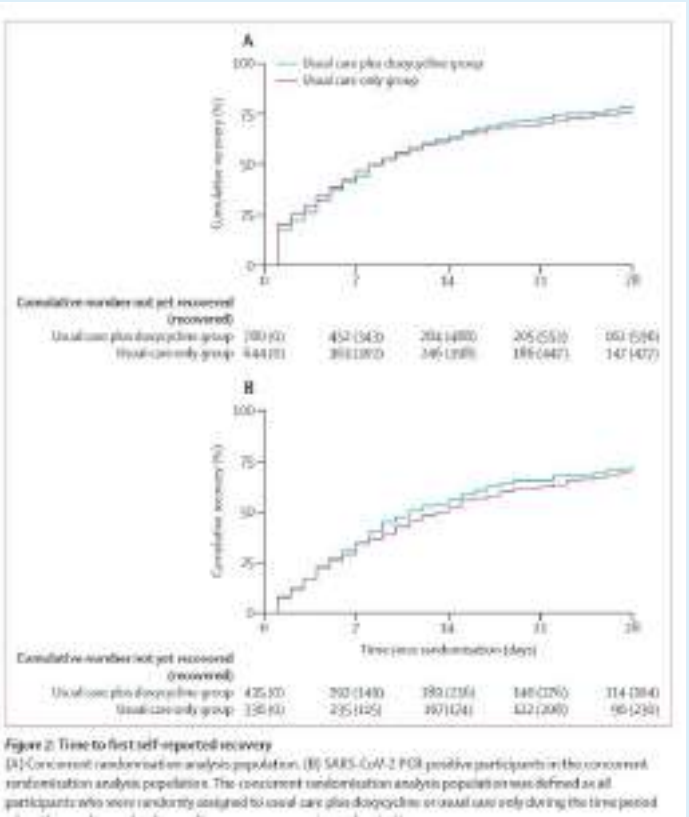


Figure 2: Time to first self-reported recovery

Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

PRINCIPLE Trial Collaborative Group*

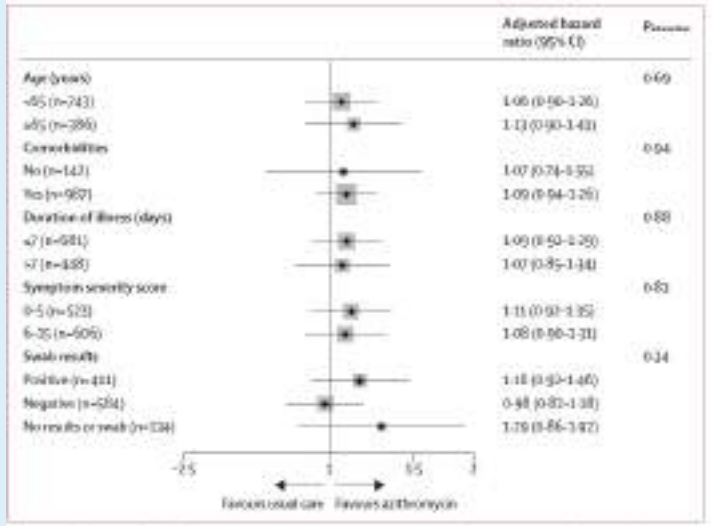


Figure 3: Subgroup analysis of time to recovery outcome (concurrent randomisation analysis population)

MSD MOVE-Out trial

- 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*

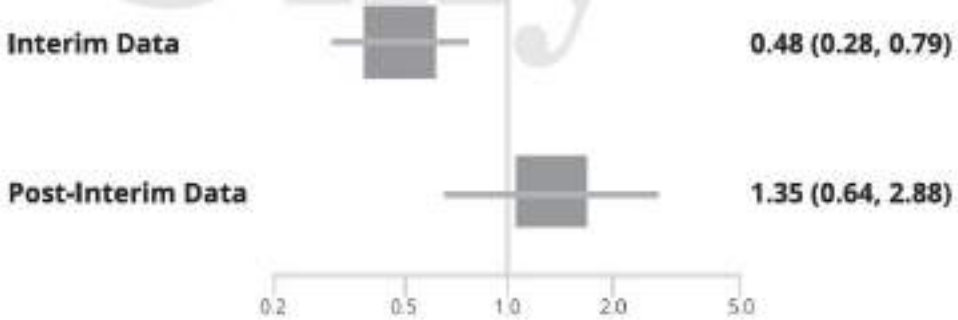


FIGURE 1. Subgroup forest plot of the interim data odds ratio versus the post-interim data (only) odds ratio with accompanying 95% CIs. Test-of-interaction subgroup effect yielded $P < 0.01$.

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!

PANORAMIC
Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community

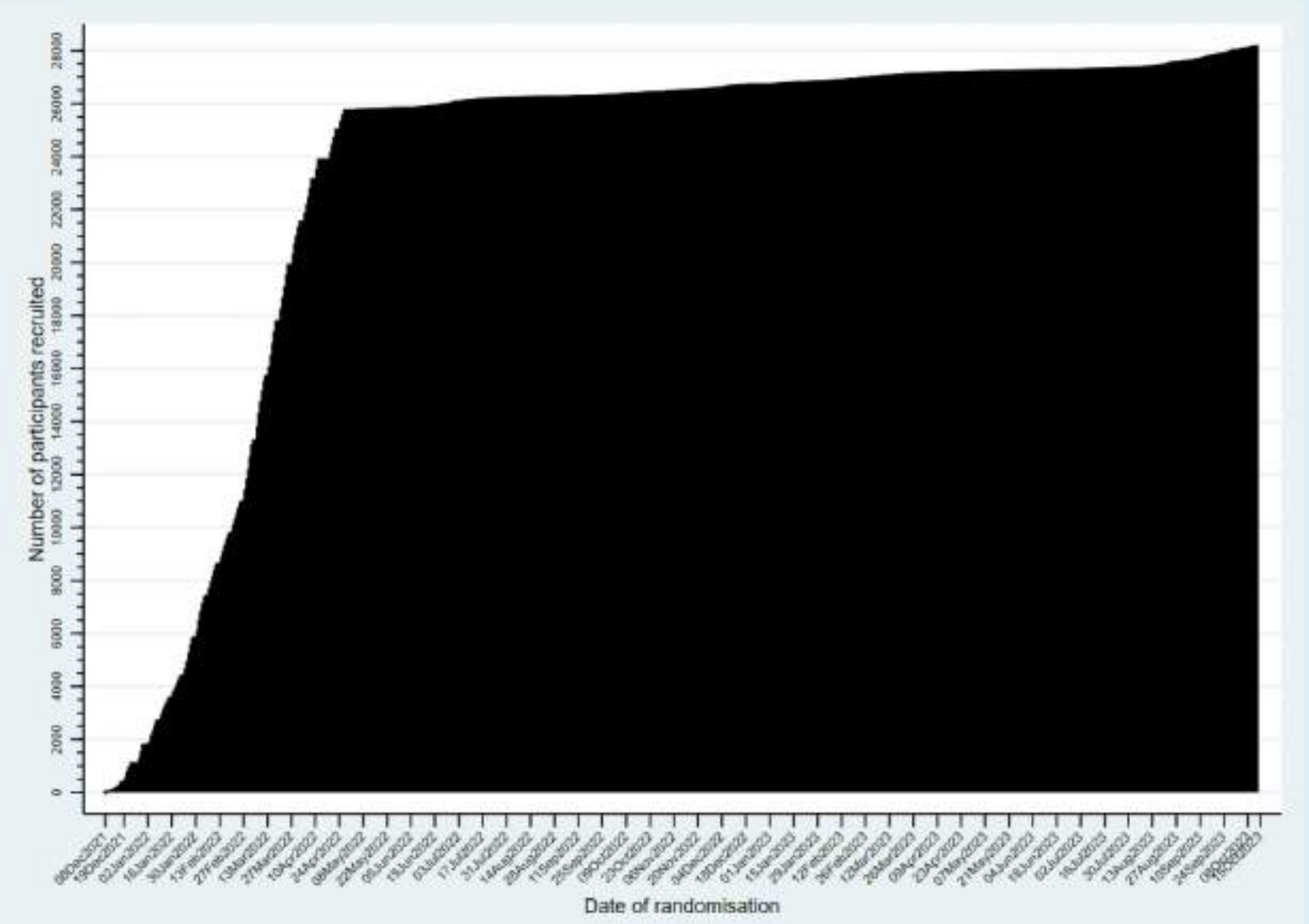
Recruitment from all four UK Devolved Administrations

>120,000 screened

>6,000 GP practices have recruited at least one participants to PANORAMIC
(each red dot represents a GP Practice)


Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial

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 ONGOOING n=>28,300

PRINCIPLE+PANORAMIC: >38,500 randomizations

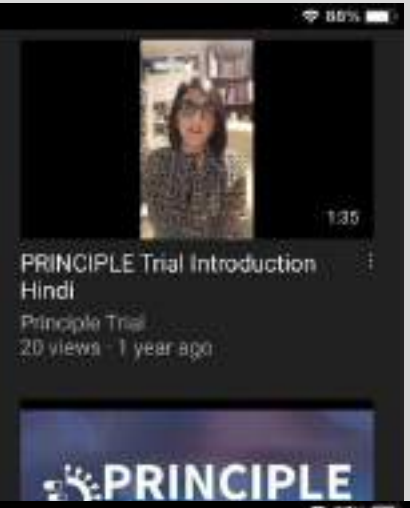
World Health Organization

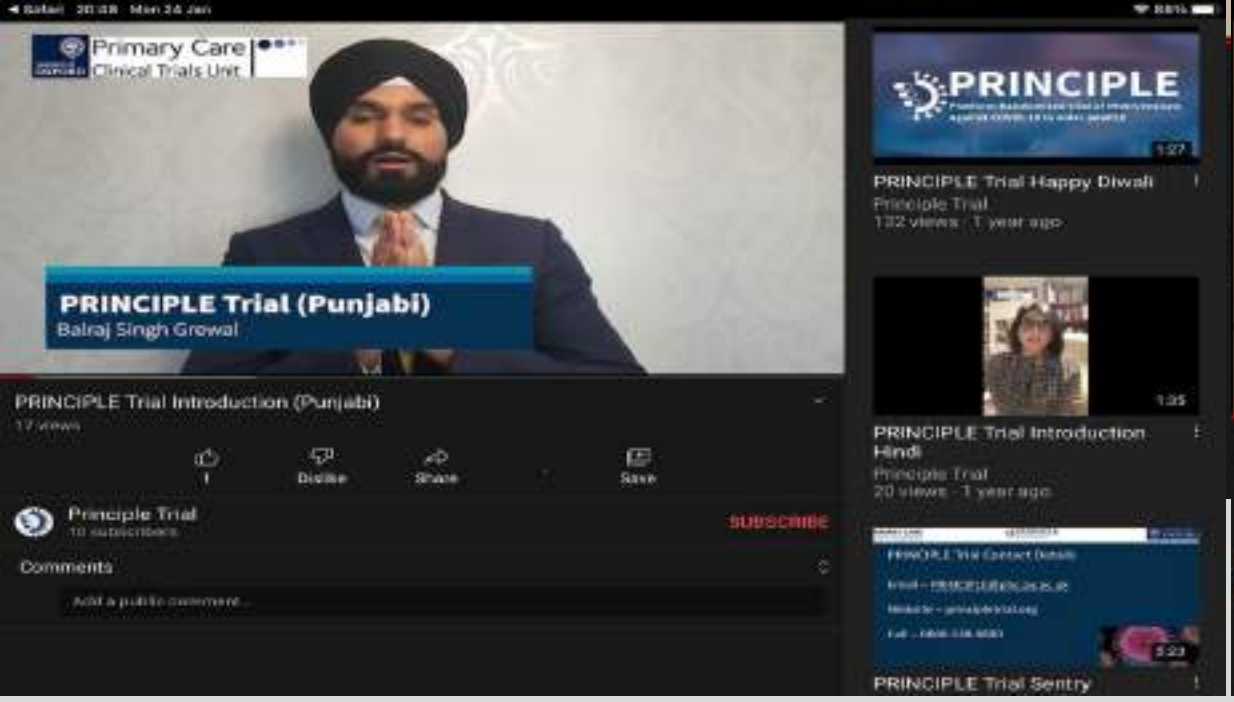
NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

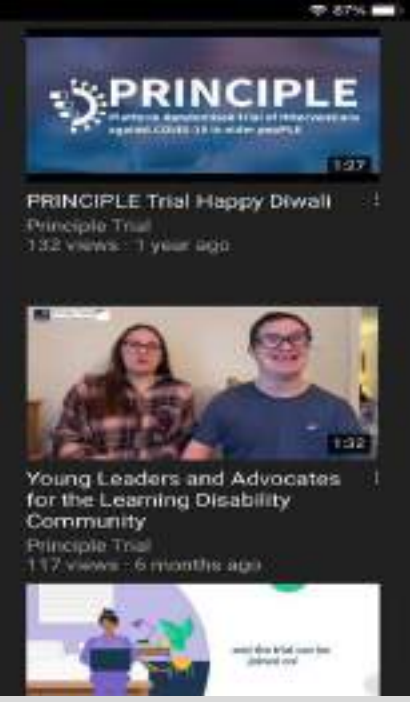
RESOURCES

PRINCIPLE
Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses

UNIVERSITY OF OXFORD







Molnuipiravir


Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial

- **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 sy**mptoms still to come.

