# Guidance for best practices for clinical trials

World Health Organization

# Guidance for best practices for clinical trials

World Health Organization

Guidance for best practices for clinical trials

ISBN 978-92-4-009771-1 (electronic version)
ISBN 978-92-4-009772-8 (print version)



**Suggested citation**. Guidance for best practices for clinical trials. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

**Cataloguing-in-Publication (CIP) data.** CIP data are available at https://iris.who.int/.

# Contents


Foreword . . . iv

Acknowledgements . . . vi

Abbreviations . . . viii

Executive summary . . . x

1. Introduction . . . 1
   1.1 Clinical research: importance and types . . . 2
   1.2 Ascertainment of treatment effects: observational studies vs clinical trials . . . 3
   1.3 The clinical trials environment: an evolving landscape . . . 4
   1.4 Persistent challenges to clinical trial enablement . . . 5
   1.5 Steps required to improve evidence generation . . . 8

2. Key scientific and ethical considerations for clinical trials . . . 11
   2.1 Good clinical trials are designed to produce scientifically sound answers to relevant questions . . . 12
   2.2 Good clinical trials respect the rights and well-being of participants . . . 20
   2.3 Good clinical trials are collaborative and transparent . . . 23
   2.4 Good clinical trials are designed to be feasible for their context . . . 24
   2.5 Good clinical trials manage quality effectively and efficiently . . . 25

3. Guidance on strengthening the clinical trial ecosystem . . . 27
   3.1 Clinical trial ecosystem pillars . . . 28
   3.2 Clinical trial ecosystem cross-cutting themes . . . 37

4. Conclusion . . . 41

Annexes . . . 43
   Annex 1. Provisions for rapid funding and approval of good randomized evidence generation in emergencies . . . 44
   Annex 2. Recommendations for Member States, research funders and researchers . . . 46

References . . . 54

# Foreword

A core role of World Health Organization (WHO) is to support strengthening of national capabilities in the health sector. WHO considers that strengthening of country-led research and development (R&D) ecosystems to advance health science and facilitate faster and more equitable access to safe and effective health interventions is of the utmost importance to a country's population health and economic well-being. Clinical trials are an essential component of a strong country-driven R&D ecosystem.

Unnecessary bureaucracy, uncoordinated approval processes and the lack of an enabling environment are currently barriers in some countries and as a result slow down and prevent equitable access for people to health innovation that can save and transform lives. In 2022 the World Health Assembly adopted resolution (WHA 75.8) "Strengthening clinical trials to improve high quality evidence on health interventions and to improve research quality and coordination", which called on WHO to develop this guidance. Throughout the guidance a major focus is to address public health priorities through clinical and public health research, and in particular to address the health needs of developing countries in an equitable manner. Importantly, enhancing clinical trial capacity is essential for all countries with many efficiency gains possible in high-income countries as well as middle- and low-income countries. Therefore, the reforms called for can have a major impact worldwide.

This guidance has a number of recommendations. Firstly, patient, participant and community engagement are placed centrally in the trial planning and implementation phases to ensure the research meets public needs and maintains trust. Secondly, major new recommendations are included on reforms that enable trials in underrepresented populations such as children, pregnant women and older adults. Thirdly, the guidance lays out how to focus trial design and oversight on the key scientific and ethical considerations that determine whether trials are ethical, efficient and informative. Here risk based and proportionate approaches are advocated so that we move away from one size fits all oversight or audit, to those that are tailored to risk.

For the first time in WHO guidance, recommendations are provided that can practically assist national health authorities, regulatory authorities, funders and others in how best they can facilitate clinical trials and research to enable evidence generation on health interventions. Sustained domestic support and resources are the only way to finance this transformation. Longstanding recommendations, also referred to in previous World Health Assembly resolutions, on a minimum spending of 2% of health budgets on Science and R&D, and 5% of health-related development assistance on research have not been met by many countries, and in other countries resources are needed for reform rather than supporting uncoordinated processes.

Countries that choose to prioritize and resource a reformed clinical research ecosystem, enabling the work of their clinical researchers with input from the public, private sector and local communities, will gain major benefits including:

- Improved trust between the public and the health research community
- Better locally derived evidence for clinical practitioners and public health decisions
- Improved health outcomes, faster and more equitable access to innovation and medical products that are better tailored to individual patient needs, and hence progress towards health-related sustainable development goals (SDGs)

- National resilience and security including a more robust clinical trial ecosystem ensuring faster response to health crisis
- Healthier populations and more productive economies
- Economic benefits from a thriving science and innovation ecosystem that provides opportunities for jobs, spin outs into new small and medium sized companies along with private sector investment

In coordination and collaboration with its partners, WHO is committed to provide support to countries that wish to apply this guidance to reform, improve and streamline their oversight and approval processes and hence strengthen their clinical research system.

**Jeremy Farrar**
Chief Scientist
World Health Organization

# Acknowledgements

The WHO Secretariat thanks all Member States for their guidance and direction and gratefully acknowledges the valuable inputs of many individuals and partners throughout the development of this document. The Secretariat conducted stakeholder consultations on the most relevant existing guidance documents for best practices regarding clinical trials. Permission from Council of International Organizations of Medical Sciences (CIOMS) *(1)* and the Good Clinical Trials Collaborative (GCTC) *(2)* for incorporation or adaptation of their guidance is gratefully acknowledged.

The development of the guidance in the WHO secretariat was overseen by Jeremy Farrar, Chief Scientist, and John Reeder, Director of the Department of Research for Health, Science Division. Vasee Moorthy, Senior Advisor in the Department of Research for Health, led the overall development process with invaluable support from Wei Zhang, Technical Officer, Department of Research for Health.

The Technical Advisory Group (TAG) for Development of Best Practices for Clinical Trials was constituted through a public call for nominations. The TAG members are Akbar Fotouhi (Tehran University of Medical Sciences, Iran (Islamic Republic of)), Evelyn Gitau (African Population and Health Research Center, Ethiopia), Herman Goossens (University of Antwerp, Belgium), Marian Knight (University of Oxford, United Kingdom of Great Britain and Northern Ireland), Roli Mathur (Indian Council of Medical Research, India), Ann Meeker-O'Connell (Independent expert, United States of America), Sharon Nachman (Stony Brook Children's Hospital, United States of America), John Norrie (University of Edinburgh, United Kingdom of Great Britain and Northern Ireland), Thomas Nyirenda (European and Developing Countries Clinical Trials Partnership, South Africa), CS Pramesh (Tata Memorial Centre, India), Fiona Russell (University of Melbourne, Australia), Sofia P. Salas (Universidad del Desarrollo, Chile), Karla Soares-Weiser (Cochrane, United Kingdom of Great Britain and Northern Ireland), Fergus Sweeney (Independent expert, Ireland), Huixia Yang (Peking University First Hospital, China), and Nonhlanhla Yende-Zuma (Centre for the AIDS Programme of Research, South Africa). They provided essential technical advice throughout. Advice was also received from An-Wen Chan, Chair of the International Clinical Trials Registry Platform (ICTRP) advisory group.

WHO acknowledges the significant contribution of Christina Reith, Associate Professor at the Nuffield Department of Population Health, University of Oxford, United Kingdom, for her extensive senior technical writing support during the drafting and consolidation stages, which played a pivotal role in the guidance development. WHO also recognizes the valuable technical input and critical review provided by colleagues from regional offices and headquarters, including WHO Regional Office for Africa: Joseph Chukwudi Okeibunor; WHO Regional Office for Americas: Luis Gabriel Cuervo Amore, Ludovic Reveiz, Carla Saenz; WHO Regional Office for the Eastern Mediterranean: Arshad Altaf and Arash Rashidian; WHO Regional Office for Europe: Marge Reinap; WHO Regional Office for South-East Asia: Manju Rani; WHO Regional Office for Western Pacific: Mengji Chen and Kidong Park; WHO Health Emergencies Programme: Janet Diaz, Nina Gobat, Ana Maria Henao Restrepo, Jamie Rylance and Steven Mcgloughlin; Digital Health and Innovation: Alain Labrique; Gender, Rights and Equity - Diversity, Equity and Inclusion: Shirin Heidari; Global HIV, Hepatitis and STIs Programmes: Nathan Ford; Global Malaria Programme: Lindsey Wu; Global TB Programme: Francesca Conradie, Fuad Mirzayey, Samuel Schumacher and Matteo Zignol; Health Emergency Intelligence and Surveillance Systems: Chikwe Ihekweazu; Immunization, Vaccines and Biologicals: Joachim Maria Hombach; Maternal, Newborn, Child and Adolescent Health and Ageing: Nigel Rollins; Mental Health and Substance Use: Rodrigo Cataldi; Quality Assurance of Norms and Standards: Lisa Askie; Regulation and Prequalification: Samvel Azatyan, Marion Laumonier, Hiiti Sillo and Marie Valentin; Research for Health: Tanja Kuchenmueller, Katherine Littler, Ghassan Karam, Martina Penazzato,

Andreas Reis and Anna Laura Ross; Sexual and Reproductive Health and Research: Avni Amin, Mercedes Bonet Semenas and Mariana Widmer; Special Programme for Research & Training in Tropical Diseases: Garry Aslanyan, Anna Thorson and Mahnaz Vahedi.

WHO express gratitude to the GCTC and the CIOMS for close collaboration during the writing of this document, as well as to the WHO Collaborating Centre for research information sharing, e-learning, and capacity development, based in the Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, University of Oxford, United Kingdom of Great Britain and Northern Ireland, for their technical support in conducting the online global stakeholder survey on barriers and priority actions for strengthening clinical trials ecosystems as part of the guidance development. Thanks are also extended to the many hundreds of participants who contributed their valuable expertise and insights through the online public consultation and in-person regional and global consultations throughout 2023 and early 2024. Although it is not possible to name all here, without their support and expertise this guidance would not have been possible. Inputs were received from leading research funders, national health authorities, national ethics authorities, national regulatory authorities and civil society and nongovernmental organizations.

The development of this guidance was made possible through funding from the EDCTP2 programme, supported by the EU (European Union (grant number CSA2023WHO-3454-WHORCT)), with funding from the National Institute for Health and Care Research (NIHR) in the United Kingdom (where NIHR is funded by the Department of Health and Social Care). The NIHR Global Health Research portfolio supports high-quality applied health research for the direct and primary benefit of people in low- and middle-income countries, using international development funding aid from the Government of the United Kingdom, to support global health research. The views expressed in this publication are not necessarily those of EDCTP, NIHR or the Department of Health and Social Care in the United Kingdom.

# Abbreviations

| | |
|---|---|
| **AI** | Artificial Intelligence |
| **AIDS** | Acquired Immune Deficiency Syndrome |
| **AVAREF** | African Vaccine Regulatory Forum |
| **CDC** | Centers for Disease Control and Prevention |
| **CDISC** | Clinical Data Interchange Standards Consortium |
| **CIOMS** | Council for International Organizations of Medical Sciences |
| **COMET** | Core Outcome Measures in Effectiveness Trials |
| **CONSORT** | Consolidated Standards of Reporting Trials |
| **COVID** | coronavirus disease |
| **CTTI** | Clinical Trials Transformation Initiative |
| **CTU** | clinical trial unit |
| **DMC** | data management committee |
| **EC** | ethics committee |
| **EDCTP** | European & Developing Countries Clinical Trials Partnership |
| **EEA** | European Economic Area |
| **EMA** | European Medicines Agency |
| **ESSENCE** | Enhancing Support for Strengthening the Effectiveness of National Capacity Efforts |
| **FDA** | Food and Drug Administration |
| **GCTC** | Good Clinical Trials Collaborative |
| **GLOPID** | Global Research Collaboration for Infectious Disease Preparedness |
| **HIC** | high-income countries |
| **HIV** | human immunodeficiency virus |
| **ICH** | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| **ICHOM** | International Consortium for Health Outcomes Measurement |
| **ICTRP** | International Clinical Trial Registration Platform |
| **IRAS** | Integrated Research Application System |

| | |
|---|---|
| **IRB** | Institutional Review Board |
| **JPIAMR** | Joint Programming Initiative on Antimicrobial Resistance |
| **LMIC** | low- and middle-income countries |
| **MHRA** | Medicines and Healthcare products Regulatory Agency |
| **NCA** | National Competent Authority |
| **NITAG** | National Immunization Technical Advisory Groups Network |
| **NRA** | National Regulatory Authority |
| **PAHO** | Pan American Health Organization |
| **PRISMA** | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| **PROMs** | Patient Reported Outcomes Measures |
| **RCT** | randomized clinical trial |
| **R&D** | research and development |
| **REC** | research ethics committee |
| **SAGER** | Sex and Gender Equity in Research |
| **SCTI** | Standardized Data Collection for Cardiovascular Trials Initiative |
| **SDTM** | Study Data Tabulation Model |
| **SPIRIT** | Standard Protocol Items: Recommendations for Interventional Trials |
| **TB** | tuberculosis |
| **TDR** | UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases |
| **UKCDR** | UK Collaborative on Development Research |
| **WHO** | World Health Organization |

# Executive summary

## Objective

This document responds to requests by the World Health Assembly to the Director-General in resolution WHA75.8 (2022) on strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination *(3)* to identify and propose best practices and other measures to strengthen the global clinical trial ecosystem and to review existing guidance and develop new guidance as needed on best practices for clinical trials. This guidance updates and adapts the previous work of the World Health Organization (WHO) on research capacity *(4)* for the context of well-designed and well-implemented clinical trials as framed in resolution WHA75.8 (2022). It aims to enhance clinical research efficiency, minimize research waste and provide guidance on sustained clinical trials that are always functional and active for endemic conditions and can pivot in time of emergency or pandemics.

Section 1 provides an introduction. For key scientific and ethical considerations for well-designed and well-implemented trials the reader should refer directly to Section 2. For guidance on strengthening the clinical trial ecosystem, including capacity development and addressing inefficiencies, refer to Section 3 and for recommendations to Member States, research funders and researchers refer to Annex 2.

## Scope

This document is intended to provide guidance to WHO's Member States and any staff members of non-State actor organizations whose work is related to clinical trials in any way, including the planning, conduct, analysis, oversight, interpretation and funding of all clinical trials to assess the effects of any health intervention for any purpose in any setting. Such staff members include those involved in educating others about clinical trials.

The remit includes:

- any design for a clinical trial: but with a focus on randomized clinical trials, including comparisons of two or more interventions, whether blinded or not, and whether parallel, cluster, crossover, factorial, adaptive platform, decentralized or other design;

- any health intervention: including (but not limited to) administration of pharmaceutical medicines, cells and other biological products, and vaccines; surgical or radiological procedures; diagnostics; use of medical devices, nutritional measures; cognitive, behavioural and psychological interventions; supportive or preventive care, including process-of-care changes; physical therapy interventions; digital and public health approaches; traditional or herbal measures; and screening processes. The interventions may be novel or pre-existing but being used in a different way (for example, repurposed or optimized) or to gain further knowledge about current practices;

- any purpose: including (but not limited to) evidence for guideline development; recommendations for clinical practice or public health strategies; and health technology assessments;

- any setting: any geographical, economic or societal context, and any context including clinical trials based in hospital, primary care or community settings; or where the intervention is delivered directly to a participant;

- any role: including researchers and clinicians, patient and public groups (including trial participants), regulators and other national health authorities, ethics committees and institutional review boards, research funders, and all trial sponsors (academic, government, nonprofit and commercial).

There will often be important local, national or regional contextual factors or regulations that are crucial to consider, and national bodies working with local patient groups and affected communities are best placed to ensure appropriate local adaptation of this guidance and compliance with universal scientific and ethical standards.