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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’**

World Health Organization

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

Paediatric WG

Nigel Rollins and Martina Penazzato

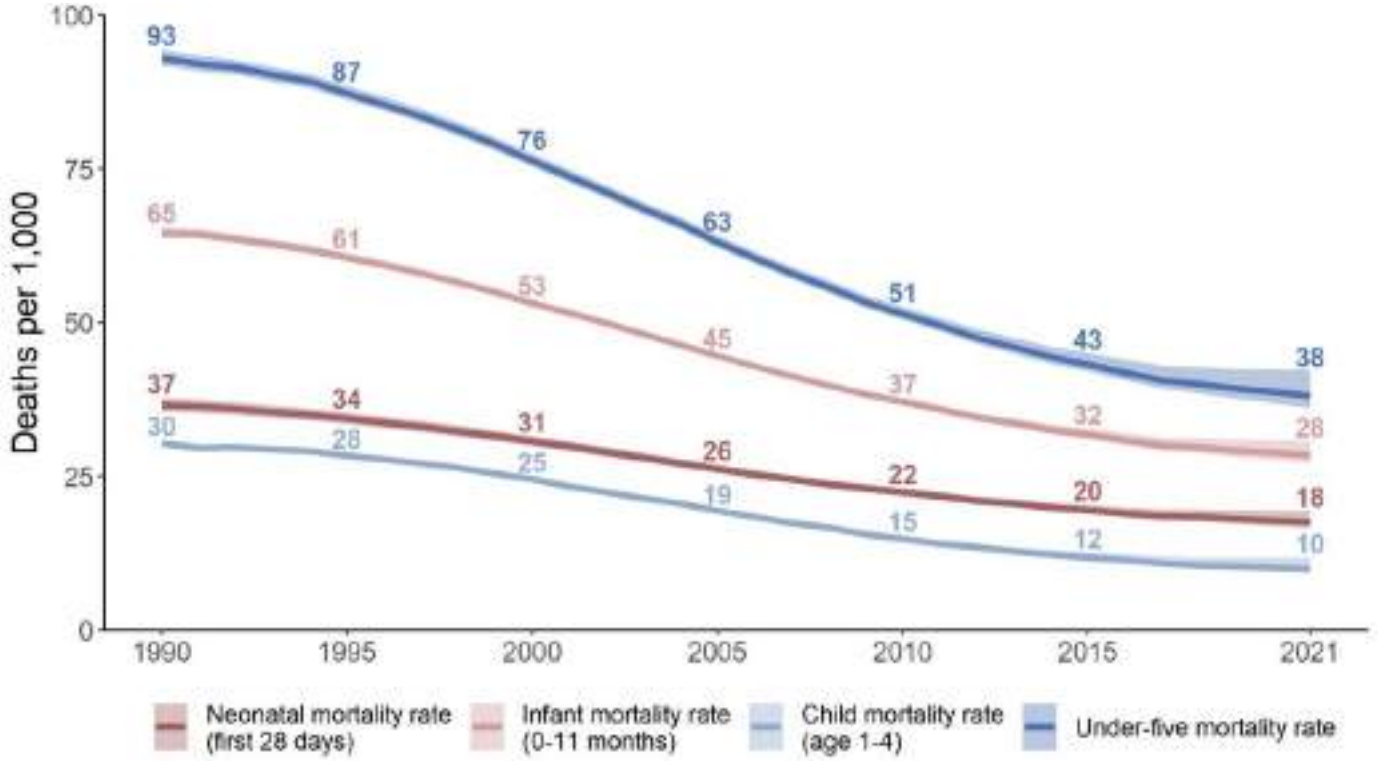
On behalf of

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

World Health Organization

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



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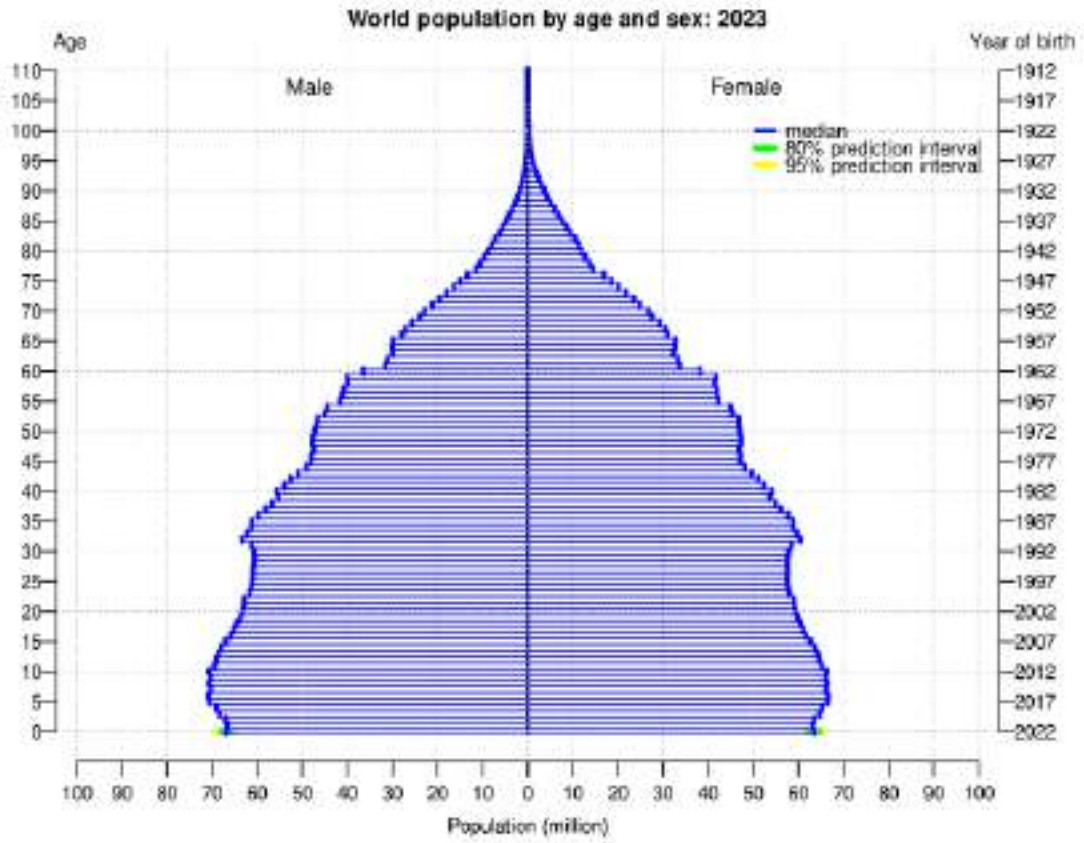
Source: UNIGME report https://childmortality.org/wp-content/uploads/2023/01/UN-IGME-Child-Mortality-Report-2022.pdf

Why invest in paediatric research?

- Rates of decline of infant and child mortality have been levelling off since 2015
- Growing child populations in LMICs
  - **By 2100, 8 of 10 people will live in Africa or Asia**



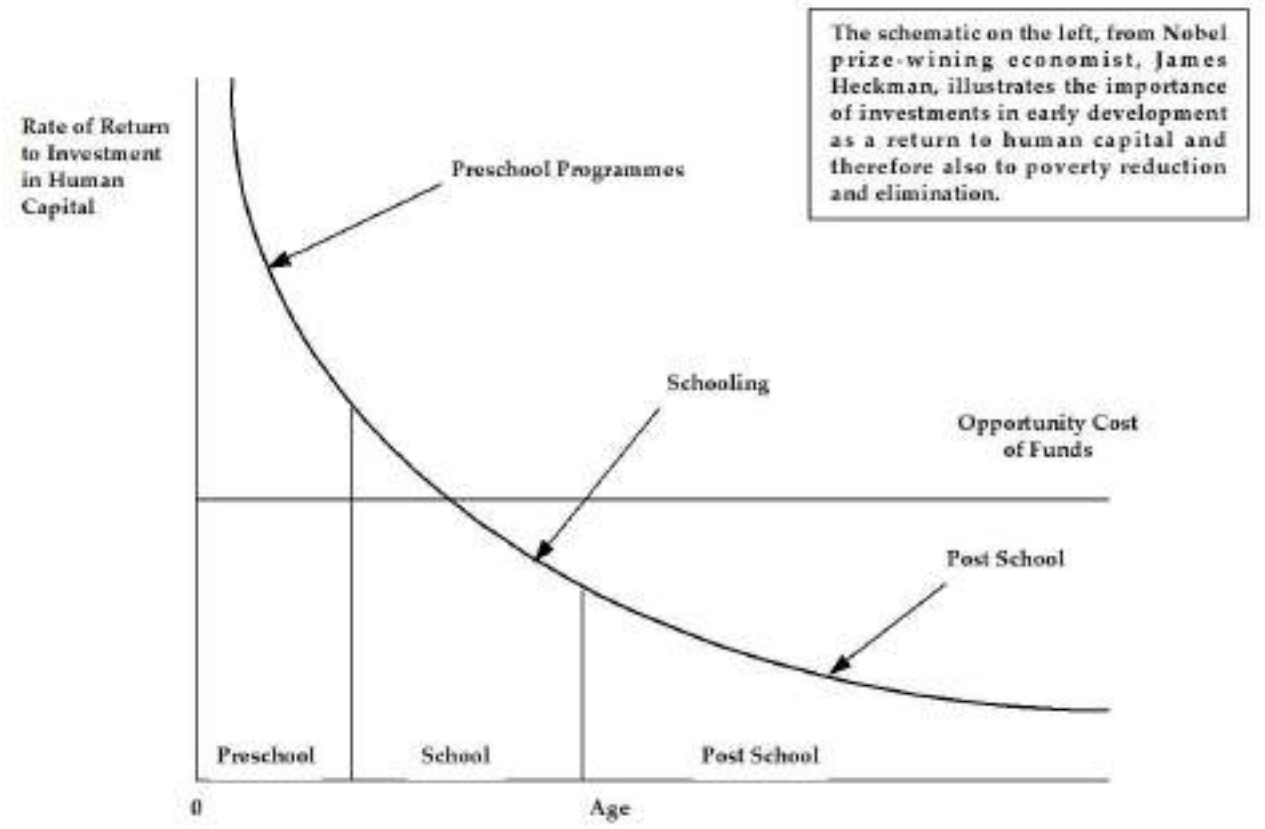
United Nations, DESA, Population Division. *World Population Prospects 2022*. http://population.un.org/wpp/

World Health Organization

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)

Figure 1: Rates of Return to Human Capital Investment Initially Setting Investments to be Equal Across all Ages



Rates of Return to Human Capital Investment Initially Setting Investments to be Equal Across all Ages

World Health Organization

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


THE LANCET

Building the foundations for sustainable development: a case for global investment in the capabilities of adolescents

Summary

*"If we **change** the **beginning of the story**, we **change the whole story**"*

World Health Organization

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

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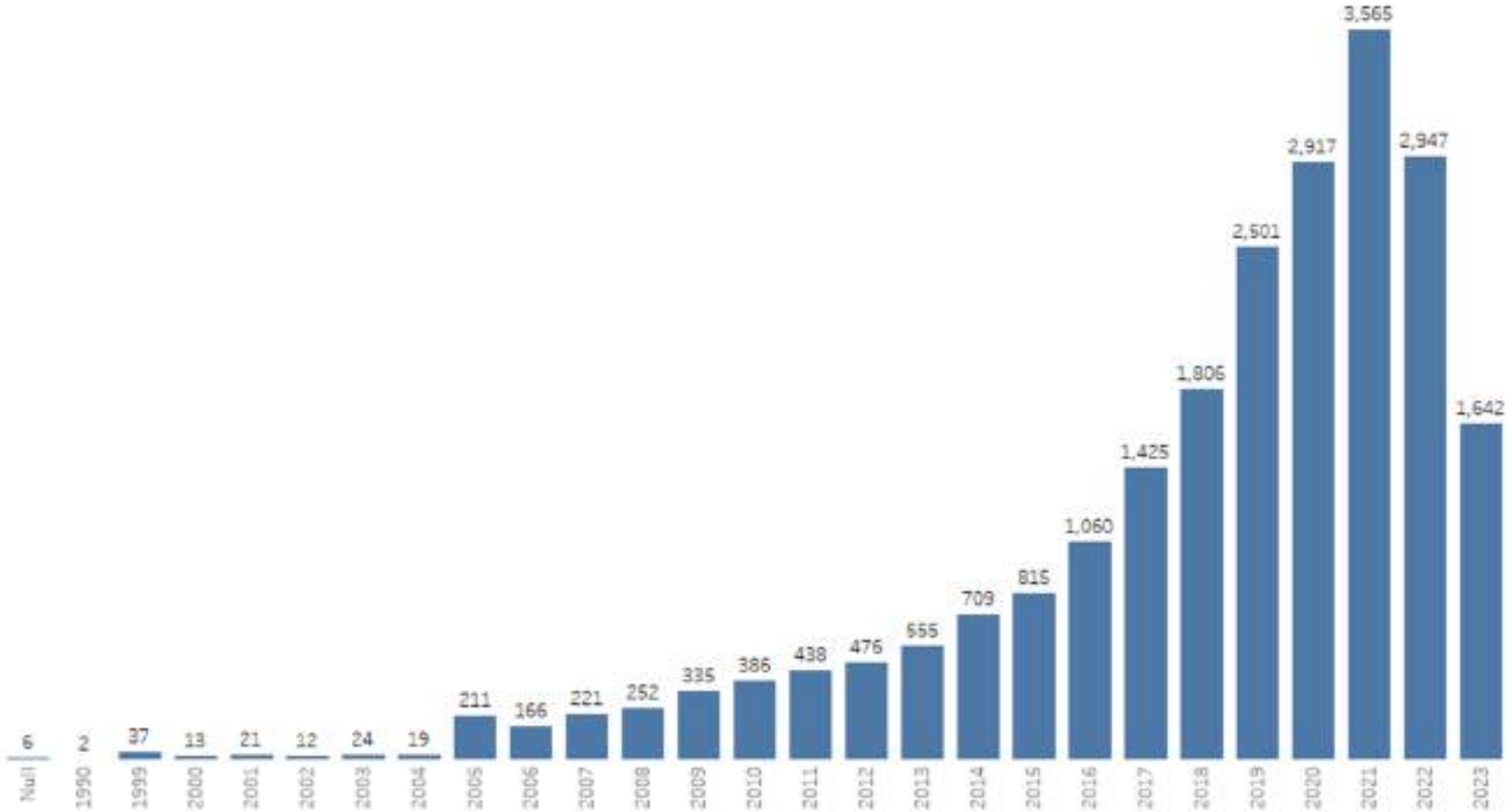
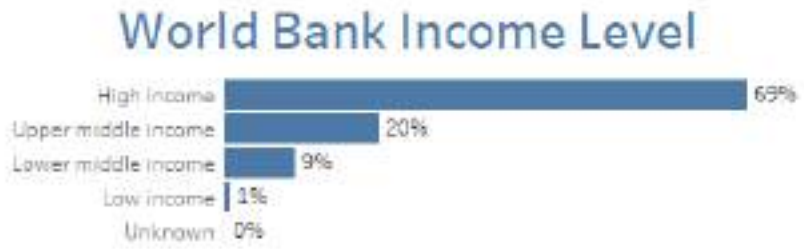
Only 10% of ongoing registered clinical trials include children

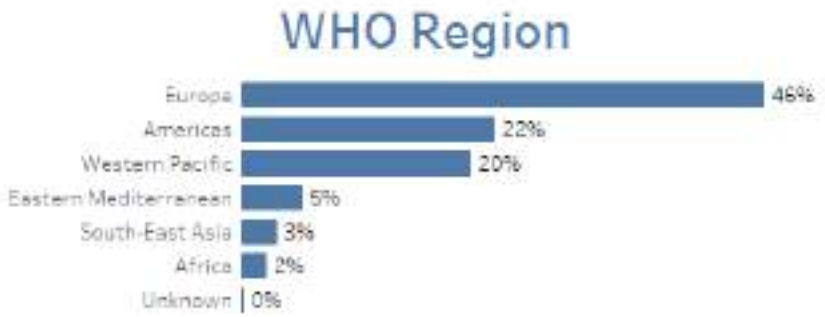


World Health Organization

International Clinical Trials Registry Platform (ICTRP), October 2023

… And 70% of these are conducted in High income settings
Only 10% in LMICs

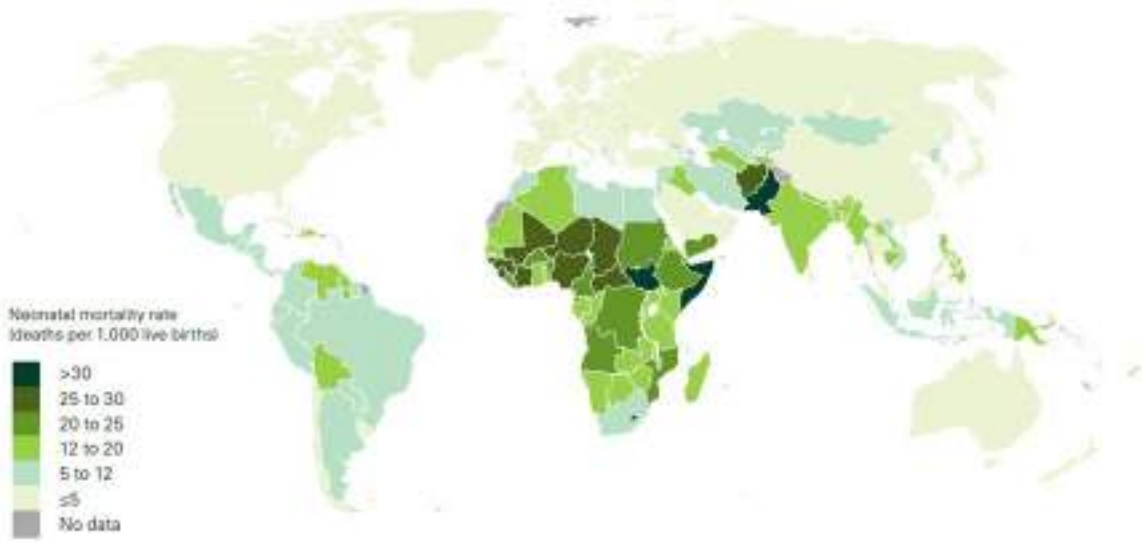




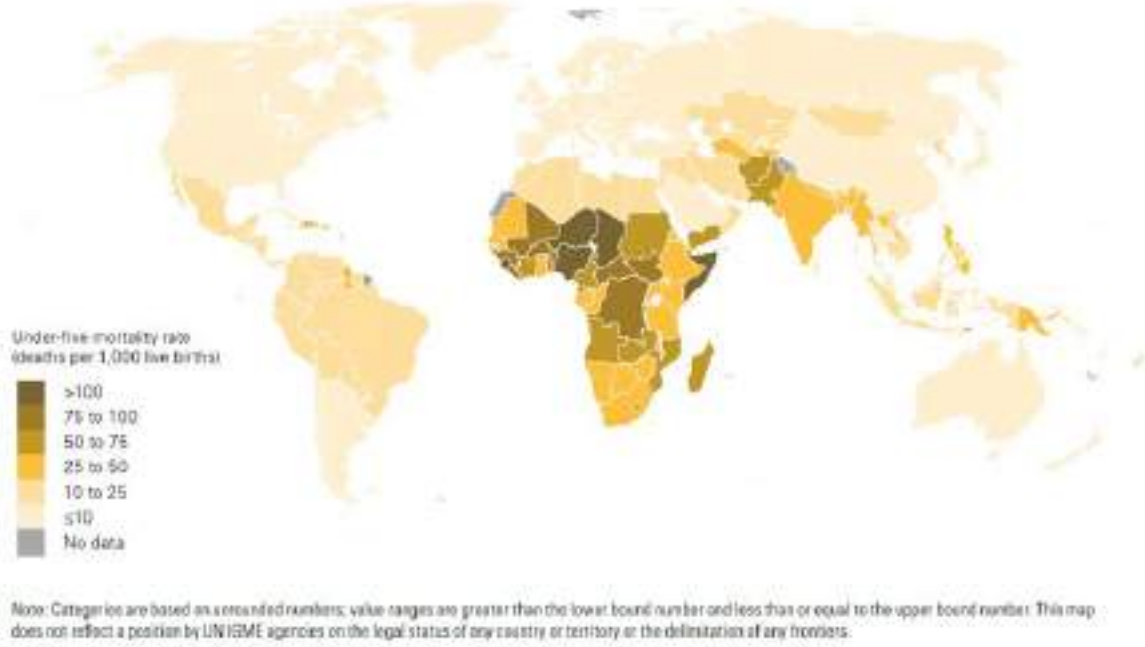
World Health Organization

International Clinical Trials Registry Platform (ICTRP), October 2023

…where 70% of the under 5 mortality is occurring



Neonatal mortality



Child mortality

World Health Organization

Source: UNIGME report https://childmortality.org/wp-content/uploads/2023/01/UN-IGME-Child-Mortality-Report-2022.pdf

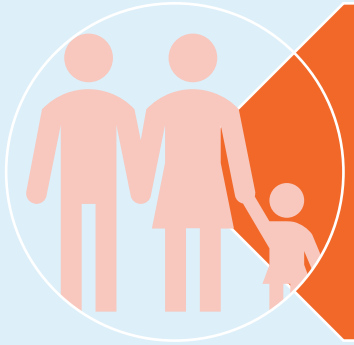
Only a fraction of global research priorities are being addressed across the child health domain

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

World Health Organization

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
- INFASTRUCTURE & LOGISTICS
- TRIAL METHODOLOGY
- NATIONAL LEADERSHIP AND STEWARDSHIP

Disproportionately affecting paediatric research

- ETHICS and REGULATORY
- FUNDING
- RESEARCH CAPACITY

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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

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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

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Progress is possible if … in addition to responding to cross-cutting challenges

Action	Rationale	Outcome
1. Coordinated process to facilitate alignment and action between key stakeholders: researchers, communities, national authorities, ethics and regulatory bodies and funders	Continued high mortality in low resource settings; continued major evidence gaps to improve interventions and their delivery; failure to conduct high quality research in low resource settings	An effective process that generates high-quality evidence over a defined time horizon for a limited set of research priorities that address survival, health and development in countries.