This document aims to complement other guidance in order to support implementation of universal ethical and scientific standards in the context of clinical trials, with a focus on under-represented populations; it does not represent a legal standard and does not supersede any existing guidance. In particular, this guidance shares many common concepts and principles with guidance produced by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) *(5)*, especially the ICH E8(R1) General Considerations for Clinical Studies guideline *(6)*, *(*the draft ICH E6(R3) Good Clinical Practice guideline *(7)*, and the ICH E9 statistical principles guideline *(8)* and its associated addendum *(9)*. In addition, it shares attributes with two further recent guidance documents that were highlighted through WHO's public consultation process in 2022: those of the Council for International Organizations of Medical Sciences (CIOMS) on clinical research in resource-limited settings *(10)* and the Good Clinical Trials Collaborative (GCTC) *(11)*. Both the CIOMS and GCTC guidance have served as sources, with adaptations as needed, for this document. Additional sources highlighted through the consultation include the World Medical Association's (WMA) Declaration of Helsinki *(12)* on medical research involving human subjects, the WMA Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks *(13)* and CIOMS' International Ethical Guidelines on Health-related Research involving Humans (2016) *(14)*.

For clinical trials designed to support submission to regulatory authorities concerned with medicinal products, trial sponsors should also refer to the ICH guidelines, in particular ICH E8 (R1) *(6)* and ICH E6(R3) *(7)* and other relevant ICH guidelines, along with any relevant guidance issued by the authorities to which they plan to submit. As noted above, the scope of this WHO guidance is restricted to neither medicinal products nor clinical trials conducted in support of regulatory approval.

## Approach to development

In March 2023, under the guidance of the WHO Technical Advisory Group (TAG) for the Development of Best Practices for Clinical Trials, the initial guidance was drafted by Vasee Moorthy and Christina Reith, drawing from existing CIOMS and GCTC guidance. The TAG provided feedback on this draft in writing and during a teleconference in May 2023. This feedback was incorporated into a revised draft, which was published on the WHO website for public consultation from July to September 2023.

The WHO Secretariat disseminated the public consultation for the draft guidance to regional offices, relevant headquarters technical programs, professional networks, non-state actors in official relations with the WHO, and other key stakeholders in clinical research. A total of 179 responses from 48 countries were received, with approximately 30% from academic stakeholders, followed by non-governmental organizations and national health or regulatory authorities. Additionally, the WHO Secretariat organized a consultation with private sector

representatives at a side event during the 76th World Health Assembly and held an information session to gather feedback from Member States in September 2023.

A global stakeholder survey was launched in August 2023, in collaboration with the WHO Collaborating Centre for research information sharing, e-learning, and capacity development, to identify barriers in conducting clinical trials and propose priority actions. Nearly 3000 participants worldwide responded to the survey. Outcomes from the global stakeholder survey were further discussed in in-person consultations held in Brasilia, Brazil; Lusaka, Zambia; Delhi, India; Cairo, Egypt; Kuala Lumpur, Malaysia; and Geneva, Switzerland, attended by about 300 experts and stakeholders. These consultations provided additional input for the draft guidance on strengthening the clinical trial ecosystem.

The final guidance, prepared by Vasee Moorthy and Christina Reith, integrated all received feedback. In April 2023, a TAG meeting was held to review the final draft before its submission for executive clearance and publication.

Declarations of interest were collected from all members of the WHO Technical Advisory Group (TAG) that oversaw the development of the guidance and any relevant interests are publicly disclosed on the website for the TAG.

# 1. Introduction

Community health services for parents and children in Gyabankrom, Central Region, Ghana.

# 1. Introduction

## 1.1 Clinical research: importance and types

Clinical research is indispensable for resolving public health challenges. Clinical research studies can be thought of as spanning five generic areas of activity:

- measuring the magnitude and distribution of the health problem;
- understanding the diverse causes or the determinants of the problem, whether they are due to biological, behavioural, social or environmental factors;
- developing solutions or interventions that will help to prevent, mitigate or cure the problem;
- implementing or delivering solutions through policies and programmes; and
- evaluating the impact of these solutions on the level and distribution of the problem.

Clinical studies broadly fall into two groups: non-interventional and interventional.

Non-interventional studies are observational in nature (hence sometimes known as observational studies), in which health outcomes are typically compared between individuals who received or were exposed to a certain factor and those who did not, and in which the allocation to treatment or exposure is not predetermined by a study protocol.

In contrast, interventional clinical studies (known as clinical trials) evaluate the effects of prospectively assigning subjects to one or more interventions on health outcomes. For comparisons of two or more interventions, a key aspect of such prospective assignment is the process of randomization to help to ensure that the efficacy and safety of treatments are assessed reliably; the key importance of why this matters is discussed in Section 1.2 and Section 2. Such clinical trials are known as randomized clinical trials (RCTs), with the intervention to which a participant is allocated sometimes referred to as an "arm" of a clinical trial. RCTs may involve prospective allocation of *individuals* to interventions or prospective allocation of a *group* of people (for example, in a particular community, school or region), and are sometimes known as cluster RCTs. There are, however, some circumstances where prospective assignment necessarily does not support randomization, such as clinical trials very early in an intervention's development, or in some oncological, rare disease and diagnostics trials whereby only one intervention is tested (that is, "single arm" trials).

Clinical trial interventions may include (but are not limited to) administration of pharmaceutical medicines, cells and other biological products, and vaccines; surgical or radiological procedures; diagnostics; use of medical devices, nutritional measures; cognitive, behavioural and psychological interventions; supportive or preventive care, including process-of-care changes; physical therapy interventions; digital and public health approaches; traditional or herbal measures; and screening processes. The interventions may be novel or pre-existing but being used in a different way (for example, repurposed or optimized) or to gain further knowledge about current practice. In RCTs, interventions may include placebo or another comparator (sometimes known as a control) and may provide no additional active intervention beyond usual practice or standard care.

Clinical trials may be carried out at any level of the health system, from home, community or primary level care through to secondary, tertiary or intensive care settings.

In addition to traditional parallel-group RCTs, a range of further trial designs exists, including (but not limited to) crossover, factorial, adaptive and platform trials. In addition, the variety of options for performing any of these trial designs is wide, depending on the nature of the trial. These can include decentralized trials, point of care trials and more traditional investigator location-based trials, or, more commonly, combinations of these elements in a single trial.

Platform, basket and umbrella trials all use master protocols *(15–18)* which allow simultaneous evaluation of multiple interventions within the same overall trial structure. Platform trials are designed to study multiple interventions among people with one or more closely related diseases (for example, cancers due to genomic subtypes) or health conditions (for example, pneumonia). They may use a common control group (for example, treatment A vs treatment B vs a common control) or, more efficiently, a factorial design that involves more than one randomized comparison (for example, treatment A vs placebo A and treatment B vs placebo B) such that some participants may get more than one active treatment while a minority receives a placebo. They are efficient and flexible, allowing for modification of the ongoing trial in the light of accumulating trial data, with new research questions being introduced as amendments rather than as new trials. For example, arms can be added to test new interventions once initial questions have been addressed, while existing arms may be discontinued if it becomes apparent that an intervention is ineffective or harmful based on predefined decision algorithms. Such platform trials can be open-ended and with intervention arms added at different points in time. In particular, the emergence of large adaptive platform trials with pragmatic features embedded into health systems was pivotal in generating evidence for use of therapeutics in coronavirus disease (COVID-19).

Increasingly, trials also use streamlined "decentralized" approaches *(19)* (where some aspects are delivered in or close to people's homes) or point-of-care designs (where a trial is conducted in clinical practice settings). Such trials can address critical questions in clinical care settings rather than in specialized research environments. *(20)*

All clinical trials should help to resolve important uncertainties about the effects of health interventions. Depending on the context, the results may be needed to determine whether to proceed with development, further evaluation of the intervention or inform regulatory licensing, clinical guidelines and/or health policy. In each case, any uncertainties applying to the specific question(s) that remain at the end of the clinical trial should be sufficiently small to allow meaningful decisions to be made.

## 1.2 Ascertainment of treatment effects: observational studies vs clinical trials

Observational studies and clinical trials are both highly valuable in clinical research and may be complementary. However, they must be designed and analysed appropriately, and used in the right context *(21–24)*. Robust observational studies can be extremely useful for identifying associations of risk factors with disease (with good examples being smoking with lung cancer, and blood pressure and cholesterol with cardiovascular disease), but their value for the assessment of the effects of treatment is more limited. Observational studies may also have an important role in the identification of large effects (adverse or beneficial) of an intervention on rare health outcomes that would not normally be expected to occur, particularly those that are not likely to be related to the indications for (or contraindications to) the intervention of interest.

A major limitation of observational studies is their inherent potential biases. One of the most important of these is confounding, in which a factor is associated with an exposure of interest (but is not a direct consequence of it) and, independently, influences the risk of the outcome of interest. For example, "confounding by indication (or contraindication)" may occur when a treatment tends to be provided more (or less) frequently to individuals with conditions associated with increased or decreased risks of the outcome of interest. This type of bias can produce misleading estimates not just of the size but also of the direction of treatment effects, and these can remain even after statistical adjustment for observed differences between different groups

of individuals. Equally, biases can arise owing to differences in ascertainment or detection of an outcome. In addition, the reliability of recall of treatment exposure can differ between those who develop a certain outcome and those who do not. These potential biases mean that observational studies can be unreliable for determining the effects of health interventions, especially when (as can often be the case) the effects of the treatment of interest are only moderate or null *(25)*.

Discussion of design considerations and methods to avoid bias and confounding in observational studies is beyond the scope of this guideline. However, this limitation is highly relevant because most interventions for most common serious conditions have only modest effects on health and disease, even if they have a large effect on intermediate features (for example, physiological or laboratory tests). However, even modest improvements in health can be important, particularly if the intervention can be used widely for a common condition or if multiple interventions with moderate effects can be used in combination, provided any benefits are not substantially offset by detrimental effects. Therefore, it is vital that these modest effects are detected reliably. This requires clinical trials that ensure stringent control over systematic errors such as biases and confounding factors (which, in general, requires proper methods in randomization, blinding and masking, as well as appropriate statistical analysis) and strict control of random error (which necessitates appropriate sample sizes). RCTs therefore have a central role in generating the evidence needed to inform the development and implementation of health interventions, because they can reliably determine whether a health intervention is safe and effective by ensuring that any biases or random errors inherent in the study design are small with respect to the expected treatment effect. The results of such RCTs and their associated meta-analyses (whereby data from multiple clinical trials addressing a similar research question are statistically combined) *(21)* have been transformative in advancing global public health.

## 1.3 The clinical trials environment: an evolving landscape

The clinical trial environment has evolved substantially since the concepts of clinical trials were introduced, with important changes having also taken place in the social, ethical and regulatory environment globally. There is now a broader recognition of the very large health, social and economic returns on investments in research. Clinical trials and the development of interventions are being supported by industry, non-industry parties (such as academic institutions), government agencies and public–private partnerships, sometimes with support from external partners in translational research.

In terms of ethical principles there have been revisions of the Declaration of Helsinki *(12)* and development of guidance on clinical trials, notably the CIOMS international ethical guidelines *(14)*.

In terms of regulatory guidelines, ICH clinical trial guidelines are available, in particular ICH E8(R1) *(6)* and ICH E6(R3) *(7)*. There is also recent guidance from the Good Clinical Trials Collaborative *(11)*, as well as the creation of new or updated guidance or pathways being developed by regulators.

Also, interest has grown in trials methodology, including increasing use of flexible and practical approaches to trial design, with a growing recognition of how routinely collected data, sometimes known as real world data, can add value and drive efficiency of clinical trials. For example, data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (such as electronic health records, medical claims data, data from product or disease registries, and data gathered through digital health technologies) can be used to help with the enrolment and outcome ascertainment in trials *(26–29)*.

Patient organizations and advocacy groups have come to the fore globally in recent years, advocating patient, community and public involvement in clinical trials as a cornerstone in the design and conduct of clinical trials. However, more remains to be done to ensure that trial design and implementation include adequate engagement with patients, communities and the public. This guidance includes elements on

such engagement that will not only help to ensure that clinical trials are relevant to the populations they are intended to serve, but also raise awareness of the role of clinical research in public health and the quality of life. Guidance and initiatives for patient involvement and good participatory practice in clinical trials have been developed, by WHO and others, available across a range of interventions and settings *(30–38)*.

The way in which information is shared and communicated is also rapidly evolving. This provides valuable opportunities for more efficient, collaborative and transparent trial processes, but also presents potential risks in terms of a growing potential for global propagation of misinformation or "fake news" which is detrimental to public health. Well-designed RCTs and the maintenance and promotion of clear, valid sources for reliable information on their design and results are a strong defence against misinformation.

In areas of medicine where clinical trials are common, such as oncology, cardiovascular disease and some infectious diseases, patient outcomes have markedly improved as interventions and service delivery have been iteratively enhanced.

While the focus of this guidance is on later-stage RCTs that evaluate safety and effectiveness of interventions, earlier-stage translational research is another valuable area that has emerged as central to advancing health outcomes, by acting as the bridge between basic science and later-stage evaluations.

Applications of artificial intelligence (AI) in the clinical trials arena were advancing rapidly at the time of finalizing this guidance, including but not restricted to drug and vaccine discovery and molecule design, AI-enhanced diagnostic approaches, predictive modelling of trial outcome intended to improve trial design, participant recruitment and retention and digitization.

All these factors have significantly changed the environment for clinical trials. However, the research landscape must continue to evolve to fulfil its potential.

## 1.4 Persistent challenges to clinical trial enablement

There is an urgent need to avoid wasteful procedures and make clinical trials more efficient so that they can be done on an adequate scale to produce reliable evidence at reasonable costs. This is because, despite the widely recognized importance of clinical trials, **in many areas of health the evidence base remains weak, with decision-making processes lacking results from enough well-designed and well-conducted clinical trials. This problem is global, affecting high-, middle- and low-income countries.** The result can be failure to identify and use effective and safe interventions or the continuing use of ineffective or hazardous interventions; for example, millions of doses of ineffective treatments were used during the COVID-19 pandemic. As a consequence, resources are wasted through both direct immediate costs and indirect downstream costs, unnecessary harm or suffering may be caused, and trust is reduced in those who develop or use health interventions. The need to reduce research waste is a long-recognized global issue affecting clinical trials across a spectrum of settings, with urgency to address this problem having been the focus of much discussion. However, it was particularly highlighted by the research response to the pandemic of COVID-19: more than 22 000 COVID-19-related clinical trials were registered, of which the vast majority are thought to have contributed little to the evidence base. A small proportion of such clinical trials (whether publicly or non-publicly funded), probably less than 10%, were well-designed and well-implemented (with a widespread problem being that many such clinical trials were not randomized and/or sufficiently large to answer their intended question) and contributed meaningfully to policy recommendations by WHO and other bodies.