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2. Prioritization process and agreement on 5 major evidence gaps **with broad set of stakeholders** (community, national authorities, researchers and funders etc)	Ensure multi-stakeholders input into prioritization of research questions to match the need of communities affected	5 research priorities identified with potential for high impact on survival and improved health and development among infants and children living in low resource settings

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3. Establish research collaborations to tackle research questions including **capacity development mechanisms** with coordinated and high-quality approach	Skill and power inequalities within research communities (global north and south); priority research not implemented; research capacity for future	Dedicated research consortia that can ensure high quality evidence generated in a timely manner

World Health Organization

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World Health Organization

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5. Policies and activities enabling research environment including **ethical and regulatory aspects**	Existing or perceived barriers impede the timeliness and quality of priority research	Alignment of ethical and regulatory principles in support of rapid implementation of prioritized research

World Health Organization

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6. Build the environment for **knowledge translation including capacity for future research**	To anticipate and accelerate communication of study findings and their implication for policy and practice	Rapid dissemination of study findings and translation into policy change and practice at global and national level + capacity incrementally established for future research

We must all be active contributors….

Stakeholders	Roles/Responsibilities
1. Community	Contribute to prioritization, advocacy and study design and dissemination via community advisory boards
2. Researchers	Contribute to prioritization, establish collaborations to implement the key priorities and ensure rapid knowledge sharing
3. Funders	Explore matching funding opportunities to support prioritized research, catalize engagment of additional funders
4. National ministries	Contribute to prioritization, provide political support to implementation and knowledge sharing
5. IRBs and regulators	Gather to review principles and policies in support of rapid implementation of research questions prioritized
6. WHO	Convene stakeholders and facilitate prioritization, technical advocacy and knowledge translation
7. Private sector	Contribute to implementation of priority research via financial and technical support

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..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

World Health Organization

Thank you

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, Fiona Russell, Shane Norris, Judd Walson Jim and Zhang

World Health Organization

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

Enabling high quality trials in pregnant and lactating women

Arri Coomarasamy
Shivaprasad Goudar
Mercedes Bonet
Mariana Widmer

World Health Organization

Outline

- Context & problem statement
- Barriers
- Suggested priorities
- Looking forward to 2030

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Pregnancy and lactation

Pregnancies: ~250.4 million per year*

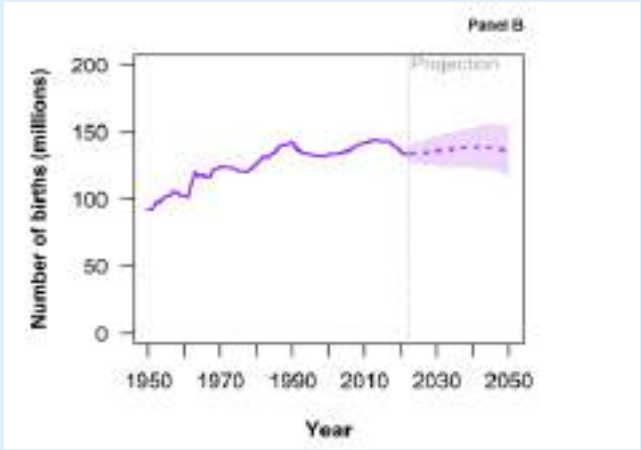
- Births 134 million**
- Miscarriages 23 million
- Abortion 73 million

Lactating women: ~ 60 million women

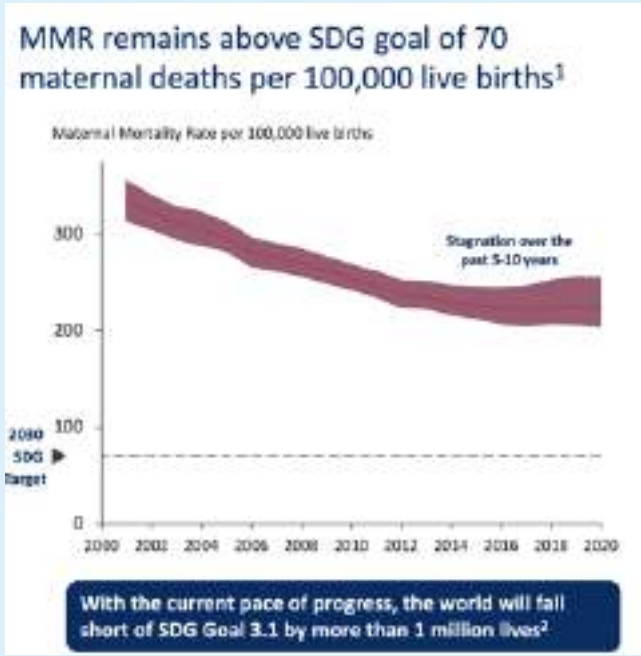
Maternal deaths: 287,000 per year***

- Haemorrhage: 74,000 per year
- Preeclampsia: 40,000 per year
- Sepsis: 32,000 per year

A maternal death every 2 minutes



**Source: United Nations Department of Economic and Social Affairs, Population Division (2022). World Population Prospects 2022: Summary of Results. UN DESA/POP/2022/TR/NO. 3



MMR: Maternal mortality ratio.
***Source: Trends in maternal mortality 2000 to 2020: estimates by WHO, UNICEF, UNFPA, World Bank Group and UNDESA/Population Division. 2023

*Bearak J, et al. Unintended pregnancy and abortion by income, region, and the legal status of abortion: estimates from a comprehensive model for 1990-2019. Lancet Glob Health. 2020. doi: 10.1016/S2214-109X(20)30315-6.

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)

Disease	RCTs available in MEDLINE
Diabetes	39,332
Asthma	11,257
COVID-19	4,914
PPH	788
Preeclampsia	1090

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.

Accelerating Innovation for Mothers. Concept Foundation, 2023

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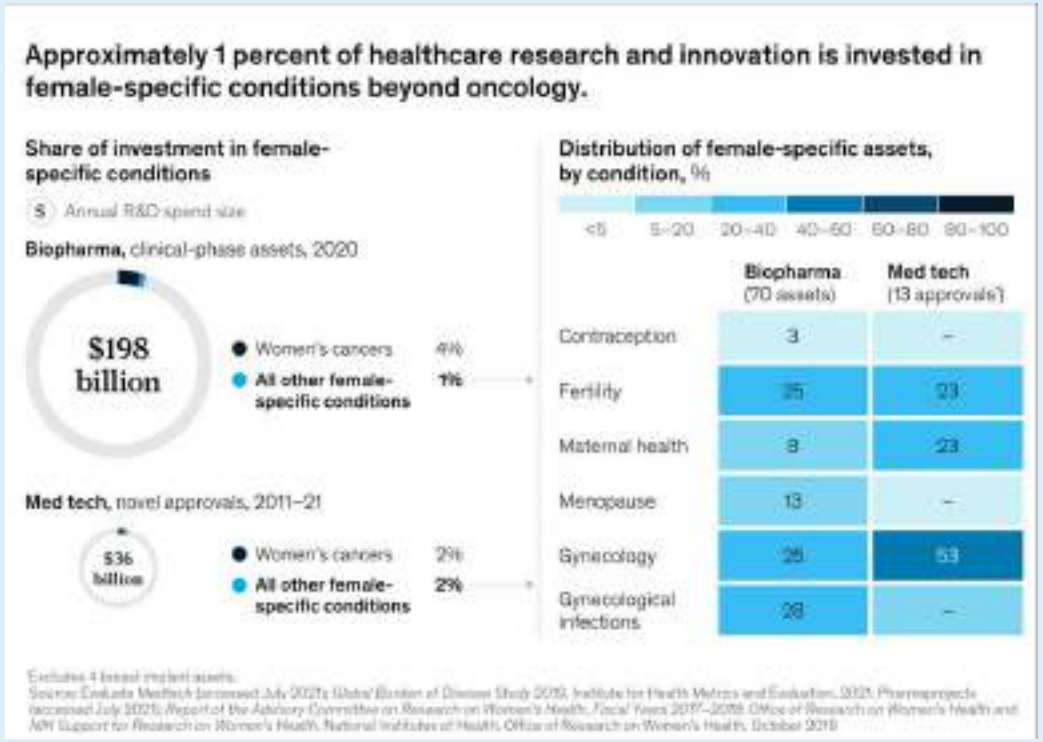
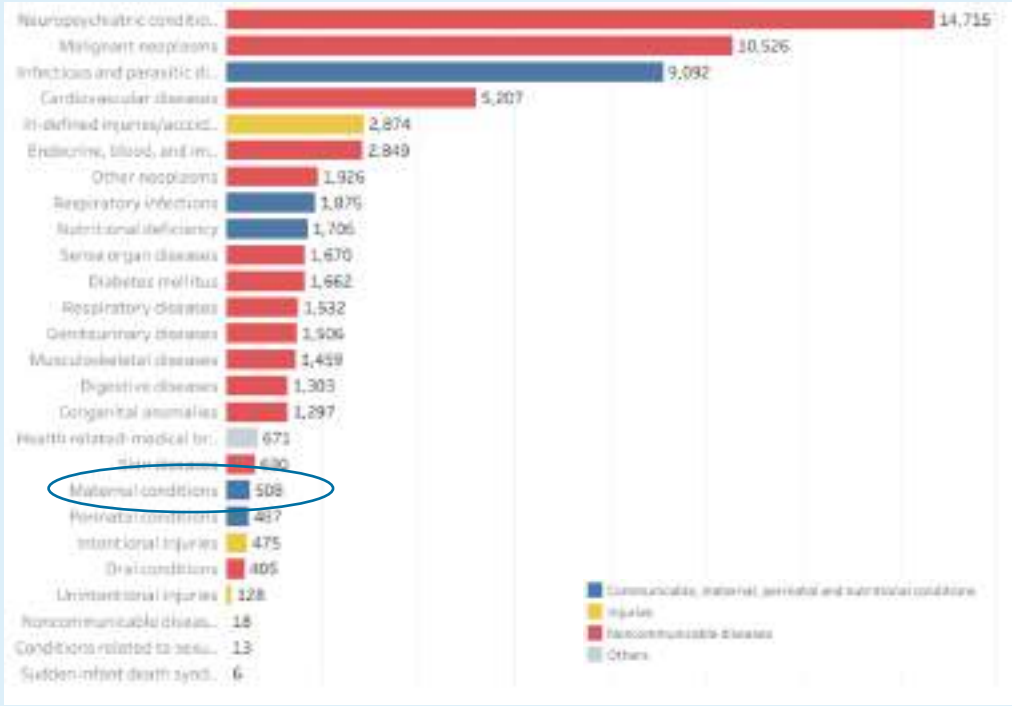
Why aren’t matters improving? (2/2)

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)]

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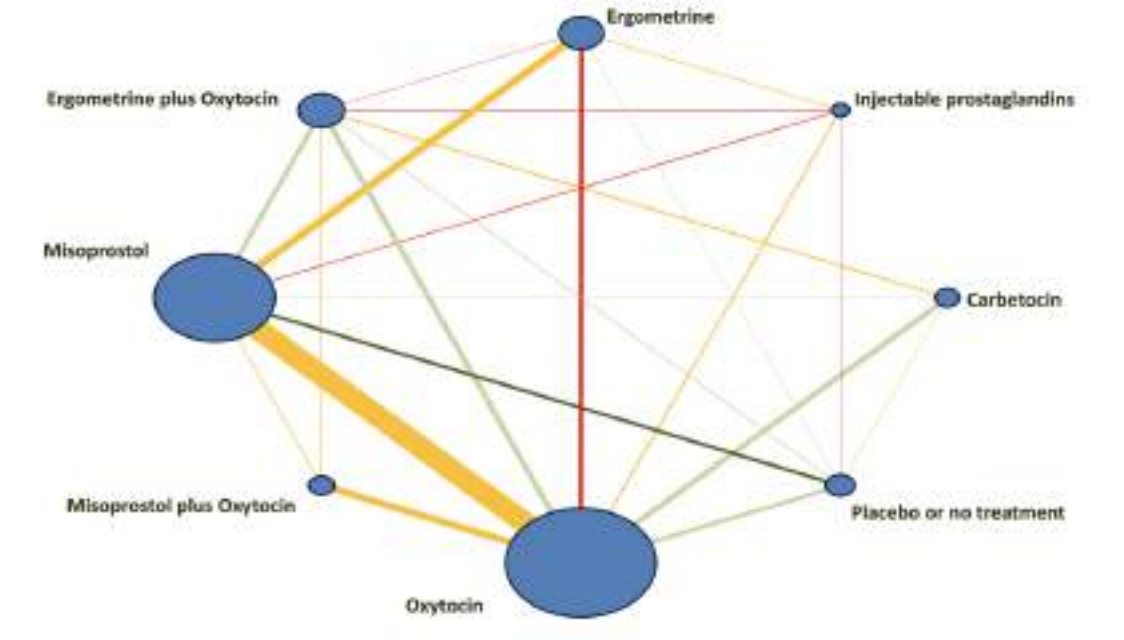
An example: RCTs available for uterotonic treatment of postpartum hemorrhage, topmost killer of women postpartum

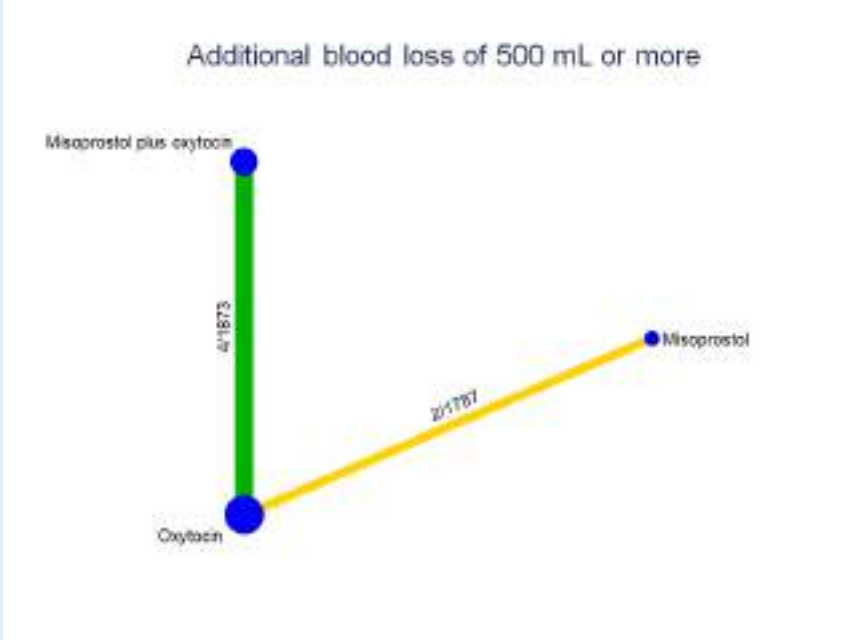
What we wanted!

Large number of good quality RCTs



What we found!

7 studies involving 3738 women



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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

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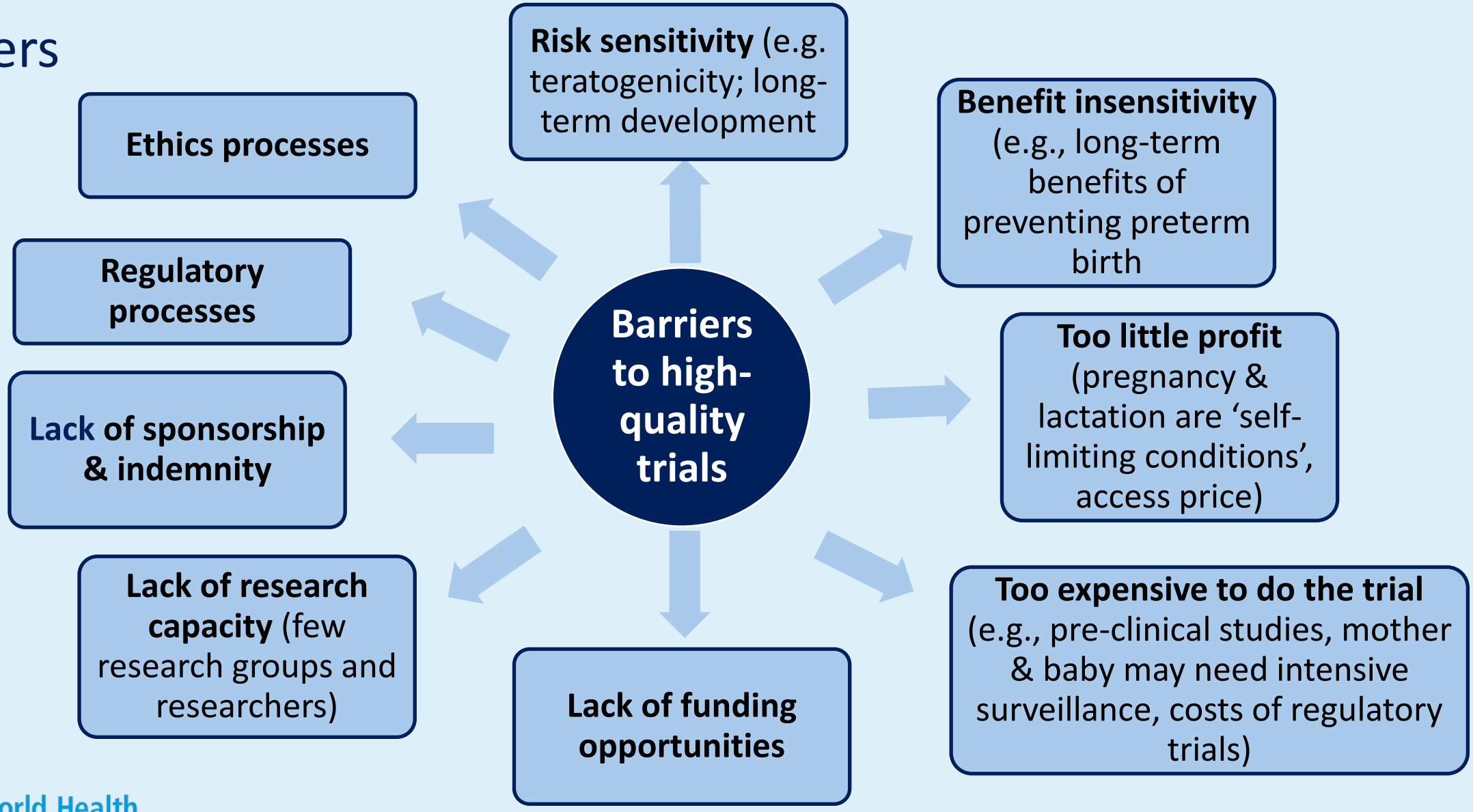
Barriers



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Some unique issues

Barrier related to	Description
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

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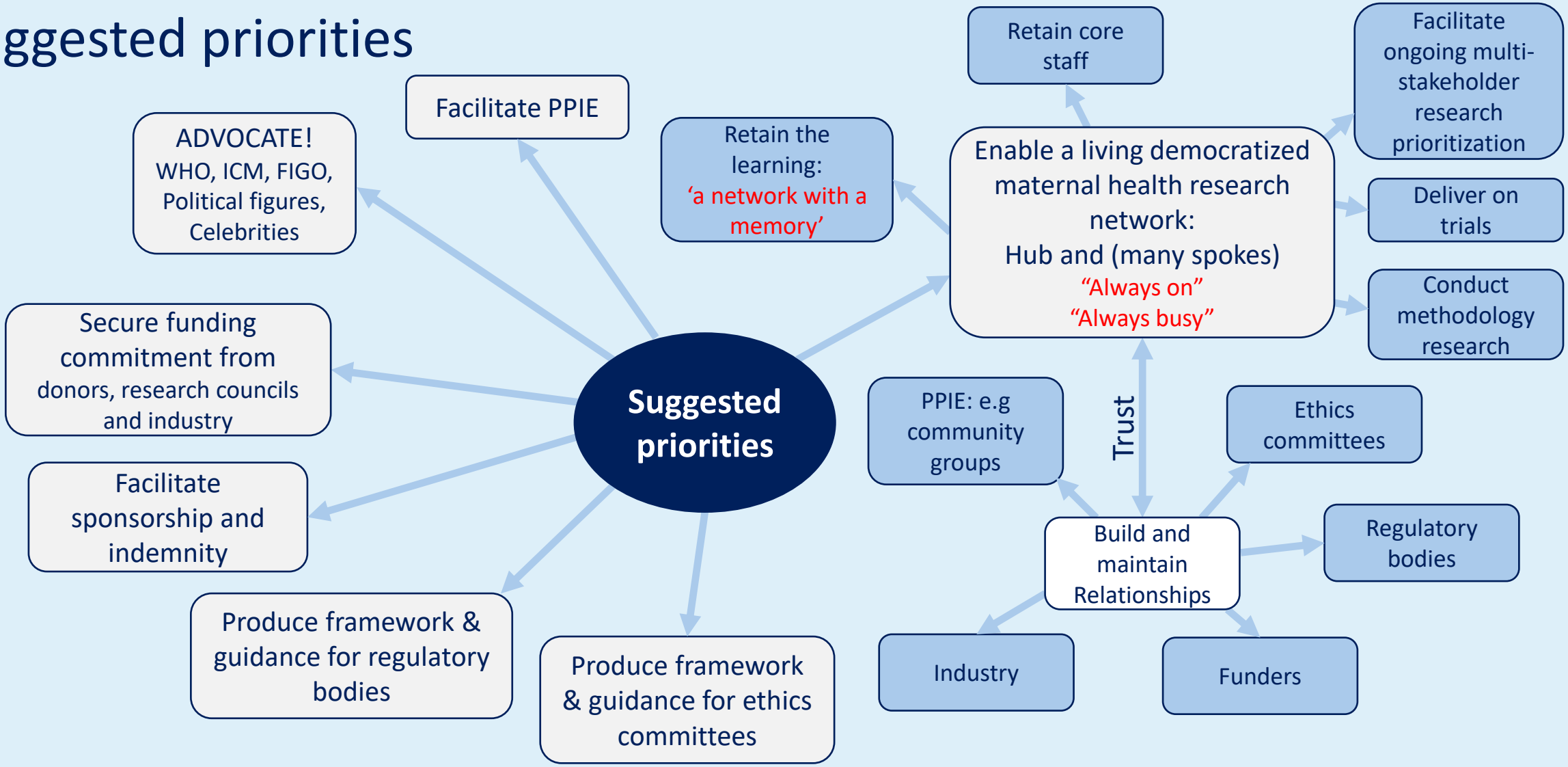
Suggested priorities



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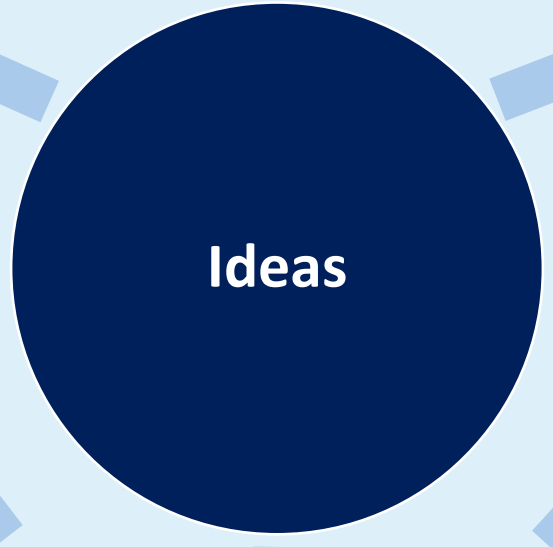
Looking forward to 2030!