This waste in clinical trials results from various factors. These include clinical trials never being done or completed, failure to articulate clear research questions, duplication of previous research, use of inefficient trial processes, failure to produce scientifically robust and clinically relevant answers, or results never being published. The lost opportunity cost of trials that are poorly designed or not completed and reported is significant and results in draining of available resources which

are not then available to conduct and complete well-designed trials. Additionally, a prevailing risk-averse mentality hampers innovation and the adoption of new perspectives, leading to disproportionately burdensome trial processes and data collection practices. The absence of efficient and coordinated procedures for approving clinical trials poses a significant challenge, characterized by vast intercountry and inter-regional heterogeneity in approval processes by regulatory and ethics authorities. Some countries have mature systems, but these may still have significant inefficiencies and over-utilise risk-averse approaches. If approval processes are unduly lengthy, enthusiasm and the ability to enrol large numbers in local populations may wane. Such delays can lead to a reduction in evidence generated for exactly the types of people such authorities are trying to benefit. Many countries also lack the necessary resources for a robust infrastructure or have not yet achieved adequate efficiency. The multitude of applications with various processes and lengthy timelines results in delayed initiation of trials and may lead to a loss of motivation to engage in clinical research. This issue intensifies for multiregional or international trials, important for achieving both statistical power and broad representativeness. Intermittent use of clinical trial infrastructure also specifically needs to be addressed to avoid periodic fallow or "cold" periods in clinical trial activity, primarily driven by project-based research and intermittent clinical trial funding. This problem results in inefficiencies, skill loss and neglect of key areas in the clinical trial ecosystem.

A lack of adequate funding for clinical trials remains a major issue globally with ongoing disparities in investment and access to clinical trial infrastructure especially when taken in context of global disease burden *(39)*. The result is inequity and a lack of justice in fairly accessing affordable, safe and efficacious interventions, the consequences of which were particularly highlighted during the COVID-19 pandemic.

This state of affairs is particularly prominent in resource-limited settings and areas where the traditional model of development of interventions does not provide incentives for research and development (R&D), with trials undertaken in high-income countries (HICs) historically dominating, focusing on diseases prevalent in those settings. The result has been an increasingly conducive clinical trials environment, infrastructure and capacity to address the health priorities of HICs and commercial market interests. In contrast, the limited health care and research capacity and/or commercial viability in low- and middle-income countries (LMICs)[1] means that clinical research in these regions has often focused on observational or implementation studies conducted after the registration or approval of an intervention in HICs. However, populations in (LMICs) bear the highest burden of preventable disease globally, facing several specific challenges. First, they continue to face a high level of communicable diseases, such as neonatal sepsis, malaria, tuberculosis, chronic hepatitis B and C, HIV infection/AIDS, diarrhoeal diseases and neglected tropical diseases, and in some areas are being seriously impacted by epidemic outbreaks of diseases, which affect different regions in different ways. In 2021, children up to 14 years of age accounted for 25% of the global population and 42% of the population in low-income countries *(40)*. Secondly, neonatal, maternal and nutritional diseases are prevalent, and neonatal, under-5 and maternal mortality is high in LMICs, although declining. In addition, LMICs have similar rates of noncommunicable diseases to those in upper-middle- and high-income countries but lack adequate clinical trial focus outside such more affluent settings. Thirdly, although the disease burden in LMICs has decreased since 1990, with communicable diseases projected to fall further over time, their burden from noncommunicable diseases will become proportionally higher.

Although trials in LMICs do take place, they tend to be funded by international donors from HICs, or by industry, as opposed to being able to be resourced by LMICs themselves. There is therefore a pressing need to promote and advance efficient and sustained well-designed and well-implemented clinical trials that address local health needs across all stages of clinical research in LMICs and other resource-limited settings *(39)*, encompassing both communicable and noncommunicable diseases in

[1] The World Bank's bands of income levels are commonly used to classify countries in terms of resources. In this document the term LMICs refers to the World Bank country classifications, whereas resource-limited settings refer to locales that may be common in low-income countries but may also exist in middle- and high-income countries, for example in remote and/or deprived communities. Moreover, a setting can change over time and may no longer be considered low-resource or newly become low-resource.

order to address the morbidity and mortality risks affecting people in those settings. If this does not occur, entire populations could miss out on the vaccines, diagnostics and other interventions that are needed as part of sustainable development globally.

Moreover, conducting research in LMICs can foster capacity-building. By investing in training programmes and constructing laboratory facilities that meet international standards, research funders can contribute to the development of the necessary infrastructure and resources to execute high-quality research in LMICs. This, in turn, can lead to functional international networks and a sustained and equitable global health research landscape.

Inequities in post-trial access to interventions tested in clinical trials also remain a major concern, especially in relation to LMICs. Indeed, there have been examples of trials where the disease burden in LMICs led to them being targeted for inclusion in clinical trials, yet these data were then used to file for marketing authorization in HICs or high-resource settings, often leading to availability of interventions in the latter but not the former. Similarly, trials of diagnostics that took place in LMICs or low-resource settings have sometimes failed to provide any post-diagnostic support for those with the diagnosed condition. These are examples of exploitation and a clear breach of ethical principles, and there must be a more systematic end-to-end approach for ensuring that new interventions are globally affordable and accessible, from discovery through to development and distribution.

Inequities in leadership in clinical trials is an unresolved barrier. Local researchers, funders, communities and organizations should share an equal leadership role in prioritization, design, implementation and reporting of clinical trials..

A further major challenge is that clinical trial cohorts have often lacked diversity, with under-representation of certain populations, resulting in them being underserved by clinical trials, including (but not limited to):

*Groups by demographic factors*

- age extremes: neonates, infants, children and adolescents (despite this group representing a large proportion of the population in some settings) and older people (with elderly patients often being excluded from clinical trials on account of their being more comorbid and hence thought likely, but incorrectly, to obscure potential effects of an intervention even when there is a comparator group; this is an issue since they often carry a significant burden of disease and therefore represent a population in whom absolute effects of an intervention may be particularly large)
- women of child-bearing age
- pregnant and lactating women
- different ethnic minority groups
- male/female sex (depending on trial context, although women were often previously under-represented);

*Groups by social and economic factors*

- people living in remote areas
- socioeconomically disadvantaged
- socially marginalized people
- stigmatized populations including LGBTQI+ people
- people in alternative residential circumstances (for example, migrants, asylum seekers, refugees, occupants of care homes, prison populations, traveller communities, the homeless and those of no fixed abode)
- religious minorities
- people who do not attend regular medical appointments
- people who face language barriers and digital exclusion/disadvantage
- carers
- military veterans;

*Groups by health status*

- multimorbidity
- people who lack the capacity to give consent for themselves
- cognitive impairment
- learning disability
- people with neglected tropical diseases
- people with addictions
- people with multiple health conditions or those who are severely ill
- people with physical disabilities or who are visually/ hearing impaired
- people with rare diseases and genetic disease subtypes.

Such lack of clinical trial inclusivity and diversity can lead to trial results being less generalizable to groups who would potentially benefit from the findings, despite them often being groups with the highest burden from a particular disease or condition. This weakness has impeded the quality of available evidence for decision-making, leaving huge uncertainties related to care and inequitable access to interventions. It can also reduce the willingness of people in those under-represented groups to accept treatment recommendations based on a trial's findings.

Finally, although patient and community engagement in clinical trials has improved, there remains a lack of broadly applicable disease-agnostic standard practice for such involvement. This inadequacy can lead to inappropriate trial design and implementation, mistrust in research, and failure of clinical trials to start, reach completion or produce results meaningful to the populations they are intended to serve.

## 1.5 Steps required to improve evidence generation

The above issues urgently need to be addressed to advance global public health. This requires identification of relevant research questions, proportionate design and conduct of clinical trials and strengthening of the global clinical trials environment, or "ecosystem".

### 1.5.1 Identification of a relevant research question

A prerequisite for conducting a good clinical trial is identification of an important and relevant research question, the answers to which will fill gaps in evidence to inform research priority setting. Clinical trials should principally focus on public health and disease areas of national and global priority and address questions that are clinically pertinent to the communities and populations affected by them; at the same time, they should consider epidemiological trends to address potential (and future) health threats. It is vital not only to identify a relevant question but also to ascertain if it has already been robustly answered. This can be facilitated by conducting and reporting systematic reviews (for example, according to the guidelines on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) *(41)*) as part of clinical trial planning. Such reviews comprehensively evaluate and synthesize available evidence, and as such can consolidate existing knowledge and improve future clinical trials by providing insights into the strengths and limitations of prior studies, as well as guide the selection of interventions and outcome measures. By conducting a systematic review researchers can prevent unnecessary duplication and minimize research waste *(42, 43)*, and such reviews should be promoted by funders and seen as complementary to clinical trials. However, it should also be borne in mind that systematic reviews may be subject to bias, either because trials with more promising results are more likely to be published and known about than those with less promising results or because such reviews may under-represent certain populations if the existing evidence is not relevant to them (for example, trials in LMICs may not be prominent owing to research having historically been done in HICs).

Therefore, additional measures (such as policy gap analysis) may also need to be considered as part of the process of identification of a relevant research question. Such reviews should include both available evidence from clinical trial results and review of ongoing research available in clinical trial registries such as the primary registries from International Clinical Trials Registration Platform (ICTRP) *(44)* and ClinicalTrials.gov *(45)*.

### 1.5.2 Efficient and risk-proportionate design and conduct of clinical trials

Clinical trial quality can be defined as fitness for purpose, where the purpose is to provide reliable results of sufficient robustness to enable informed decision-making based on the trial outcomes. Attributes of clinical trial quality include good trial design, conduct and appropriate analysis.

One area identified as a potential barrier to clinical trials has been over-interpretation of existing regulations and guidance for clinical trials. A frequent consequence has been excessive bureaucracy, which has also resulted in unnecessarily onerous and disproportionate trial procedures, with, for example, even minor trial processes or trial staff changes (which do not materially affect the reliability or safety of a trial) often requiring extensive documentation for no benefit. This lack of proportionality has sometimes had the adverse consequence of reducing rather than improving the number of reliably informative trials across a range of settings.

Instead, trial "quality" should focus on good design and processes that assure the absence of errors that matter to decision-making – that is, errors that have a meaningful impact on the safety of trial participants or credibility of the results (and thereby the care of future patients) – and not be confused with the volume of paperwork (including collecting and filing documents), the length of clinical trial protocols and other documentation *(46)*. Crucially, trial processes should be proportionate to their context and any associated risks, with efficient implementation. Streamlining and quality are not opposed. Enabling such an approach need not compromise the robustness of the data generated to answer relevant scientific questions; rather it can substantially enhance available evidence from high-quality clinical trials and hence population health worldwide.

**Section 2 of this document provides high-level guidance for clinical trial design and conduct** with a focus on the key scientific and ethical features that should be universal to all clinical trials in order to enable them to produce reliably informative, high-quality evidence relevant for informing national and international guidelines and decision-making, regardless of context. **A proportionate approach focusing on the main considerations and what really matters can enable more good quality trials to be conducted.**

### 1.5.3 Strengthening of the global clinical trial ecosystem

For clinical trials to achieve their intended aims, measures must be taken to enhance the capabilities to conduct relevant trials globally. This requires: action by not only those designing and conducting clinical trials but also all parties involved in prioritizing, funding, approving and overseeing clinical trials; investment in and availability of clinical trial infrastructure globally; and efficient communication between all those involved. Crucially, patients and communities should be seen as a key part of the clinical trials ecosystem and involved at all stages of the lifecycle of a clinical trial.

**Section 3 of this document provides high-level guidance and recommendations on best practices for the strengthening of the ecosystem for clinical trials, including enabling actions.**

# 2. Key scientific and ethical considerations for clinical trials

Patients at the Radboudumc Amalia Children's Hospital use VR headsets for relaxation, entertainment, meditation, and hypnosis.



# 2. Key scientific and ethical considerations for clinical trials

**Reliably informative, ethical and efficient clinical trials ("good" trials) need to address the following five key points which capture the necessary qualities of a well-planned, well-run and clinically relevant trial. They should:**

- **be designed to produce scientifically-sound answers to relevant questions**
- **respect the rights and well-being of participants**
- **be collaborative and transparent**
- **be designed to be feasible for their context**
- **manage trial quality effectively and efficiently.**

**The methods and approaches needed to apply these qualities will differ in small or large ways from trial to trial, but their validity is universal.**

## 2.1 Good clinical trials are designed to produce scientifically sound answers to relevant questions

Clinical trials should help to resolve important uncertainties about effects of health interventions. Depending on the context, the results may be needed to determine whether to proceed with development or further evaluation of the intervention or to inform regulatory licensing, clinical guidelines and/or health policy. In each case, relevant uncertainties applying to the specific question(s) that remain at the end of the trial should be sufficiently small to allow meaningful decisions to be made.

As indicated in Section 1.2, most health interventions only have moderate effects, and clinical trials intended to reliably ascertain such effects typically require clinical trials with the following features: randomization without foreknowledge of intervention allocation so as to ensure that any differences in health outcomes observed between the randomized groups are due to either the effect of the study intervention or the play of chance (that is, control for systematic errors), as well as blinding/masking of allocated trial intervention (where feasible) to further minimize bias.

### 2.1.1 Robust intervention allocation

**Key message.** Randomization requires generation of an unpredictable allocation schedule with concealment of the intervention to which a particular participant has been allocated until after the point of randomization. It should be impossible to predict in advance to which study intervention an individual trial participant or individual cluster (for instance, hospital or city in a cluster clinical trial) is likely to be allocated, so that investigators, health care providers and other staff involved and potential participants are not aware of which intervention to which they will be assigned.

**Why this is important.** Randomization allows for like-with-like comparisons so that subsequent differences in health outcomes between the groups (beneficial or adverse) are due either to the play of chance or causally to differences in the study intervention. The absence of adequate concealment of allocation before randomization can lead to selection bias (that is, the decision to enter a particular participant in a trial can be influenced by knowledge of which intervention they are likely to be assigned to).

### 2.1.2 Blinding/masking of allocated trial intervention (where feasible)

**Key message.** Knowledge of the allocated trial intervention may influence the behaviour of participants, those who care for them, and those

assessing study outcomes (particularly if these are subjective in nature). These problems can be avoided through use of placebo medications or dummy interventions and by ensuring that those individuals or systems responsible for assessing participant outcomes, as well as all who are responsible for care of participants, are unaware of the intervention allocation.

**Why this is important.** In many clinical trials, knowledge of the allocated intervention can influence the nature and intensity of clinical management, the reporting of symptoms or the assessment of functional status or clinical outcomes, introducing bias. Where feasible, masking (or blinding) participants, investigators, health care providers, and those assessing outcomes to the assigned intervention through use of placebo medications or dummy interventions can help to prevent such issues, as can the use of information that is recorded separately from the clinical trial (for instance, in routine clinical databases and disease registries). These considerations are important for the assessment of both the efficacy and the safety of the intervention, including processes relating to adjudication of outcomes and considerations of whether an individual health event is believed to have been caused by the intervention. If blinding of an allocated trial intervention is not feasible (for example in trials of different types of patient management or surgical procedures), blinded or masked outcome assessment should be pursued for objectively determined outcomes, for example through use of a prospective randomized open-label blinded endpoint (PROBE) design (see also Section 2.1.9 ascertainment of outcomes).

All good clinical trials should include the features set out in sections 2.1.3–2.1.12.

### 2.1.3 Appropriate trial population

**Clinical trials often exclude populations that the intervention may well benefit, sometimes precluding access to certain interventions for the populations excluded from the trials.**

**Key messages.** The eligibility criteria should be tailored to the question that the trial sets out to answer. Inclusion criteria should not be unnecessarily restrictive. Efforts should be made to include a broad and varied population (for example, with appropriate balance of sex/gender, age, race/ethnic and socioeconomic diversity), unless there is a good medical or scientific justification for doing otherwise.

Exclusion criteria should be focused on identifying individuals for whom participation would place them at undue risk by comparison with any potential benefits (for example, based on their medical history or concomitant medication), for whom the benefits have already been reliably demonstrated, or for whom the intervention is not relevant.

**Why this is important.** Inclusive eligibility criteria increase the relevance and generalizability of the findings. They may sometimes allow assessment of whether there is good evidence of material differences in the effects (beneficial or adverse) and/or acceptability of an intervention or its delivery in any particular subgroup (for example, based on specific genetic, demographic or health characteristics), even though statistical power to detect whether such differences exist may be limited. Populations should not be excluded based solely on an argument of potentially insufficient statistical power to detect subgroup specific effects.

Guidance has been developed to improve inclusion of underrepresented groups *(47–50)*. Decentralized or point-of-care trials may help to increase the diversity of clinical trial enrolment by increasing trial accessibility. In addition, diversification of trial staff can help to improve community engagement and diversification of recruited clinical trial populations *(51)*.

Specific examples of populations that have typically been excluded from clinical trials (either explicitly or by implicit exclusion) include pregnant and lactating women, infants and children, and older adults. This practice has been hugely detrimental and such people should be eligible for trial enrolment unless a valid justification is provided for their exclusion (for example, if there is a serious safety concern or a contraindication to a certain intervention or if they are at very low risk of the health issue the trial seeks to address). Some ways to foster enablement of clinical trials in two specific groups are outlined below in subsections (a) and (b). Recommendations

related to inclusion of older adults, another important frequently-excluded group, are contained in Annex 2.

### (a) Enabling clinical trials in pregnant and lactating women and women of child-bearing age

Demand for facilitation of inclusion of pregnant and lactating women *(52)* and women of child-bearing age in clinical trials is growing. Their participation requires consideration of the specific barriers they may face to enrolment, owing to not only the incorrect perception that this is a default ethical or scientific position but also practical issues. Some of these potential barriers, such as limited literacy to provide informed consent and legal restrictions (for example, third party consent requirements), are common to many populations, whereas others are more prevalent in women, such as the need for child-care provision and, particularly in some regions, mobility restrictions. Many clinical trials could enable recruitment of pregnant and lactating women by assessing pre-existing evidence for the safe use of the same or similar intervention in this population, such as its use for a different clinical indication. Due consideration should be given to the severity of the condition for which the intervention is intended in this population, and the potential for improved outcomes in both the recipients and their offspring. For trials of novel interventions for maternal disease where there is no pre-existing evidence of use of the same or similar interventions in this population, preclinical reproductive toxicology studies should be reviewed to guide decision-making. Where maternal disease is severe, maternal and pregnancy outcomes are expected to be poor and reproductive toxicology studies are reassuring, benefits to women of inclusion in a trial are likely to outweigh any potential risks. For diseases with high fatality for which no alternative interventions are available, reproductive-toxicity studies should be expedited, and pregnant individuals included as far as possible in clinical trials of new interventions. In several therapeutic areas, practical ways to accelerate investigation of new interventions in pregnant and lactating women have been developed, with calls to action involving multiple stakeholders. There is now ethical guidance for the inclusion of pregnant women in the development of vaccines against emerging pathogens, and subsequent vaccination programmes as well as for advancing research into HIV and co-infections in pregnant women *(53, 54)*. An ICH guideline (E21) is also currently in development for inclusion of pregnant and lactating women in clinical trials *(55)*. Excretion of a drug or its metabolites into human milk should be examined where applicable and feasible, and offspring of breastfeeding women enrolled into clinical trials monitored for any effects of an intervention *(6)*.

### (b) Enabling paediatric clinical trials

Children should not be an afterthought in clinical development programmes but considered from the outset *(56)*, with inclusion as early as possible in clinical trials of interventions of potential benefit to them. Wherever possible, extrapolation of adult efficacy and safety data to children should be considered. Use of age-agnostic trial enrolment and standardized weight-band dosing for children, with parallel enrolment of all children across all weight bands, should also be considered, potentially coupled with enrolment by development stage. Such an approach could mitigate against enrolment of children being done in an age-stratified way (that is, starting with older children), which disadvantages younger patients. Development of appropriate paediatric interventions should be prioritized with attention given to factors such as palatability of formulations, flexibility for weight-based dosing and stability for use in a wide range of geographical locations. Use of pharmacometric modelling and simulation techniques (such as creation of synthetic control arms) may help to improve the design of some paediatric trials. Several initiatives are underway to enable paediatric clinical trials. In particular, in 2016, the World Health Assembly adopted resolution WHA69.20 on promoting innovation and access to quality, safe, efficacious and affordable medicines for children *(57)*. WHO and other stakeholders have joined forces to accelerate access to effective paediatric diagnostics and medicines, notably for HIV infection and tuberculosis *(58–60)*, and the Global Accelerator for Paediatric Formulations Network (GAP-f) *(61)* was created to build on and formalize the model developed within the HIV community to provide a sustainable mechanism to ensure that safer, more effective and more durable paediatric formulations are developed and made available to children against an accelerated timeline. Measures such as the FDA Paediatric Research Equity Act *(62)* and EU Paediatric Regulation *(63)* have also enabled trials in this population.

The use of global networks may further enable clinical trial participation in such populations. For example, the Global Network for Women's and Children's Health Research *(64)* is a partnership dedicated to improving maternal and child health outcomes and building health research capacity in resource-poor settings by testing cost-effective, sustainable interventions that provide guidance for the practice of evidence-based medicine.

### 2.1.4 Adequate size

**Key message.** A clinical trial should be sufficiently sized and statistically powered to provide a robust answer to the question it sets out to address.

**Why this is important.** For the effects of health care interventions to be reliably detected or reliably refuted, random errors must be small by comparison with the expected size of the effect of the intervention. The best way to minimize the impact of random errors is to study sufficiently large numbers of participants who will develop the health outcome that the intervention is intended to prevent or treat (noting that clinical trials assessing impact on discrete health outcomes such as mortality will require more participants than those assessing impact on continuous measures such as laboratory results as is often the case in early-phase trials) *(65)*.

Trials in early stages of drug development (for example, first-in-human trials) have a specific objective for which a smaller size is typically appropriate. In some scenarios it is challenging to enrol large numbers of participants, such as trials assessing interventions for rare diseases. For such trials, it may be helpful to contribute to a broader collaboration to conduct them, through large, multicentre clinical trials, or to select a clinically relevant outcome for which the effect size is expected to be larger (for example, a clinically validated physiological or imaging biomarker). It may be possible to reduce the impact of random errors through statistical analyses or by making assessments at a time when the effects of the intervention are expected to be greatest. Use of alternative study designs to facilitate recruitment (such as point-of-care and decentralized trials) may help to ensure adequate trial size. Meta-analysis may be particularly helpful when the effects of an intervention on an outcome are likely to be moderate and too few cases have occurred in any individual trial to assess the effects sufficiently reliably or to assess whether there any important differences in treatment response between different patient groups *(21–23)*. Use of core outcomes (see Section 2.1.7) may facilitate prospective meta-analyses.

### 2.1.5 Adherence to allocated trial intervention

**Key message.** Efforts should be made to facilitate and encourage adherence to the allocated intervention(s) where appropriate and feasible.

**Why this is important.** Although there may be instances in which it is appropriate for trial participants to stop their allocated intervention (for example, in the case of a major intolerance), the potential ability for the trial to accurately determine and quantify the impact of the intervention (whether beneficial or harmful) should be carefully considered. For RCTs, if trial participants allocated to an active intervention do not receive it as planned or if those allocated to the control group (for example, placebo or usual care) start to receive the active intervention, then the contrast between the two study groups is lower. Consequently, the ability to assess any difference in outcome between the arms of the trial is reduced (and a false conclusion that there is no meaningful difference between the interventions when in fact there is one is more likely). Adherence to allocated trial intervention may be facilitated through for example, pre-randomization "run-in" phases (on placebo or even active intervention) and supporting trial participants to continue (for example, where feasible, options for remote follow-up rather than in-person clinic visits).

### 2.1.6 Completeness of follow-up

**Key message.** Participant outcomes should be ascertained for the full duration of the clinical trial, regardless of whether a participant continues to receive the allocated intervention or ceases to do so (because, for instance, of perceived or real adverse effects of the intervention), with every effort made to proactively minimize the loss of data. In some cases, it may also be appropriate to continue follow-up for many years after the main analyses have been reported.

**Why this is important.** For RCTs, continued follow-up of all randomized participants (even if some stop their assigned intervention) maintains the like-with-like comparison produced by the randomization process. Premature cessation of follow-up or post-randomization exclusion of participants should therefore be avoided as it may introduce systematic bias, particularly as the type of people excluded from one intervention group may differ from those excluded from another. Incomplete follow-up may reduce the statistical power of a clinical trial (that is, the ability to distinguish any differences in outcome between the interventions) and underestimate the true effects (benefits or hazards) of the intervention. Extended follow-up can allow for detection of beneficial or harmful effects of the study intervention that may persist or emerge months or years after the initial randomized comparison.

### 2.1.7 Relevant measures of outcomes, as simple as possible

**Key message.** The outcomes that are assessed in a clinical trial need to be relevant to the question being addressed and should be as simple as possible. When trials are intended to achieve marketing authorization or change policy, it is often helpful to discuss the choice of trial outcomes with regulators and/or policy-makers. Use of standardized core outcome sets (that is, the minimum outcomes that should be measured and reported in all clinical trials of a specific condition, reflecting outcomes relevant to decision-makers and patients) should be considered for all trials, to enable the results of studies being compared, contrasted and combined (for example, in later meta-analyses) as appropriate. Outcomes may include physiological measures, symptom scores, participant-reported outcomes (PROMs) *(66)* (that is, measurement tools that patients use to provide information on aspects of their health status that are relevant to their quality of life, including symptoms, functionality, and physical, mental and social health), functional status, clinical events or use of health care services. The way in which these are assessed should be sufficiently robust and interpretable (for example, clinically validated in a relevant context, particularly for surrogate outcomes given their potential limitations *(67)*).

**Why this is important.** The ways by which the consequences of the intervention are measured should be sensitive to the expected effects of the intervention and appropriate to the study question, and in general should be applicable and clinically or scientifically meaningful for the relevant population. The choice of outcomes may vary depending on the extent of prior knowledge of the effects of the intervention (for instance, early trials may assess the effects on imaging and laboratory markers whereas later trials study the effects on clinical outcomes) or change over time according to the changing epidemiology of a condition (for example on account of pathogen mutation and associated impact on clinical effects). It is rarely possible or desirable to assess the full range of potential outcomes in a single trial. Instead, there should be a focus on providing a robust answer to the specific, well-formulated question that can have impact on patients and policy. Use of core outcomes can both enhance the ability to undertake meaningful comparisons as part of evidence synthesis and decrease research waste. Several initiatives for the use of core outcomes already exist for both disease-agnostic and disease-specific outcomes, including the International Consortium for Health Outcomes Measurement *(68)*, Core Outcome Measures in Effectiveness Trials *(69)*, Standardized Data Collection for Cardiovascular Trials Initiative (70), Standardised Outcomes in Nephrology *(71)*, and the International Alliance of Mental Health Research Funders' Common Measures in Mental Health Science Initiative *(72)*.

### 2.1.8 Proportionate, efficient and reliable capture of data

**Key messages.** Data collection should focus on the key aspects needed for assessment and interpretation of the trial results as specified in the protocol and should not be excessive. The extent to which information (for example, on participant characteristics, concomitant treatments, clinical events and laboratory markers) is detected and recorded, and the means and level of detail to which this is done, should be tailored to each clinical trial. In general, data collection should be kept to the simplest level possible to answer the question, and collecting non-essential variables should be avoided.

Tools and methods for data collection, storage, exchange and access should enable the trial to be conducted as designed, support privacy and security, and enable reliable and consistent analyses. Digital

technology and routine collection of health care data can provide alternative or complementary means to record information about participants and their health at study entry, during the intervention and follow-up period, and for many years beyond, where available and appropriate.

**Why this is important.** The volume, nature and level of detail of data collection should be balanced against its potential value. Disproportionate data collection wastes time and resources. It places an unnecessary burden on trial participants and staff, distracts attention from those aspects of the trial that have greatest consequence for the participants, and reduces the scale (number of participants and duration of follow-up) of what is achievable with available resources. In some trials, it may be appropriate to measure some features (for example, intermediate biomarkers) in a subset of participants, chosen on the basis of baseline characteristics or random selection, or at a limited number of timepoints. The choice of method used for data collection can have an important bearing on trial reliability and feasibility. Use of data standards (for example, the Clinical Data Interchange Standards Consortium Study Data Tabulation Model [CDISC SDTM] *(73)*) can help to ensure data quality and data integrity, as well as to facilitate potential meta-analysis and data sharing. Use of digital technology and routinely-collected health care data can improve the relevance and completeness of information collected (for instance, by reducing loss to follow-up) as well as reduce the burden on those conducting the trial and its participants, provided that the data are used appropriately.

### 2.1.9 Ascertainment of outcomes

**Key message.** Processes for ascertaining study outcomes should adopt an approach that is not influenced by the intervention trial participants or randomized groups receive. These measures include the frequency and intensity of assessments. For RCTs, particular care should be taken to ensure that the people assessing, clarifying and adjudicating study outcomes are not influenced by knowledge of the allocated intervention (that is, the outcome assessment is blinded or masked). Equally, the methods for acquiring, processing and combining sources of information (in order, for example, to define participant characteristics or clinical outcomes) should be designed and operated without access to information about the intervention allocation for individual participants or knowledge of the unblinded trial results.

**Why this is important.** If the methods used to assess, clarify or classify outcomes differ between the assigned interventions, the results may be biased in one direction or other leading to inappropriate conclusions about the true effect of the intervention. Therefore, the approach used to assess what happens to participants should be the same regardless of the assigned intervention, and those making judgements about the occurrence or nature of these outcomes should be unaware of the assigned intervention (or features, such as symptoms or laboratory assays, that would make it easier to guess the assignment) for each participant.

### 2.1.10 Statistical analysis

**Key messages.** The trial should be designed to robustly answer a clearly articulated key question on which the primary analysis should focus. It is not good practice to seek to answer multiple questions through secondary analyses, which can often be misleading. Trial results should be analysed in accordance with the protocol and statistical analysis plan, with the latter being developed and clearly specified when the protocol is written, and finalized at the latest before the study results become known (that is, before conduct of any unblinded analyses on study outcomes). Any analyses conducted after the initial results are known should be clearly identified as such *(8)*. For RCTs, the main analyses should follow the intention-to-treat principle, meaning that outcomes should be compared according to the intervention arm to which the participants were originally allocated at randomization, regardless of whether some of those participants subsequently received some or none of the intended intervention, and regardless of the extent to which the post-randomization follow-up procedures were completed.

Subgroup analyses should be interpreted cautiously, with due consideration given to prior understanding of disease mechanism, especially if they are not prespecified or are multiple in number (whether

prespecified or not). In general, any prognostic features that are to be used in analyses of intervention effects in clinical trials should be irreversibly recorded or identified before randomization. Reporting on data disaggregated by sex (consistent with the Sex and Gender Equity in Research [SAGER] guidelines) *(74)* can be valuable. Any findings should be interpreted with respect to other existing evidence and clinical context.

**Why this is important.** A statistical analysis plan should be specified before any knowledge of the trial results (for example, unblinding of the treatment allocation in a RCT) in order to avoid the possibility that choices about the analysis approach may be biased *(8)*. For RCTs, a particular strength is the existence of a randomized control group with which to compare the incidence of all health events. Consequently, it is possible to distinguish those events that are causally impacted by allocation to the intervention from those that are part of the background health of the participants. Analysing all participants according to the intervention to which they were originally allocated ("intention-to-treat" analysis) is important because, even in a properly randomized trial, bias can be inadvertently introduced by the post-randomization removal of certain individuals from analyses (such as those who are found later not to meet the eligibility criteria, who do not adhere to their allocated study treatment or who commence an active intervention having been allocated to a control group) if the reason for removal might have been influenced by the treatment allocation. Additional analyses can also be reported; for example, when the frequency of a specific side-effect is being described, it may be justifiable to analyse its incidence only among those who received the active intervention, because randomized comparisons may not be needed to assess large effects. However, in assessing moderate effects of the treatment, "on-treatment" or "per protocol" analyses can be misleading, and intention-to-treat analyses are generally more trustworthy for assessing whether there is any real difference between the allocated trial interventions in their effects.