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

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 **stimulated market**

Funding at least doubled between 2025 and 2030

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

A **Roadmap** to guide us, with monitoring framework to track our progress

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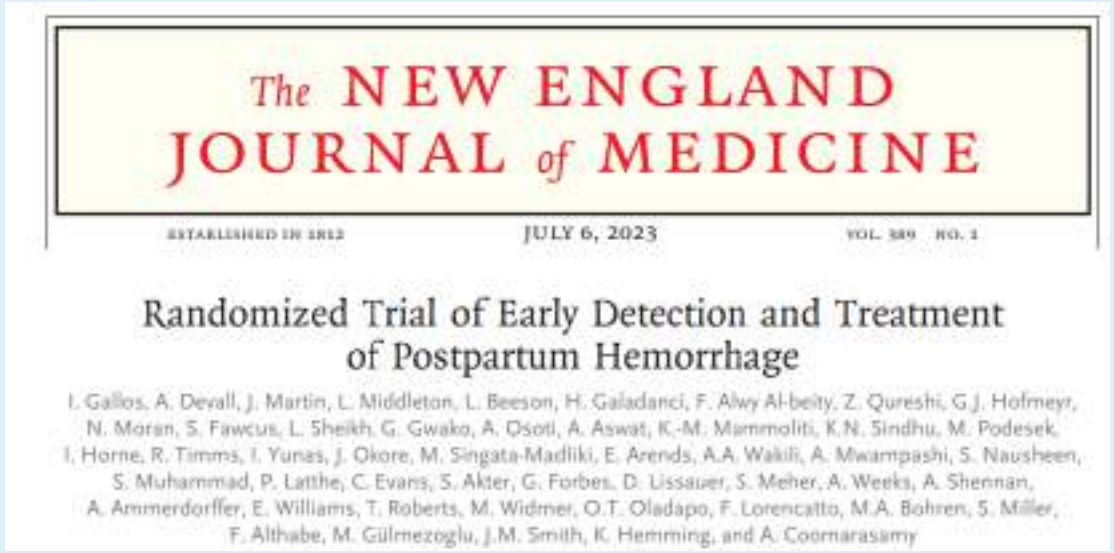
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

June 27, 2018

Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth

M. Widmer, G. Piaggio, T.M.H. Nguyen, A. Osoti, O.O. Owa, S. Misra, A. Coomarasamy, H. Abdel-Aleem, A.A. Mallapur, Z. Qureshi, P. Lumbiganon, A.B. Patel, G. Carroli, B. Fawole, S.S. Goudar, Y.V. Pujar, J. Neilson, G.J. Hofmeyr, L.L. Su, J. Ferreira de Carvalho, U. Pandey, K. Mugerwa, S.S. Shiragur, J. Byamugisha, D. Giordano, and A.M. Gülmezoglu, for the WHO CHAMPION Trial Group*



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 6, 2023 VOL. 389 NO. 1

Randomized Trial of Early Detection and Treatment of Postpartum Hemorrhage

I. Gallos, A. Devall, J. Martin, L. Middleton, L. Beeson, H. Galadanci, F. Alwy Al-beity, Z. Qureshi, G.J. Hofmeyr, N. Moran, S. Fawcus, L. Sheikh, G. Gwako, A. Osoti, A. Aswat, K.-M. Mammoliti, K.N. Sindhu, M. Podesek, I. Horne, R. Timms, I. Yunas, J. Okore, M. Singata-Madliki, E. Arends, A.A. Wakili, A. Mwampashi, S. Nausheen, S. Muhammad, P. Latthe, C. Evans, S. Akter, G. Forbes, D. Lissauer, S. Meher, A. Weeks, A. Shennan, A. Ammerdorffer, E. Williams, T. Roberts, M. Widmer, O.T. Oladapo, F. Lorencatto, M.A. Bohren, S. Miller, F. Althabe, M. Gülmezoglu, J.M. Smith, K. Hemming, and A. Coomarasamy

World Health Organization

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).

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

*Clinical Trials in **CRITICAL CARE**: The Role of Networks*

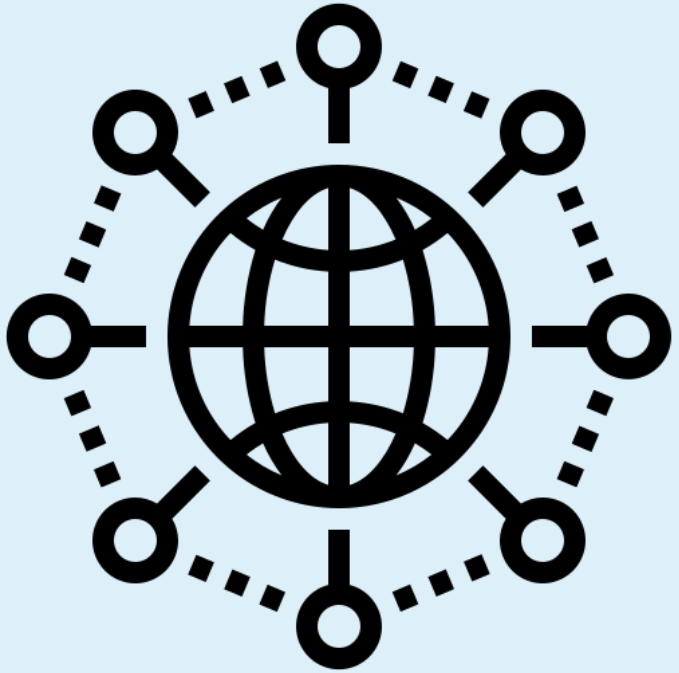
Fernando Bozza, MD, Ph.D

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

World Health Organization

Agenda

- Collaborative Networks in Critical Care
- Critical Care and Pandemic Response
- Equitable Governance→ The Path Forward



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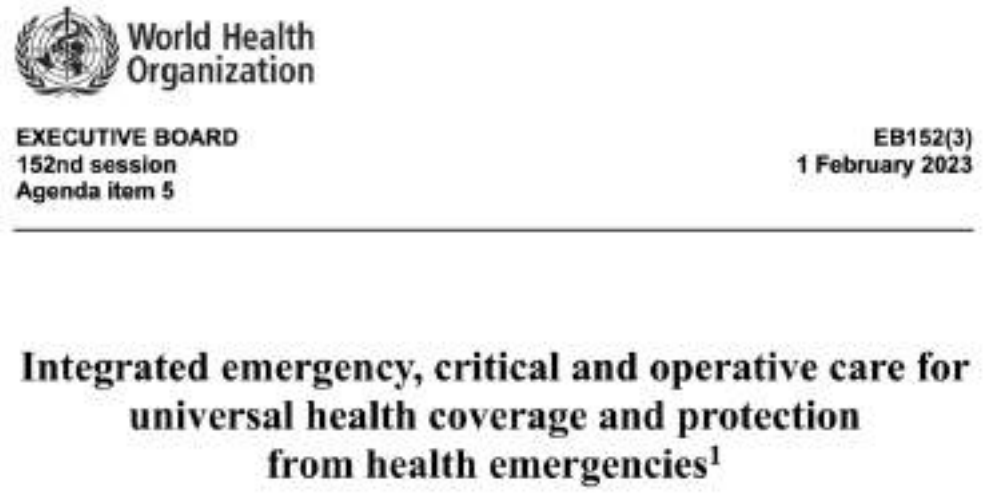
BRICNet
Brazilian Research in Intensive Care Network

ISARIC

FIOCRUZ
Fundação Oswaldo Cruz

Critical care is a foundation of emergency response



World Health Organization

EXECUTIVE BOARD
152nd session
Agenda item 5

EB152(3)
1 February 2023

Integrated emergency, critical and operative care for universal health coverage and protection from health emergencies[1]

"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;

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Clinical research networks are key drivers of quality and capacity

World Health Organization

EXECUTIVE BOARD
152nd session
Agenda item 5

EB152(3)
1 February 2023

Integrated emergency, critical and operative care for universal health coverage and protection from health emergencies[1]

"CALLS ON Member States..."

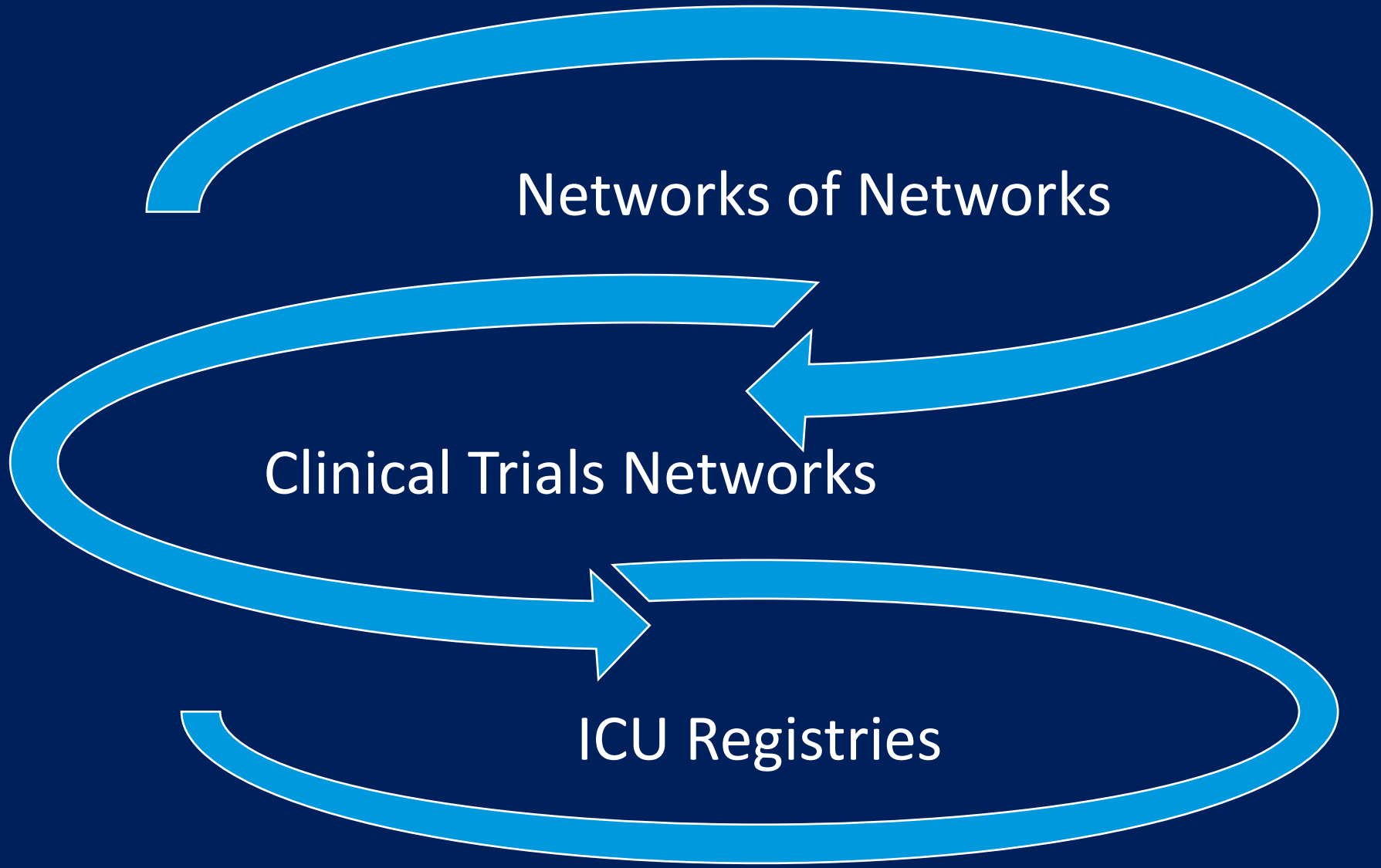
(2) to increase clinical trial capability, and strengthen clinical trials policy frameworks, particularly in developing countries, to enable a greater number of clinical trial sites that can conduct well-designed and well-implemented clinical trials, and to ensure readiness for coordination of trials through existing, new or expanded clinical trial networks that meet relevant regulations and internationally harmonized standards, promoting sharing of information and best practices on efficient and ethical clinical trial design and delivery, and in designing, preparing and conducting clinical trials;

"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;

World Health Organization

The ecosystem of critical care research



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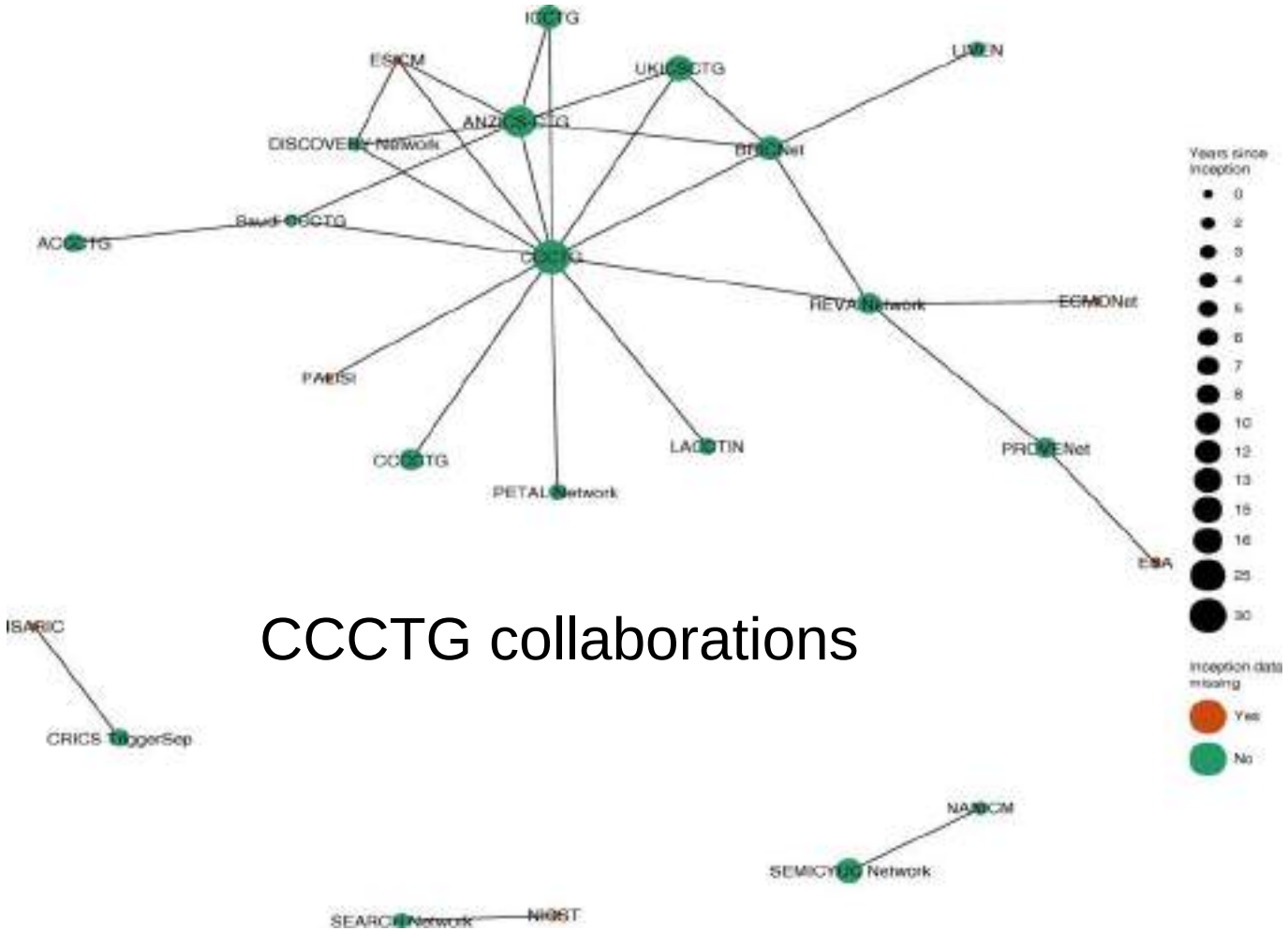
ICU registries provide benchmarking and data infrastructure

14 registries

22 countries

Global research collaborators

Critical care networks build capacity and improve care



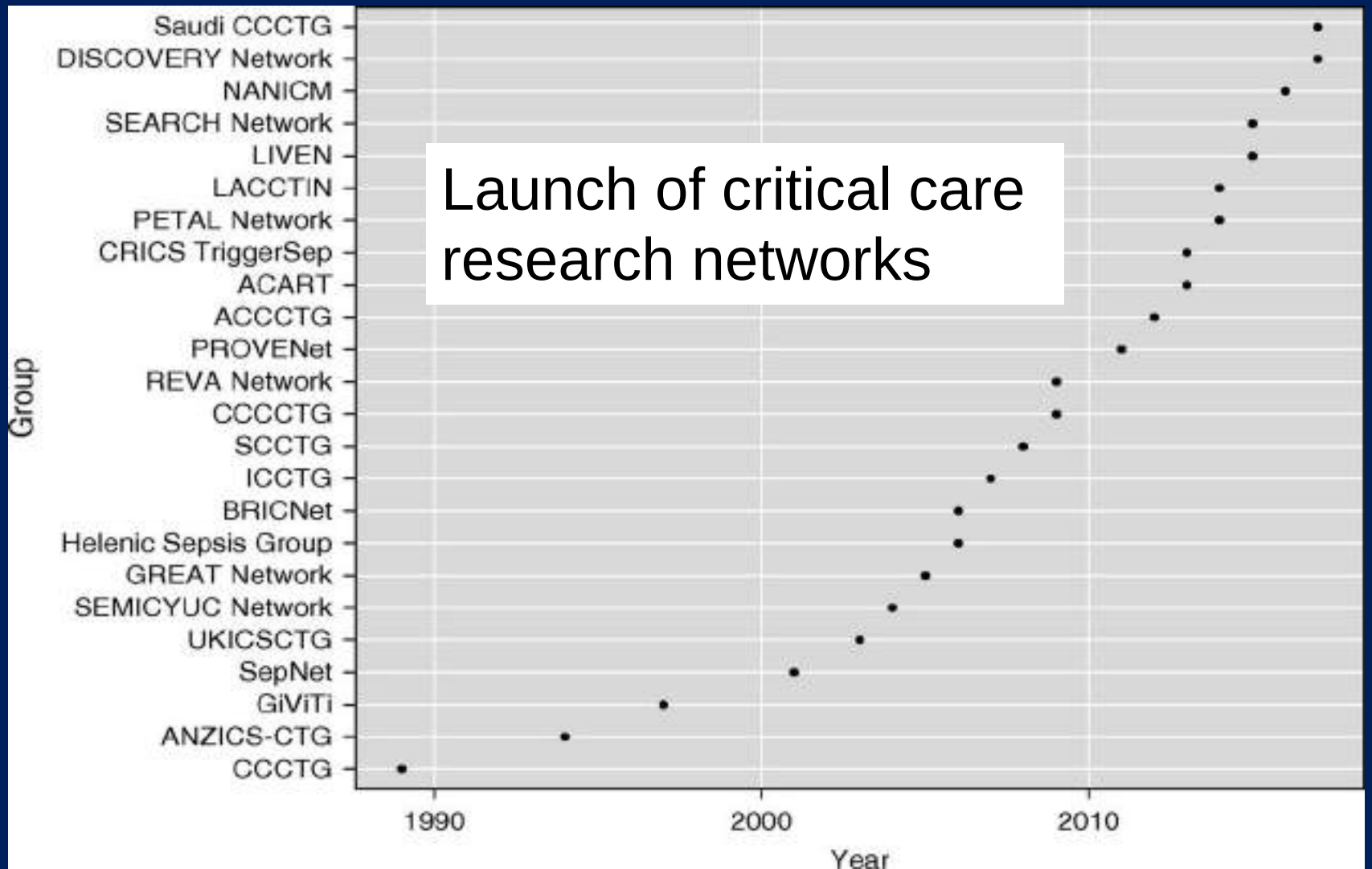
CCCTG collaborations

Burns et al. 10.1164/rccm.202001-0098LE

Growing global trend of investigator-led critical care trials groups

- ANZICS CTG
- ARDSNet
- BRICNet
- CCCTG
- CRISMA
- ESICM CTG
- George Institute
- GiViTI
- Hellenic Sepsis Group
- ICNARC
- ICCTG
- ICS CTG
- LASI
- Scandinavian CTG
- Scottish CTG
- SepNet
- SOAP investigators
- USCIITG

Growing global trend of investigator-led critical care trials groups



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Burns et al. 10.1164/rccm.202001-0098LE

Networks of networks drive rapid collective response

MEMBER ASSEMBLY 2020

CLINICAL RESEARCH NETWORKS
ADDRESSING COVID-19 & FUTURE CHALLENGES'

25-27 FEBRUARY 2020

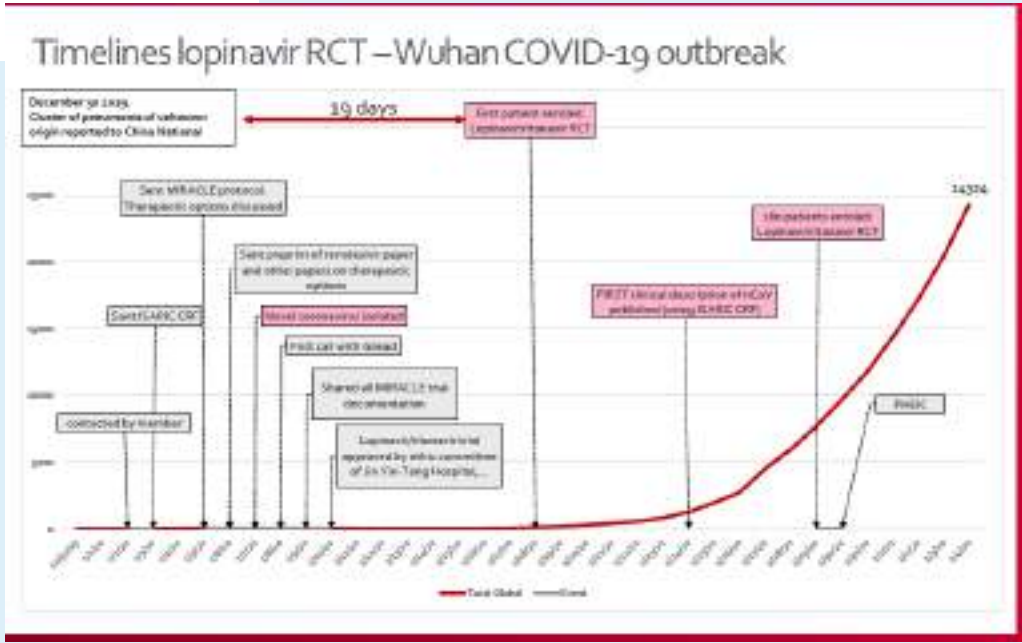
Research priority #1: Characterisation of a novel disease