One of the most important sources of bias in the analysis is undue concentration on just part of the evidence (such as selective emphasis on the result in one subgroup or subsidiary outcome out of many that is defined after consideration of the data). Apparent differences between the therapeutic effects in different subgroups of study participants can often be produced solely by the play of chance. Subgroups therefore need to be relevant, prespecified and limited in number. Analysis of results in subgroups determined by characteristics observed after randomization should be avoided because, if the recorded value of some feature is (or could be) affected by the trial intervention, then comparisons within subgroups that are defined by that factor might be biased. It is important to interpret results in specific subgroups (for example men and women) cautiously and consider whether they are consistent with the overall result. Failure to do so can lead to people in those subgroups being treated inappropriately (given an intervention that is ineffective or harmful) or untreated inappropriately (not being given an intervention that would benefit them) when there is no good evidence that the effect varies between them. Although a sound statistical approach is critical in clinical research, it is equally important to focus on the clinical magnitude and relevance of any effect size rather than solely its statistical significance *(75–78)*, as well as any new findings in the context of previous findings (for example, using the Grading of Recommendations Assessment, Development and Evaluation [GRADE] approach*(79)*).

### 2.1.11 Assessing beneficial and harmful effects of the intervention

**Key messages.** Data generated during the course of conducting a clinical trial may reveal new information about the effects of the intervention which is sufficiently clear that it necessitates alteration of the ways in which the trial is conducted and participants are cared for or which is sufficiently compelling as to warrant a change in the use of the intervention both within and outside the trial. Potential harms of the intervention should be considered alongside potential benefits and in the wider clinical and health contexts.

**Why this is important.** Not every health event that happens in a trial is caused by one of the interventions; individuals involved in a trial may suffer health events that have nothing to do with the trial or the interventions being studied. (The less

healthy the participants in the trial, the more likely that any health event is related to factors other than the intervention.)

Assessing whether signals (for example, rates of clinical events or laboratory abnormalities) seen among those allocated to receive a health intervention are significantly more or less frequent than in a control group (where applicable) provides a reliable assessment of the impact of the intervention. It provides a fair assessment of which events are causally impacted by allocation to the intervention compared with those that are part of the background health of the participants. In an ongoing trial, such unblinded comparisons should be conducted by a group (such as a data monitoring committee, also known as a data and safety monitoring board) that is independent (or protected by a firewall) from the trial team to avoid prematurely unblinding the emerging results to those involved in running the trial.

By contrast, reports of individual events that are believed (for instance, by the participant or a doctor) to be caused by the intervention are much less informative, owing to the lack of a comparison with the incidence of the event in any control group and the inherently imprecise judgement of causality. The exceptions are events that are rare in the types of people involved in the trial but known to be potentially strongly associated with particular interventions (for example, anaphylaxis or bone marrow failure in association with medicines), which can be viewed as events of special interest for reporting and analysis. Depending on the type of trial, the degree of knowledge of the intervention(s) and the population in which they are being studied, the protocol may specify certain events that require, or indeed do not require, to be collected and recorded. Equally it may specify which recorded events might be expected to occur in the population of interest and hence which may not require reporting in an expedited manner.

Effects of health interventions may differ (they may be harmful or beneficial) and follow different time courses, and may occur at different frequencies and in particular groups of individuals. Some interventions (such as surgery or chemotherapy) may be associated with little or even a hazardous effect in the short-term but provide longer-term benefit. It should also be recognized that for many interventions the benefits may not be apparent on an individual basis, such as where a detrimental outcome has been prevented (for example, a stroke or infection).

### 2.1.12 Monitoring emerging information on benefits and harms

**Key messages.** An independent data monitoring committee provides a robust means to evaluate safety and efficacy data from an ongoing trial, including for RCTs unblinded comparisons of the frequency of particular events, without prematurely unblinding any others involved in the design, conduct or governance of the trial. For many clinical trials, particularly in early-phase trials, the functions of a data monitoring committee could be provided internally from the entity running the trial, but those involved should nonetheless be rendered independent by being adequately protected by a firewall from the trial team to ensure that awareness of results does not introduce bias (or the perception of bias). Use of a charter that details the structure and organization of the data monitoring committee can promote transparency and facilitate such committees to operate more effectively. Some trials may not require a data monitoring committee (for example, if the trial is short-term and would not be modified regardless of interim data), although they may still benefit from some form of independent oversight.

A data management committee (DMC) should include members with relevant skills to understand and interpret the emerging safety and efficacy data, and where appropriate take into consideration patient and public perspectives. A DMC should review analyses of the emerging data, unblinded to any randomized intervention group so as to be able to make informed decisions given knowledge about the potential adverse effects of a specific treatment (which would not be possible if they were not unblinded). The DMC should advise the trial organizers when there is clear evidence to suggest a change in the protocol or procedures, including cessation of one or more aspects of the trial. Such changes may be due to evidence of benefit or harm or futility (where continuing the trial is unlikely to provide any meaningful new information). In making such recommendations, a DMC should take account of both the unblinded analyses of the trial results and

information available from other sources (including publications from other trials).

**Why this is important.** All those involved in the design, conduct and oversight of an ongoing trial should remain unaware of the interim results until after the conclusion of the study so as not to introduce bias into the results (as in the case, for example, of stopping the trial early when the results happen by chance to look favourable or adverse). The requirement for, and timing and nature of, any interim analyses should be carefully considered so as not to risk premature decision-making based on limited data.

## 2.2 Good clinical trials respect the rights and well-being of participants

Ethical clinical trials *(12–14)* combine the search for answers to important questions with scientific validity and appropriate protection and respect for all involved, particularly participants. Independent review of proposals for new research, through an institutional review board (IRB), research ethics committee (REC) or equivalent is an important governance tool and can help to ensure appropriate steps are taken to protect the rights and welfare of participants.

### 2.2.1 Appropriate communication with participants

**Key message.** At all stages of a clinical trial (before, during and after), relevant, easily-understandable information should be shared with trial participants (or, where applicable, their legal representatives), with a careful balance of the duty to inform against the risk of information saturation and account being taken of the clinical context. Information should be provided in a clear manner and in suitable languages and formats for the intended audiences. Co-developing and piloting such clinical trial information with target populations is valuable.

The most important information for participants' decision-making should be clearly highlighted and excessive length of information materials and consent forms should be avoided.

**Why this is important.** Providing timely and relevant information to participants during a trial facilitates ethical research with benefits to both the participants and the quality of the trial results. It is essential that potential or recruited trial participants are appropriately informed, but presenting excessive or exhaustive detail can work against this objective by overwhelming, confusing or disconcerting potential participants. Care should be taken to communicate effectively and enable relevant discussion, taking into account accessibility (for example, to those who are illiterate). In some circumstances it can be helpful to provide information in visual, audio, animated or interactive computer-based formats. The exact approach may be influenced by the context of the research, including clinical, cultural or other issues. At the end of the trial, the key results should be made available to participants in a form that is accessible and understandable. As specified in Section 2.3.1, the development of clinical trial information in partnership with patients, the public and communities can facilitate the inclusion of diverse populations.

### 2.2.2 Relevant consent

**Key messages.** The trial consent process should clearly explain to potential trial participants (or, where applicable, their legal representatives) the reasons why the trial is being done, the questions it is seeking to answer, what is involved for them, and the potential benefits and risks of participation *(12)*. Where appropriate, this should include an assent process for those lacking capacity to give full consent such as children and minors *(56)*. The extent, nature and timing of information provided before and during the informed consent process should be guided by the level of additional risks and commitment that participation in the trial would involve in the context of the usual clinical care or circumstances that the same individuals would normally receive. The information provided should prioritize the needs and expectations of the prospective participant rather than those of the organization or individuals conducting the trial. **Consent information should be widely accessible and readily understandable (for example, with respect to readability), avoid legalistic or other technical language, and be as succinct as possible.** Approaches to obtaining and maintaining ongoing

consent and communication should be relevant to the trial it relates to, with due consideration given to cultural and community contexts. Where appropriate, electronic consent mechanisms may be used *(80)*. The consent process should facilitate optimal use of data where possible through inclusion of wording that allows for appropriate and relevant future application of data or for use of biological samples in research *(13)*. Where co-enrolment in another clinical trial is not possible this should be scientifically justified. Where payment for clinical trial participation is offered, this should also be explained and justified. Conversely reimbursement for costs incurred by participants is a broadly accepted practice in many contexts and should be distinguished from payments to participate.

**Why this is important.** Consent is valid if it is informed, voluntary and competently given before entry into a trial. There are some situations in which an individual cannot give informed consent (for example, for infants, minors or individuals lacking decision-making capacity, in which case consent should be obtained from the participant's guardian or legally authorized representative) or it is not practical to do so because of the urgency of the medical situation (for example, in cases of trauma or medical emergencies, in which case consent should be sought later in the trial if and whenever the participant recovers the capacity to consent or from their guardian or legally authorized representative once they are available). For some trials and in some individual situations, explicit consent may be modified or waived *(14)*. In such cases, there should be minimal additional risks and burdens to participation in comparison to the usual care a prospective participant might receive outside the trial. Waivers or modifications of informed consent may also be necessary in some clinical trials in which the intervention is directed at an entire community (cluster randomized trials), making it impossible to avoid the intervention. Such situations should not automatically preclude the conduct of clinical trials (which may be the only way to provide reliable information on how best to manage such health issues) but appropriate safeguards should be put in place to maintain the rights of the individuals who participate. Electronic consent processes may improve trial efficiency (for example, to facilitate decentralized approaches or point-of-care designs). Data from clinical trials should also be used to optimal efficiency to minimize potential waste of research resources. Being in one clinical trial should not necessarily automatically preclude being in another. Similarly, based upon the principle of clinical equipoise, participation in a clinical trial should not unduly penalize trial participants seeking insurance (for example, travel or medical) without a firm scientific rationale for this to be the case. Although it can be justifiable to reimburse those taking part in clinical trials for their time and commitment, care should be taken to ensure careful balance against undue influence.

### 2.2.3 Changing consent

**Key message.** Participants should be free to stop or change the nature of their participation without affecting the usual care received. Where possible and acceptable to the participant, efforts should be made to determine the intended meaning of such individual decisions and to explain the potential impact of any such decisions.

**Why this is important.** It is the right of participants to change their mind about whether they wish to continue in the trial at any point, but it should be noted that the term "withdrawal" can mean different things to different people. The meaning can range from wanting to stop receiving the study intervention to stopping attending study visits in person (but perhaps be happy to be contacted or for information about their health outcomes to be collected from their regular doctors or from routine health data systems) to having their biological samples no longer assayed or stored or their data no longer being processed or shared. Therefore, it is clearer to avoid the term and instead try to clarify with the participant(s) what level of participation they want to have and what they want to cease. If this is not properly explored and the withdrawal is interpreted with prejudice to mean complete removal from the study, trial participants may be unnecessarily and inadvertently lost to full or partial follow-up, with possible implications for the reliability of trial findings, and may miss out on aspects of the clinical trial that matter to them (such as attendance at study visits or being informed about progress and results of the study).

### 2.2.4 Implications of changing consent

**Key message.** The rights of an individual participant to change or withdraw consent for use of trial data should be balanced against scientific and ethical requirements.

**Why this is important.** Removing data can result in unreliable or inconclusive findings, with ethical and clinical safety consequences for both participants continuing in the trial and the care of future patients. (For example, important safety signals may be missed.) It can be appropriate to make data that have already been collected available for analysis in order to demonstrate or preserve research integrity. Those involved in a trial and those whose care may be influenced by its results should be able to be assured that the data are valid and that they have not been modified through inadvertent, deliberate or malicious means.

### 2.2.5 Managing the safety of individual participants in the clinical trial

**Key messages.** Detection and management of safety of trial participants should be tailored to the trial population and to what is already known about the intervention. Such approaches may be modified as new information emerges (for example, from other trials or clinical studies in the relevant population). In some circumstances it may be appropriate to exclude some groups of individuals from a trial if the likely risk to their health is excessive (compared with potential gain) and cannot be mitigated by reasonable clinical strategies. For some blinded trials, there may be occasions when knowledge of the allocated intervention for an individual participant could materially influence the immediate medical management of the participant. In such circumstances, it should be possible for the treatment allocation to be unblinded and disclosed to the relevant medical team without delay.

**Why this is important.** The procedures used to detect, investigate and respond to unwanted health events for individual participants should be shaped by what is already known about the effects of the intervention from previous research or usage, as well as the background epidemiological and clinical features of the intended trial population (for example, their demographics, comorbidities and any concomitant intervention). If new information emerges during the course of the trial (for example, from other studies or as a consequence of advice provided by a trial's data monitoring committee) then processes and procedures for managing the safety of individual participants should be reviewed and may need to be modified (for example, by changing the nature and timing of assessments, providing training to trial staff, providing information to participants or amending the eligibility criteria for the trial).

### 2.2.6 Communication of new information relevant to the intervention

**Key message.** During an ongoing trial, new information may become available (from within the trial or external sources) that materially changes what is known about the effects of the intervention for some or all participants. This information should be communicated to those involved in overseeing, conducting or participating in the clinical trial for whom it is relevant (for example, because it might affect their understanding of the intervention or because they are required to take some action). Such communications and reports should be informative, timely and actionable.

**Why this is important.** Excessive, irrelevant or uninformative reports (particularly of individual cases) distract attention from those that require action. It is often preferable to produce and circulate contextualized periodic updates that are focused on safety issues that matter. Such reports may also be provided to the data monitoring committee (for consideration in the context of the unblinded emerging trial data) and to regulatory bodies (for consideration of the implications for participants in other trials and for the wider group of patients and public). The distribution of reports should be in a format and timing that is commensurate with the action that is likely to be needed and the audience for which it is intended (for example, participants, clinicians and regulators).

## 2.3 Good clinical trials are collaborative and transparent

All those involved in clinical trials share responsibility for building and sustaining the trust of collaborating partner organizations and clinical communities, participants and the wider public. Trust is undermined when clinical trials are not sufficiently relevant, fair, transparent and respectful of the rights, interests, concerns and values of all involved (especially those people who participate in them or whose care will be influenced by the results).

### 2.3.1 Working in partnership with people and communities

**Key message.** Potential participants and/or members of the relevant community provide valuable contributions to the design, execution and interpretation of the results of clinical trials.

**Why this is important.** The early involvement of a diverse range of patients and relevant members of the public can play a key role in: defining, refining and prioritizing research questions; assessing and increasing the acceptability and feasibility of the trial *(81)*; selecting trial interventions and outcomes that are relevant and meaningful to the intended population; developing the trial design and procedures; optimizing the nature and delivery of information; and encouraging dialogue about access to health care interventions that prove effective. **Working in partnership with people and communities is likely to increase trust and confidence while decreasing the risk of important groups being excluded or the needs of local populations or sectors being overlooked or misunderstood.** All relevant stakeholders should have the opportunity to learn, raise concerns and provide input into planning and implementation. To ensure broad representation, efforts should be made to ensure appropriate diversity in any such patient and community involvement.

### 2.3.2 Collaboration among organizations

**Key message.** It is important that interactions between individuals in different organizations involved in clinical trials, including those in resource-rich and resource-limited settings and among commercial, academic and health care sectors, are fair and respectful of the interests, concerns and values of all involved, including trial participants and the communities from which they come. Working collaboratively with partners and networks (whether local, national or international) (see Section 3.2.2) to consider which features of a clinical trial are critical to its quality and supporting a delivery approach that is appropriate to the setting and context can enhance a trial's resilience and efficiency.

Why this is important. Collaborative working leads to the sharing of ideas and expertise, helps to avoid misaligned approaches or substantially different priorities, and can build capacity, maximize use of resources and increase efficiency.

### 2.3.3 Transparency

**Key messages.** Clinical trials should adopt an "open science" approach wherever possible. This encompasses transparency being fostered in numerous aspects of clinical trials:

- **Registration.** Clinical trials should be registered from the outset on a publicly-available registry of clinical trials (for example, the WHO registry network *(44)*) in accordance with the WMA Declaration of Helsinki *(12)*. Where trial registries allow, they also should be updated with trial outcomes in a timely manner, even if the trial was stopped prematurely or did not meet its objective(s).

- **Trial materials.** Making other information about a trial (including its protocol and other documentation such as the statistical analysis plan) publicly available is strongly encouraged.

- **Trial reports.** Once the trial is completed, reports should be made available in a timely manner on a publicly available clinical trial registry and/or in a peer-reviewed journal (typically within 12 months but sooner, for instance, as a preprint, in public health emergencies) and should comprehensively describe the study design, methods and results in a clear and transparent manner, regardless of the trial's findings *(82)*. Negative findings are as important to report

as positive ones. Trials should be reported following established guidelines where possible (for example, the Consolidated Standards of Reporting Trials [CONSORT] guidelines for RCTs *(83, 84)*) preferably in open-access peer-reviewed publications in the context of other relevant evidence. It can be helpful for reports to be available in formats that enable both professional and lay readers to understand and interpret the results. Reporting results to participants and to the public requires different approaches from reporting results to the clinical and scientific community.

- **Trial funding.** Sources of trial funding as well as declarations of any possible conflicts of interest by those involved in designing, conducting or reporting trials should be easily accessible.

- **Data sharing.** This should be enabled at a suitable time if ethical, feasible and scientifically appropriate, with due consideration given to data protection and privacy. A data management and sharing plan should be developed in line with WHO data-sharing principles *(85)* of being effective, ethical and equitable, as articulated in the WHO policy on research data sharing.

**Why this is important.** Transparency and sharing of knowledge about health care interventions help to generate further knowledge, build and maintain trust and give confidence to both those involved in the trial and those who are not. Trial registration *(86)* can aid in the identification of gaps in clinical trials research, makes researchers and potential participants aware of recruiting trials (which may facilitate recruitment) and fosters more effective collaboration among researchers (including conducting prospective meta-analysis), and the process may lead to improvements in the quality of clinical trials. **Timely communication of the trial results (regardless of what those findings are) is vital to guide future research, reduce unnecessary duplication of effort (which wastes resources) and enable care to be guided by an up-to-date evidence base.** Good communication can also support wider efforts to foster potential collaborations and increase informed participation in clinical trials. Transparency of research communicated in a range of formats so as to make them widely accessible to patients, communities and the public is vital to foster public confidence about safety, quality and effectiveness of interventions and combat misinformation which is detrimental to public health.

## 2.4 Good clinical trials are designed to be feasible for their context

Ensuring that a trial is set up to be practicable and produce reliable, actionable results is an important scientific and ethical duty. Consideration of the context and existing resources in a proposed trial setting can better ensure effective trial design.

### 2.4.1 Setting and context

**Key message.** The design and implementation of clinical trials should recognize and be shaped by the characteristics of the settings in which they take place, including the health needs and preferences of communities, their ability to access to health care and their understanding of clinical trials, as identified through appropriate involvement, consultation and engagement with a diverse and inclusive range of patients and public.

**Why this is important.** These characteristics, alongside the nature and complexity of the research, are crucial to identification of the ethical issues at stake and the issues, burdens and benefits of running the trial in that setting. Relevant and accessible clinical trials are more likely to recruit a sufficient number of trial participants. Good patient and public involvement and education across the relevant communities help to shape successful recruitment and subsequent adoption of the results.

### 2.4.2 Use of existing resources

**Key messages.** Clinical trials should be tailored to be practicable given the available infrastructure in relevant settings. This planning includes making optimal use of pre-existing resources and facilities, including the expertise, skills, professional standards and quality oversight mechanisms associated with routine health care practice while not unduly hampering such routine care. All individuals involved in performing a trial should be qualified by

education, training or experience to perform their respective task(s), but it should be recognized that many aspects of conducting a clinical trial are in line with routine care and therefore may not require additional training, procedures or checks. Training or mentoring the existing local health workforce and dedicated researchers are both needed. Training of health workforce members to participate in research should be differentiated from training of dedicated researchers to lead research.

**Why this is important.** Clinical trials should not be wasteful of staff and participants' time, use of interventional or other medical supplies, energy or environmental resources. Existing strengths and safeguards in routine systems should not be duplicated or altered without careful justification. The closer trial processes are to routine practice (for participants and staff), the more efficiently and effectively they are likely to be executed, the fewer mistakes are likely to be made, resulting in improved quality.

## 2.5 Good clinical trials manage quality effectively and efficiently

The design and conduct of a high-quality trial require competent decision-making and coordinated execution. Good governance and good trial quality management can help to achieve these features.

### 2.5.1 Good governance

**Key message.** Clinical trials should be subject to sufficient scrutiny to support completion of informative, ethical and efficient studies and to avoid, correct or mitigate problems.

**Why this is important.** Effective and efficient governance (for example, through a trial steering committee) helps to maintain the scientific and ethical integrity of a trial and to provide advice on appropriate courses of action. It should be structured to enable both effective responses to issues that may arise, particularly when multiple organizations are involved, and reasonably consistent implementation across the trial.

Membership of trial governance structures should reflect the expertise necessary to scrutinize key roles, responsibilities and risks, and should build on the diverse strengths and capabilities of those involved. The need for a member or a component of the governance structure to have independence from trial sponsorship and management should be determined by assessing the risk that judgement and advice could be materially influenced (or perceived to be influenced) by the relationship.

Governance approaches should account for the opportunity cost of associated activities by considering the extent to which they might impede participants and communities from benefiting from an effective intervention or prolong the time an ineffective or hazardous intervention remains in use. Prolonged or excessive governance activities, which drive up unnecessary costs, deter trial designs of sufficient size or duration or discourage clinicians and participants from being involved, should be avoided.

### 2.5.2 Protecting trial integrity

**Key message.** The integrity of the results of a clinical trial should be protected by ensuring that decisions about its design, delivery and analysis are not influenced by premature access to unblinded information about the emerging results. Interim analyses of unblinded data on study outcomes should not be performed unless prespecified in the protocol or statistical analysis plan or conducted by the data monitoring committee.

**Why this is important.** Unscheduled reviews of unblinded data on study outcomes provide an unreliable assessment of the overall benefit-to-risk profile of the trial interventions. Prejudgment based on overinterpretation of interim data can affect recruitment, delivery of interventions and follow-up, risking the ability of the trial to achieve its goals *(87)*.

### 2.5.3 Planning for success and focusing on issues that matter

**Key messages.** Good quality should be prospectively built into the design and delivery of clinical trials, rather than relying on retrospectively trying to detect issues after they have occurred (when often they

cannot be rectified). Such trials should be described in a well-articulated, concise and operationally-viable protocol that is tailored to be practicable given the available infrastructure in relevant settings.

**Why this is important.** Rather than trying to avoid all possible issues, the aim should be to identify the key issues that would have a meaningful impact on participants' well-being and safety or on decision-making based on the trial results. Efforts should then be focused on minimizing, mitigating and monitoring those issues. Such an assessment should consider the context of the clinical trial and what is additional or special about it by comparison with routine care. Broadly, these considerations come under four headings:

(a) factors associated with the intervention (for example, known and potential adverse effects; comorbidities or concomitant medications that might impact safety; special requirements for administering the intervention)

(b) factors associated with evaluations required to reach the study objective that would not be expected in usual care (for example, additional invasive investigations)

(c) resource implications (for example, need for specialist imaging or laboratory assays; unfamiliar or novel procedures requiring additional training)

(d) ethical and privacy implications (for example, access to medical records and sharing of health information with pharmaceutical companies, researchers or regulators).

Such an assessment process should then be used to guide the development of approaches to mitigate errors, such as standard operating procedures, training and trial monitoring. Trial processes that add scientific or ethical value to clinical trials should be prioritized, and those that do not, or where the additional complexity outweighs the benefit, should be avoided.

### 2.5.4 Monitoring, auditing and inspection of study quality

**Key message.** The nature and frequency of any trial monitoring, auditing and inspection activities should be proportionate to any identified risks to study quality and the importance to the trial of the data being collected.

**Why this is important.** Good trial monitoring, auditing and inspection activities identify issues that matter (important deviations from the protocol or unexpected issues that threaten to undermine the reliability of results or protection of participants' rights and well-being) and provide an opportunity to further improve quality (for example, through modifications to the protocol and procedures, training and mentoring of staff, or information provided to participants). Excessive monitoring, auditing and inspection activities and failure to focus on details that have a material impact on trial quality waste resources, create distraction and demotivate staff.

**Rational monitoring takes a risk-based proportionate approach and focuses on the issues that will make a material difference to the participants in the trial and the reliability of the results** (for example, trial recruitment, adherence to allocated intervention, blinding and completeness of follow-up). It informs corrective actions, supports staff and enables improvements. It is important not to confuse more documentation with better quality. Examples of approaches that may be used include central review (including statistical analysis) of trial data and performance metrics to assess performance of staff and sites, in person or virtual support and mentoring for trial staff (for instance, through observation of study visits, with participants' consent), and visits to clinical trial sites and facilities.

Regulatory, auditing or inspection requirements should be proportionate and sensitive to the scientific and ethical qualities and objectives of a clinical trial. They should recognize the opportunity cost of, and avoid, setting irrelevant or disproportionate requirements that might discourage the conduct or participation in good clinical trials that are designed to address important questions.

# 3. Guidance on strengthening the clinical trial ecosystem

A village health volunteer gives advice to a patient at Koo Bang Luang's health promotion hospital, on 17 July 2020.

# 3. Guidance on strengthening the clinical trial ecosystem

The World Health Assembly in resolution WHA75.8 (2022) on Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination requested WHO's Director-General to identify and propose best practices and other measures to strengthen the global clinical trial ecosystem and to review existing guidance and develop new guidance as needed on best practices for clinical trials. However, the resolution does not provide a definition of the clinical trial ecosystem, and currently there is no consensus on what this should be. The Director-General therefore invited inputs on how such an ecosystem should be defined during a public consultation in October–November 2022. Although a universal definition was not established, in addition to aspects related to clinical trial design, conduct and reporting (discussed in Section 2) there were calls to include a holistic view of the ecosystem that included the following elements related to trials:

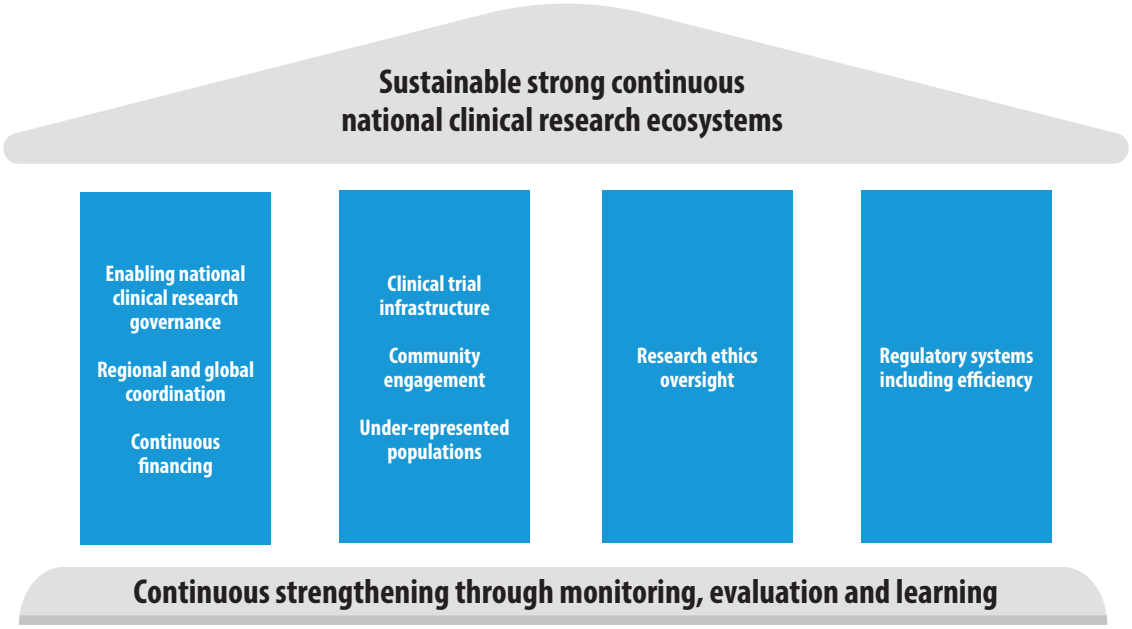
- public, patient and community involvement
- the need for long-term support, sustainability and ongoing capacity-building, particularly in resource-limited settings and LMICs
- equity and justice, with a particular focus on under-represented populations and countries with a high burden of illness
- sustained approach to funding and a shift away from "project-by-project" clinical trials infrastructure
- oversight by and liaison with regulatory bodies, ethics committees, health technology assessment authorities and other relevant national authorities
- local, national and international coordination and collaboration, with equitable and inclusive research partnerships
- sharing of practices, lesson learned, expertise and resources
- the perspective of those conducting systematic reviews, meta-analyses and developing evidence-based guidelines
- implementation research
- the need for clinical trials and evidence-based care to be more culturally embedded in society.

These inputs have fed into the guidance presented in this document and resulted in a potential model for an ecosystem involving four pillars (see Figure 1) and multiple cross-cutting themes as described in the following sections.

## 3.1 Clinical trial ecosystem pillars

**All parties should support local ownership and leadership in clinical research as part of equitable research partnerships** *(88)*. Efficient high-quality clinical trials require the relevant parties involved to engage proactively in research-priority setting, capacity strengthening through sustainable long-term funding and ensuring an enabling environment for clinical research. Research programmes and their funding should be informed by not only national but also regional and global health research priorities, and there should be mechanisms to update priorities quickly as new health problems emerge. Optimal streamlining and coordination of clinical trial approval processes are vital, and there should be an adoption of single multiagency clinical trial approval and oversight in conjunction with flexible risk-proportionate processes.

**Figure 1. Clinical trial ecosystem pillars**




*Source*: Moorthy V, Abubakar I, Qadri F, Ogutu B, Zhang W, Reeder J, et al. The future of the global clinical trial ecosystem: a vision from the first WHO Global Clinical Trials Forum. The Lancet. 2024 Jan 13;403(10422):124–6 (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)02798-8/fulltext).

Clinical trials that address relevant questions can only be enabled if all relevant parties work together with national governmental coordinating authorities for health research to agree and adequately fund research priorities. Harmonized clinical trial approval processes minimize unnecessary duplication, reduce delays and improve efficiency.