World Health Organization

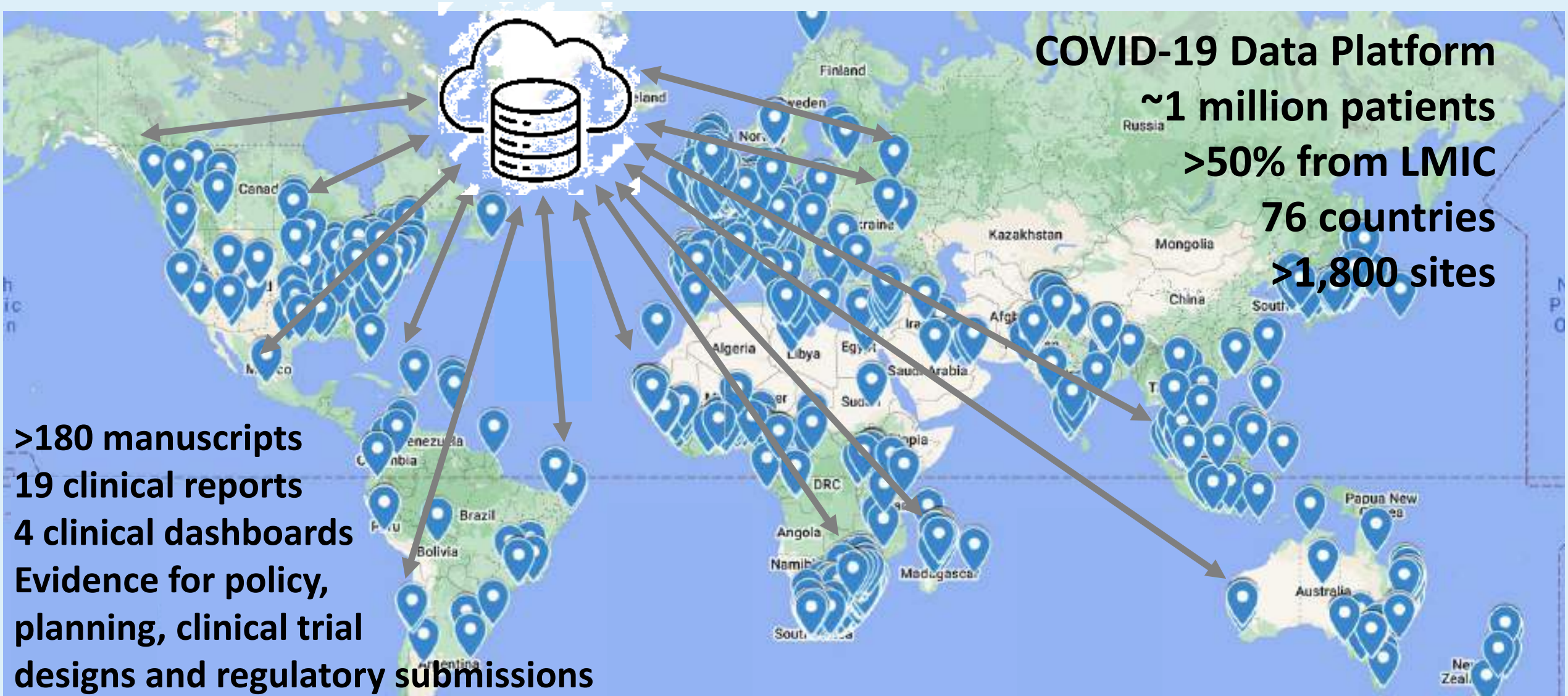
NOVEL CORONAVIRUS (nCoV)

ACUTE RESPIRATORY INFECTION CLINICAL CHARACTERISATION DATA TOOL

MODULE 1: PRESENTATION/ADMISSION CASE REPORT FORM



Networks of networks drive massive collective response



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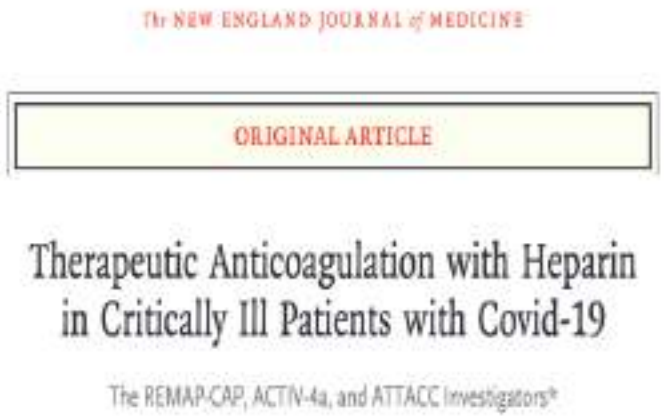
Network hubs to support international registry enabled clinical trials

REMAP-CAP

MEGA ROX 2

GenOMICC

RECOVERY
Randomised Evaluation of COVID-19 Therapy


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

ABSTRACT

BACKGROUND


Original Investigation | Caring for the Critically Ill Patient

FREE

September 2, 2020

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

The Writing Committee for the REMAP-CAP Investigators

Article Information

JAMA. 2020;324(13):1317-1329. doi:10.1001/jama.2020.17022

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

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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

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ALBERT EINSTEIN SOCIEDADE BENEFICENTE ISRAELITA BRASILEIRA

HCor

SÍRIO-LIBANÊS

HOSPITAL FERNANDES DE VENTO

OSWALDO CRUZ

bp

BCRI

BRICNet

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 joined in Toronto **from** **40** countries **over** 3 DAYS

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Beyond COVID-19: Building an Acute Illness Research Platform to Enhance Global Healthcare

Start	Themes	Issues	Improvements	Needs	Finish
Beginning of COVID-19 Pandemic	**Clinical science is a global good**	• Lack of global data • Lack of global research infrastructure	• Global trial registry • Research networks • Comprehensive data • Alignment • Collaboration • Governance	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. To offer research participation to all critically ill patients worldwide through embedding research into usual care.
	Clinical science must be rigourous, reliable, and accessible	• Clinical demands on research staff • Competition amongst trials • Research slow to start • Research not embedded in clinical practice • Few patients were studied • Inequitable research provision globally	• Learning healthcare system • Clinically embedded platform trials • Clinically embedded observational studies • Interoperable data systems and capture		

	Endogenous and external factors modify the individual response to treatment	• Causes of heterogeneity:
		  • Prognostic and predictive heterogeneity
		  • Equity and inclusiveness
		  • Different care settings
		• Consequences of heterogeneity:
		  • Different treatment effects
		  • Inefficient resource allocation
			• Biosamples and phenotyping
			• Better biological targets
			• Common Research Framework
			• PIRO (Predisposition, Infection, Response and Organ Dysfunction) Model for staging system for critical illness		

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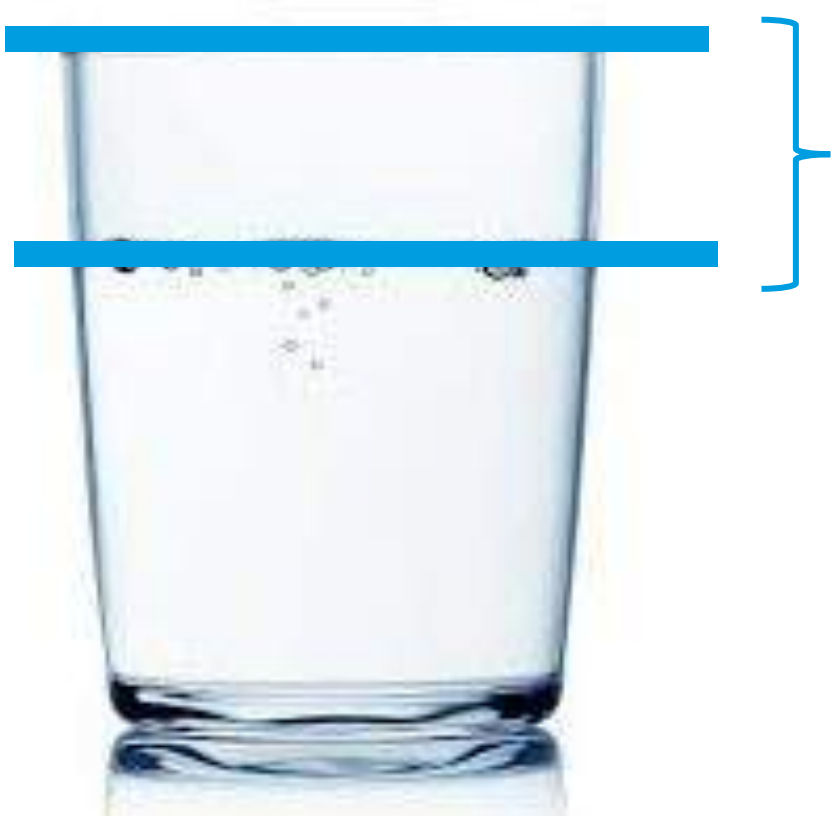
Cross cutting themes > **Patient involvement and engagement** | **Mentorship of early career researchers** | **Research leadership from the Global South**

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 heath system, value for money
- **Coordination:** Multiple funders, innovative models of collaborations

Equitable Governance: Involving LMICs in ICU Trials

Challenges

- How do you establish new models of international collaboration – local leadership X global participation?
- How do we professionalize the sites to give sustainability?
- Simplify contracts and Intellectual property?

Principles

- Access
- Diversity
- Voice
- Inclusion
- Benefit of research
- Shared knowledge and decisions

Required resources

- Professional project management teams
- ICU research networks
- Funding

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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

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THANK YOU

"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)

World Health Organization

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


RONALDO
DAVID VILLA
7

CE – WHY DO IT?

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)*

WHA 75.8 CLINICAL TRIAL RESOLUTION

World Health Organization

SEVENTY-FIFTH WORLD HEALTH ASSEMBLY
Agenda item 16.2

WHA75.8
27 May 2022

Strengthening clinical trials[1] to provide high-quality evidence on health interventions and to improve research quality and coordination

The Seventy-fifth World Health Assembly,

Recalling resolutions WHA58.34 (2005) acknowledging that high-quality, ethical research and the generation and application of knowledge are critical in achieving internationally agreed health-related development goals, WHA65.21 (2010) outlining WHO's role and responsibilities in health research, WHA66.22 (2013) and WHA69.23 (2016) on the follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, WHA67.20 (2014) on regulatory system strengthening for medical products, WHA67.21 (2014) on health intervention and technology assessment in support of universal health coverage, WHA74.6 (2021) on strengthening local production of medicines and other health technologies to improve access, and WHA74.7 (2021) on strengthening WHO preparedness for and response to health emergencies, which notes the importance of basic and clinical research and recognizes the critical role of international collaboration in research and development, including in multicountry clinical and vaccine trials, as well as rapid diagnostics test and assay development, while acknowledging the need for further rigorous scientific evidence;

Noting the recommendations made by the Independent Panel for Pandemic Preparedness and Response in their review "COVID-19: make it the last pandemic"[2] relating to health research and development, including clinical trials;

[1] "A clinical trial is defined by WHO as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc. This definition includes Phase I to Phase IV trials." Joint statement on public disclosure of results from clinical trials, 2017 (https://www.who.int/news/item/18-05-2017-joint-statement-on-registration, accessed 25 May 2022).

[2] Independent Panel for Pandemic Preparedness and Response. COVID-19: make it the last pandemic. 2021 (https://theindependentpanel.org/wp-content/uploads/2021/05/COVID-19-Make-it-the-Last-Pandemic_final.pdf, accessed 25 May 2022).

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**…"

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From Increased Recognition to Operationalization of CE to deliver on WHA 75.8 Resolution on Strengthening Clinical Trials

training manual

Good Participatory Practice
Guidelines for TB Drug Trials
2012

Critical Path to TB Drug Regimens

What is Good Participatory Practice for Emerging Pathogens?

Good Participatory Practice for Emerging Pathogens (GPP-EP): a principle-based approach to effectively engage stakeholders in the design and conduct of prevention and treatment trials for emerging and re-emerging pathogens.

Clinical trials for new or re-emerging pathogens

Good Participatory Practice (GPP) – a handbook for practitioners

Guidance Tool
for Community Advisory Boards

World Health Organization

R&DBlueprint

SCIENCE FOR AFRICA FOUNDATION

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.

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