**Four key pillars for the ecosystem to achieve these aims are:**

- **clinical research governance, funding and policy frameworks**
- **regulatory systems**
- **ethical oversight**
- **clinical research infrastructure.**

### 3.1.1 Clinical research governance, funding and policy frameworks

#### (a) Setting of research priorities

As explained in Section 1.5.1, identification of a relevant research question is of paramount importance. In setting research priorities, national government authorities coordinating health research should consider the main drivers of local disease burden and patient and community perspectives, but also how any proposed plans align with wider regional and international goals so as to maximize coordinated use of available resources and hence minimize waste.

It can be particularly beneficial for coordinating authorities to maintain active links with other national and international clinical research organizations in this context. Mapping evidence and identifying gaps may also be helpful. Notably, WHO has a key role in developing global health research priorities, having issued guidance for their development, *(89)* and regional health priorities are often set by regional organizations in liaison with WHO. Foreign stakeholders seeking to conduct clinical trials in a country should also seek to align their plans with national and regional health priorities and coordinate their work with national health research authorities. Conversely, where clinical trials are aligned with global priorities, such national authorities have some responsibility to avoid unnecessary bureaucracy or inefficiencies in enabling such trials. Trials for the purpose of local registration of interventions already registered in other jurisdictions should only be done if there is a solid scientific rationale for their conduct.

Rapid priority setting is particularly important in public health emergencies, as highlighted in resolution WHA75.8 (2022).

### (b) Funding of clinical trials

Increased sustained investment and funding nationally, regionally and internationally are paramount for clinical trial progress. Designated national funding is particularly vital, as there needs to be a commitment to invest in domestic infrastructure so that any national base can be built upon globally. Such funding can present immense challenges to LMICs in particular, but domestic investment in clinical research is needed to advance national health priorities. The WHO Council on the Economics of Health For All aims to reframe health for all as a public policy objective and ensure that national and global economies and finance are structured in such a way to deliver on this ambitious goal. *(90, 91)*

This funding should plan to encompass (but not be limited to): trial infrastructure (including both clinical trial facilities and staff; see Section 3.1.4); multiparty training (see Section 3.2.4); support for clinical trial registries (see Section 2.3.3); and development of electronic systems and new methodologies (see Section 3.2.7).

Akin to the approach for setting research priorities, patient and community perspectives must be taken into account, and national health research funders should also ensure that funding is aligned with regional and global priorities, appropriately coordinating with other parties to ensure that calls for funding are synergistic. This coordination can help to avoid duplication and mean that agreed priorities are collectively addressed in an efficient manner. There is currently a lack of funding sources for international clinical trials other than the pharmaceutical industry (which plays a crucial role) and a very small number of international philanthropic or public sector funders. Models need to be developed whereby national funders can prioritize support to the national elements of priority international trials and support the core trial infrastructure. Funders need to coordinate such funding efficiently to reduce the burden that this places on researchers.

It is vital that all funders understand that, despite the importance of seed funding for innovation and the fact that some small trials can be valuable when done in the right context, reliable and adequately sized clinical trials often necessitate substantial sustained long-term financing. Efforts should therefore be made to resist the funding of numerous smaller short-term uninformative projects conducted in isolation at the expense of those that can meaningfully address public health issues and policy. Major benefits result from coordinated mechanisms for funding *(92)*, including public-private partnerships, product development partnerships and, in some contexts, central or global funding mechanisms. Coordinated funding, when done in an agile manner, can hugely enable clinical trials by allowing different research funders to come together to work collectively towards enabling something greater than what any one funder could do. Models for coordination of funders are already available in several disease areas. Examples include: the Global Alliance for Chronic Diseases (GACD) *(93)*, which brings together major international research funding agencies specifically to address the growing burden of noncommunicable diseases in LMICs and underserved groups experiencing health disparities in HICs; the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) *(94)*; the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) *(95)*; the European & Developing Countries Clinical Trials Partnership (EDCTP) *(96)*, which funds clinical research for medical tools to detect, treat and prevent poverty-related infectious diseases in sub-Saharan Africa; and the Ensuring Value in Research (EViR) funders' forum *(97)*, which aims to advance the practices of health-related research and research funding. In the European Union, the Innovative Medicines Initiative *(98)* is an example of a large public-private partnership in the field of life sciences. As detailed in Section 2.3.3, funding of clinical research should also be transparent, for instance being accessible through research investment portals (such as WHO's Global Observatory on Health Research and Development) *(99)*. Such transparency can also help to reduce the waste of research resources and support alignment to research priorities. This consideration may be particularly important for resource-limited settings (for example, by revealing how much funding is apportioned to HICs compared with that to LMICs).

All parties involved in clinical trials have a responsibility to ensure clinical trial quality through adherence to the key design and conduct

principles outlined in Section 2, but funders can also act as gatekeepers for ensuring that this is done by making provision of funding contingent upon it (for example, through use of toolkits for trial assessment in a consistent manner worldwide). This would incentivize trials to be well-designed and well-implemented so that they inform policy and improve health outcomes, rather than focusing solely on the amount of output generated. Strategic allocation of funds could also help funders to target resources at some institutions with lower levels of capacity (but innate potential) rather than merely continuing to fund well-established institutions, which are not always representative of populations that the interventions are intended to benefit.

Clear processes for accelerating transfer of funding for research during public health emergencies should also be in place so as to minimize delays in initiation of critical research. Annex 1 details specific considerations in times of public health emergencies. In considering funding, it is vital to plan for post-trial access to ensure that the resulting interventions are accessible, affordable and equitably distributed, particularly for under-represented populations and those in LMICs. Indeed, the CIOMS ethical guidelines for medical research involving humans *(14)* have long stated the importance of ensuring post-trial access for participants involved in clinical trials, and the TRUST code *(100)* specifies that a culturally appropriate plan to share benefits should be agreed to by all relevant stakeholders and reviewed regularly as the research evolves. This principle should be enhanced and expanded to support global access to health interventions. This planning should start right from the beginning of the R&D process, as waiting until after an intervention is developed provides limited leverage opportunities to negotiate fair conditions for wider access and distribution. This process can be enabled by governments and other funders attaching concrete and enforceable conditions when they support or fund clinical trials.

### (c) Translating research evidence into practice

Health technology assessment agencies and national bodies that develop clinical guidelines should be engaged throughout the clinical trial process. They should liaise with national coordinating authorities for health research, regulators and ethics committees, but also work in partnership with end users (including patients, communities, the public and health care staff/organizations) and build in their perspectives. This cooperation will help to ensure that the formulation of recommendations in guidelines or other policy documents result in translation of clinical trial results into practice, and hence public health benefits.

Use should be made of the extensive resources on evidence-informed decision-making, such as the WHO's Evidence-informed Policy Network *(101)*, which provides guidance on translation of knowledge to health policy-making. This use of knowledge translation resources is important because even when robust evidence exists for or against particular interventions based on high-quality randomized data, it is not always adopted in practice. An example was observed during the COVID-19 pandemic, when some countries witnessed widespread use of interventions for which there was strong evidence of no benefit (such as the use of hydroxychloroquine for treatment of COVID-19). In contrast, an example of appropriate translation of research evidence into clinical practice was the process used to assess the value of administration of antenatal corticosteroids in preventing preterm infant mortality in resource-limited settings. During the development of WHO's guidelines, a research gap was identified because, although these interventions had long been recommended in high-income settings, significant uncertainty remained about the role and potential harm of this intervention in resource-limited settings. To address this question, a group of stakeholders prioritized and implemented a well-designed randomized trial in several countries in Africa and Asia. The trial results were consistent with a meta-analysis of trials conducted in high-income settings, indicating that antenatal corticosteroids reduce preterm infant mortality in both settings. Following best practices, WHO's guidelines were updated to incorporate the trial results and any other recent evidence into the global evidence base, enabling the formulation of global recommendations on the use of antenatal corticosteroids to prevent preterm infant mortality *(102–105)*. This approach exemplified the integration of guideline processes with trial design, implementation and reporting, highlighting the importance of evidence synthesis at the beginning and end of the research process.

### 3.1.2 Regulatory systems

National regulatory authorities (NRAs) typically act as the executive arm for governmental departments of health, with agreements often existing between the two parties to ensure that they work in partnership to serve patients, the public and the taxpayer, and that they discharge their accountability responsibilities effectively.

NRAs are primarily responsible for the regulatory oversight of medicinal products. For example, they are responsible for approval of clinical trial commencement and licensure (marketing authorization) of new medicinal products, helping to ensure that medicines released for public distribution are evaluated properly and meet agreed international standards of quality, safety and efficacy and that the benefit/risk ratio for the medicine is positive in the proposed indication. They also typically perform post-marketing surveillance and adverse event monitoring of established interventions. Some NRAs are mature and extensive, whereas others have much more limited capacity. As such, NRAs are a core component of the research environment, and for clinical trials to fulfil their potential NRAs must be able to robustly and efficiently support clinical trials using risk-based proportionate approaches. In addition to NRAs and ethics committees (see below), further clinical trial approval is sometimes required at a local level by institutional committees.

The WHO Secretariat can provide technical assistance for the development and implementation of NRA strengthening plans including those for the oversight of clinical trials. The WHO Global Benchmarking Tool for evaluation of national regulatory systems for medicinal products *(106)* provides a maturity-level framework for Member States to improve the functioning of their NRAs.

NRAs should act in a timely manner, have clinical trial review competency, be transparent about their document-submission requirements and provide transparency on timelines achieved for clinical trial approval. Procedures should be kept under review and any unnecessary bureaucracy should be eliminated, with approaches and procedures adapting to changes in the clinical trial landscape.
Many clinical trials do not involve generation of data for submission to NRAs. In some health condition areas most trials will not be submitted for marketing authorization approval, where for example behavioural interventions are the focus. It is important that NRAs are only involved for trials within their scope according to the local regulations.

### 3.1.3 Ethical oversight

Ethical considerations cut across all areas of health, as reflected in the wide range of health topics addressed by WHO's ethics guidance. Cornerstone reference documents for appropriate ethical practice in clinical trials include the WMA Declaration of Helsinki (1964, last updated in 2013) *(12)*, the WMA Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks *(13)*, and the CIOMS International Ethical Guidelines for Health-related Research Involving Humans (2016) *(14)*.

At a country level, local research ethics committees (RECs, sometimes known as institutional review boards [IRBs]) review all research involving human participants including clinical trial proposals and have the authority to approve, reject or propose modifications. When appropriate, RECs may also suspend or terminate clinical trials. RECs operate independently and have autonomy to make their decisions. Membership of RECs is multidisciplinary so as to ensure different perspectives, thus including members who may have community or societal perspectives or represent the interests of potential participants.

The WHO Secretariat has launched a tool that is intended to support Member States in evaluating their capacity to provide appropriate ethical oversight of health-related research with human beings *(107)*. In the Region of the Americas, the Pan American Health Organization has issued indicators for strengthening national research ethics systems and a tool for the accreditation of RECs *(108)*.

RECs should act in a timely manner, have clinical trial review competency, be transparent about their document submission requirements, and provide transparency on time taken for clinical trial approval. Procedures should be kept under review, and any unnecessary bureaucracy should be eliminated, with approaches and procedures adapting to changes in the clinical trial landscape.

### Interagency coordination and harmonization

**Given the multiple parties involved in authorizations of multicentre clinical trials, actions should be taken to reduce duplication while ensuring rigorous and prompt authorization processes. For instance, systems of parallel submission to different stakeholders (for example, NRAs and RECs), reliance mechanisms or joint reviews for the authorization of clinical trials may be helpful to promote efficiency.** In tandem, any such systems require adoption of flexible risk-proportionate processes through education and appropriate incentives.

WHO supports efforts to promote efficiency through single REC models for multicentre clinical trials, where appropriate, and encourages further work to advance single REC models.

WHO already encourages regulatory harmonization and good reliance procedures, with good practice being for regulatory authorities to take into account and give significant weight to work performed by other regulators, as appropriate. Given that clinical trials are highly important to evaluate not only medicinal products but also nonpharmacological interventions, pooling expertise into a single national body can maximize use of resources.

Development of such systems can build upon experience of regions which have already fostered them. In the European Union, clinical trial sponsors can use the EU's Clinical Trials Information System *(109)* to apply for regulatory authorization to run a clinical trial in up to 30 countries in the European Economic Area through a single online application, which includes the NRA, REC and trial registration submissions in a single process. Building upon this and the EU's Clinical Trials Regulation, the European Commission, the Heads of Medicines Agencies and the European Medicines Agency have launched an initiative to transform how clinical trials are initiated, designed and run, referred to as Accelerating Clinical Trials in the European Union Initiative (ACT EU) *(110)*. Equally, the Health Research Authority in England is a national strategic research oversight body that promotes coordinated approaches to research review across the United Kingdom of Great Britain and Northern Ireland through its Integrated Research Application System *(111)*. This is a single system for applying for the regulatory and ethics permissions and approvals for research on health and social care/community care in the United Kingdom of Great Britain and Northern Ireland. Another operationally-effective model for coordinated review of clinical trials authorization includes the African Vaccine Regulators Forum (AVAREF) *(112)*. This network's joint review procedure is endorsed by all the countries on the African continent to support R&D and strengthen the capacity of clinical trial oversight. It provides a platform for parallel review by NRAs, national RECs and all relevant local RECs and IRBs of multicountry clinical trial applications, enabling provision of coordinated review to trial sponsors with agreed timeframes for clinical trial approval. Interagency cooperation is also demonstrated by the Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP). This is a regional forum under the umbrella of the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) *(113)* which aims to improve collaboration among ethics committees reviewing health research in that region, being a project of the WHO Special Training and Research Programme in Tropical Diseases (TDR) *(114)*.

The International Coalition of Medicines Regulatory Authorities *(115)* is exploring several approaches to harmonization and collaborative assessments between agencies with the aim of streamlining and improving efficiency and coordination of procedures for multicountry trials, without undermining their quality, safety or ethical aspects. Such models need to be developed further, especially in relation to advancing coordination between RECs, action that will need investment in infrastructure at national, regional and global levels.

The HIV pandemic and epidemics such as those of Ebola or Zika virus disease highlighted the need for more interagency harmonization. In 2020, WHO published detailed guidance on rapid review of research by RECs during public health emergencies *(116)*, and the AVAREF model has been used successfully in such a context. In 2020, based on lessons learned during the outbreaks of Ebola virus disease, AVAREF published a guidance document on strategy and guidance for emergency preparedness *(117)*. This provision was later successfully used for one of the largest multicountry clinical trials in Africa, involving 13 countries and several sponsors. With this emergency provision, three options are

now available for AVAREF joint reviews, with the timelines reflecting the public health impact of the investigational product based on selection criteria.

The emergence of the COVID-19 pandemic further highlighted the particular importance of rapid review of clinical trials submissions and decision-making in public health emergencies of international concern, and as such this topic forms a core component of resolution WHA75.8 (2022). Several initiatives have already been developed to respond to any such situation. In particular, WHO has developed a R&D Blueprint for Epidemics which adopts a proactive approach to bolstering global readiness and response to potential future epidemics and pandemics, with an overarching goal of reducing the time required for the development of safe and effective medical countermeasures, both curative and preventive. The R&D Blueprint includes guidance on rapid review of research by ethics committees during public health emergencies (also see Annex 1) *(118)*. Other initiatives include a US Clinical Trials Infrastructure for Emergencies *(119)* and the 100 Days Mission report to the G7 by the pandemic preparedness partnership which discusses how best to reduce the impact of any future threats *(120)*.

The Healthy Life Trajectories Initiative *(121)* is another example of how interagency cooperation can effectively target and drive high-quality research aligned with country needs. In 2015, national research funding agencies in Canada, China, India and South Africa, with support from the WHO Secretariat, agreed to collaborate and provide support for clinical trials in each country aimed at testing interventions to mitigate the risk of childhood obesity and type 2 diabetes. These trials focused on preconception and pregnancy interventions and their impact on early growth, adiposity and early markers of metabolic disease. As part of the initiative's consortium, research teams harmonized research questions, interventions and data and biospecimen collection, and as such the research initiative embodies how a road map can optimize research investment.

### 3.1.4 Clinical research infrastructure

Efficient high-quality clinical trials require adequate infrastructure, both in terms of physical infrastructure and trial personnel. Where possible, the trials should involve use and optimization of pre-existing resources and facilities, including those associated with routine health care practice, as previously described in Section 2.4.2 so as to minimize research waste, enable the best use of limited funds and ensure that undue complexity is not introduced. Democratization of access to infrastructure can be enabled by joint use of resources. Sharing of expertise is vital; knowledge and capacity-building gained through clinical trial involvement represent an indirect benefit that extends well beyond the knowledge gained by the trial results themselves. This can, for example, support continuity in research and follow-on projects through trial staff, patients and communities becoming familiar with the principles and dividends of evidence-based care.

#### (a) Physical infrastructure

Physical infrastructure for clinical research is highly diverse, covering a range of clinical settings and research facilities, plus the logistical infrastructure necessary to support them. However, two key components of this infrastructure are typically laboratories (a core need for many types of clinical trial, depending on the intervention being assessed) and clinical research institutions and clinical trial units (CTUs). These can be established within public government-funded facilities bodies, academic institutions or the private sector, or function as a result of a partnership between such groups. Physical infrastructure also encompasses use of electronic health care systems and digital technology.

Investment in sustained, cost-efficient laboratory facilities is paramount. Factors to consider in relation to adequate laboratory infrastructure include:

- running costs of equipment
- staff requirements to support use of such equipment
- appropriate laboratory accreditation to ensure ongoing equipment maintenance and calibration (and hence quality)
- access to central/reference laboratories, where applicable, to ensure standardization (for example, for pharmacokinetics and microbiology assessments)

- appropriate sample storage and transportation facilities

- optimal commissioning and long-term maintenance of electronic laboratory systems.

Clinical trials of interventions early in development are a particular example of the need for some specialized laboratory infrastructure. Some African and Asian countries are beginning to conduct such early trials (for example, studies of Ebola virus disease vaccines were done in HICs but also in low-resource communities not experiencing an outbreak *(122)*, and late-stage clinical trials of relevant vaccines are increasingly being conducted in LMICs) *(123)*.

At lower-capacity levels, every country should be supported in establishing at least one well-functioning national clinical research institution with a focus on the design, conduct and governance of reliable, efficient clinical trials. At higher-capacity levels, numerous such clinical research institutions may already exist and may have expanded to develop specializations in certain thematic areas or types of health research (such as biomedical science, implementation science and behavioural science).

Currently there is substantial duplication of clinical trial infrastructure and lack of coordination between numerous coordinating centres for clinical trials and CTUs (which often operate using different processes even when collaborating on the same projects). In addition, smaller CTUs often struggle to provide job security, training and opportunities for career progression, which may result in high staff turnover rates, short-term contracts, job dissatisfaction and low-quality work environments. Consequently, many small CTUs cannot retain or recruit staff and are unable to take up opportunities to participate in clinical trials when offered. This situation is particularly true in rural, regional and remote areas where it is most difficult to build and retain capacity, and this further entrenches inequity of access. It is therefore widely recognized that **there is a need to foster a shift away from disease-specific clinical research institutions or CTUs to broad-based CTUs that have a disease-agnostic capability deployable to numerous scenarios** and which can then work with or develop additional clinical research sites within relevant communities to respond to public health needs. These CTUs can then access disease-specific expertise as needed. Global funders (public, private and philanthropic) need to invest substantially in developing and sustaining such disease-agnostic CTUs and associated clinical research networks (see Section 3.2.2).

**WHO is elaborating a CTU maturity framework, which may prove especially helpful in countries without pre-existing systems by providing a commonly agreed structure for developing such CTUs.** A tiered system with different metrics according to a CTU's purpose and functional maturity will be fostered, based upon consensus criteria. This system will allow for appropriate tailoring of the criteria (for example, what will be specified for CTUs acting as regional or national hubs supporting larger trials will differ from the infrastructure required in smaller local CTUs feeding into such hubs).

Access to health care and clinical facilities in general needs to be strengthened in order to facilitate clinical research and embedding clinical research within routine national healthcare systems across all care settings (home/community/primary, secondary, tertiary) should also be encouraged. Immense potential benefits stem from incorporating clinical trials into point-of-care trial processes, for instance:

- cost and efficiency savings

- embedding research personnel throughout health care systems increases democratization of staff involvement which can lead to much wider awareness of, and enthusiasm for, clinical trials

- extending trial sites from large national centres to smaller local centres or indeed patients' homes (such as in decentralized trials) and "taking trials to the people" facilitate larger sample size (hence adequate statistical power) and broader participation (hence representativeness and increased probability of meaningful results that improve patient care).

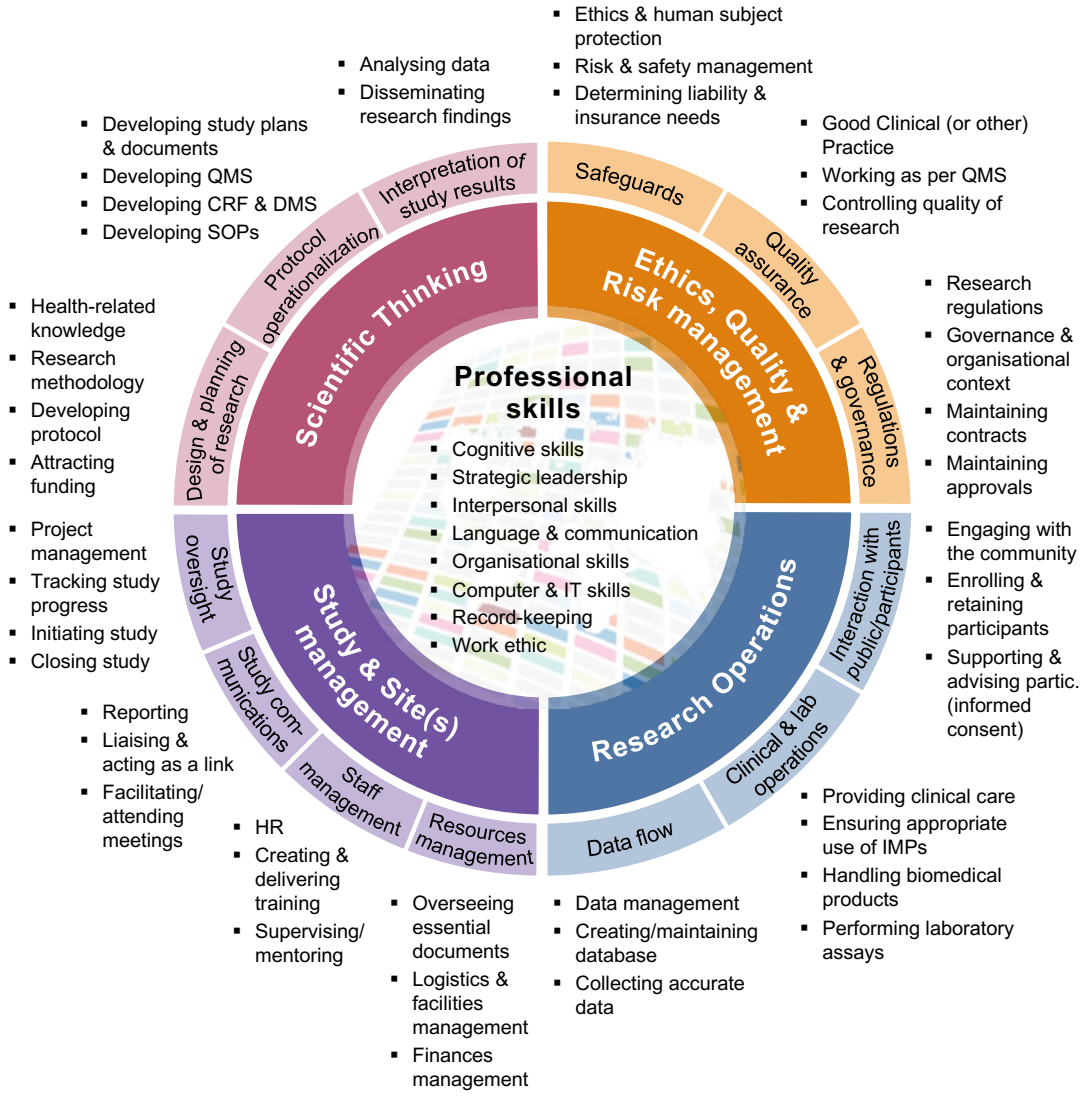
Automated and digital processes should be encouraged and supported globally to increase clinical trial speed, efficiency and transparency. Building such electronic health care systems will enable long-term research connectivity. However, such systems need to be affordable, sustainable and efficient.

### (b) Clinical trial personnel

A well-functioning clinical trial ecosystem is one that supports the careers of clinical researchers through local programmes and funding options for all career stages, including local leadership of clinical research. It is essential that training focuses on the key scientific and ethical considerations in a risk-proportionate manner as laid out in Section 2 and enables personnel to take up innovative approaches in a flexible manner.

The UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases *(114)* Global Competency Framework for Clinical Research *(124)* lists all the competencies that should be demonstrated by a clinical research team to undertake a successful study (see Figure 2). Note that in addition to the entities shown, consideration also needs to be given to entities with the necessary attributes, capability and capacity to act as clinical trial sponsor (that is, the body taking responsibility for the initiation, management and financing/

**Figure 2. TDR Global Competency Framework for Clinical Research**




TDR: UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases; QMS: quality management system; SOPs: standard operating procedures; CRF: case-reporting form; DMS: document management software/system; IMP: investigational medical product.

*Source*: UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. (2016). Development of the TDR global competency framework for clinical research. World Health Organization. https://iris.who.int/handle/10665/250672.

arranging of financing of clinical trials at national and multinational levels). Such sponsors are needed in addition to local research investigators and those in individual centres of scientific excellence even if these may be part of the resource involved.

The framework can be applied to any research study, regardless of the size of the team, place, disease focus and type of research. However, it should be noted that not all competencies are required in every research unit as some elements (such as creation and maintenance of the trial database) may be located and performed at a central coordination unit. Together with its supporting tools (such as the associated competency dictionary) *(125)*, the framework is also intended to be used to help to plan staff requirements for a study, carry out staff appraisals, guide career development and create educational curricula for research staff.

Appropriate training and mentoring of clinical trial staff are vital (see Section 3.2.4). Specific attention should be given to addressing any current barriers to recruitment and training of people potentially interested in clinical research, including the need for a minimum period of previous clinical trial experience or certain academic qualifications as this may exclude potentially promising people, especially those with fewer financial resources, those from lower resource settings or those with certain demographics.

## 3.2 Clinical trial ecosystem cross-cutting themes

The aforementioned four pillars can only optimally function if several other common factors are enabled. These cross-cutting themes include:

- patient and community engagement
- collaboration, coordination and networking
- use of common systems and standards
- training and mentoring
- risk-proportionate efficient approaches
- sustainability
- innovation
- transparency.

### 3.2.1 Patient and community engagement

As already described in sections 1.4 and 2.3.1, partnership with patients and communities (including, for example, not just patients but patient organizations' representatives, individual patient advocates, family members, carers and supporters) is vital to the clinical trial ecosystem to ensure that clinical trials are designed to answer questions relevant to the populations they are intended to serve, to foster trust, enable diversity and instil a sense of the importance of clinical research in the wider population. This should be a norm and embedded in an appropriate manner in all trials; it is not an optional extra and should be a continuous cycle of knowledge sharing and dissemination as opposed to sporadic campaigns launched immediately pre-trial. Expertise in engagement therefore needs to be developed as part of the core set of skills needed to design and conduct clinical trials appropriately. Lack of feedback on how patients' input or data were used can result in patients questioning the value of their engagement and subsequently a lack of commitment to future opportunities; this must be avoided.

### 3.2.2 Collaboration, coordination and networking

As already described in Section 2.3.2, reliably informative, high-quality clinical trials that address relevant questions require all relevant parties to communicate and collaborate so as to effectively share ideas and expertise, reduce duplication and misaligned approaches, build capacity, maximize use of resources and increase efficiency. The need for improved fairness in clinical research has also been highlighted by the UNESCO-supported TRUST Global Code of Conduct for equitable research partnerships *(100)*, and by the Enhancing Support for Strengthening the Effectiveness of National Capacity Efforts (ESSENCE) and UK Collaborative on Development Research (UKCDR) Good Practice Document, a research capacity initiative *(88)*.

Clinical research networks and discipline- and disease-specific consortia can play a crucial role in enabling coordination between parties, accelerating the generation of high-quality evidence and reducing waste. Numerous such networks were identified through the public consultation that the WHO Secretariat held in late 2022. Many such networks already exist in HICs, such as the European Clinical Research Infrastructure Network (ECRIN) *(126)*, United Kingdom's National Institute for Health and Care Research's Clinical Research Network (NIHR CRN) *(127)*, and the pan-Canadian consortium Accelerating Clinical Trials (ACT) *(128)* which was established to facilitate, optimize and accelerate high-quality, high-impact RCTs.

However, there is also a wealth of networks in other settings. On a global footing, the Clinical Research Initiative for Global Health (CRIGH) *(129)* and The Global Health Network (TGHN) *(130)* aim to optimize clinical research programmes by, for example, sharing methods and processes, developing standards and encouraging international cooperation, while the Global Network for Women's and Children's Health Research *(64)* is dedicated to improving maternal and child health outcomes and building research capacity in resource-poor settings. The ARO Alliance for ASEAN and East Asia (ARISE) *(131)* promotes clinical research and development in the Asian region, and the Indian Clinical Trial and Education Network (INTENT) *(132)* is an example of how different regions can work towards developing disease-agnostic networks for clinical trials. In Brazil the Ministry of Health is establishing a national clinical research network, and WHO's African Region has also been the focus of major networking and strengthening of research capacity, bolstered by international strategic partnerships such as the African Union-European Union Innovation Agenda *(133)*. However, trials in other regions are often hampered by major gaps in such networks, as identified in parts of Latin America, the Caribbean, Eastern Europe, WHO's Eastern Mediterranean Region and parts of Asia, meaning that further collaborations and initiatives need to be developed to truly allow global cooperation to fulfil its potential.

Engaging with nongovernmental organizations may also be essential to do research in parts of the world that are inaccessible for research because of conflict and/or political reasons.

Member States are encouraged to consider developing platforms to facilitate collaboration in their countries, such as maintaining a database of all national clinical research institutions so that researchers, funders and other parties who want to partner with a particular institution know what capacities exist in the country.

### 3.2.3 Use of common systems and standards

Data sharing can be hugely valuable in the context of, for example, meta-analyses. As already outlined in sections 2.1.7 and 2.1.8 **use of data standards, common approved protocol templates** (for example, which include standard items based upon those described in the Standard Protocol Items: Recommendations for Interventional Trials [SPIRIT] guidelines*(134)*) **and core outcomes can allow for collection of data that enables more efficient amalgamation of datasets**. Data sharing should take into account concerns about data privacy and security, with appropriate anonymization measures being taken to remove any patient identifiable information. As stated in Section 2.3.3, **a data management and sharing plan should be developed in line with WHO data-sharing principles of being effective, ethical and equitable, as articulated in the WHO policy on research data sharing** *(85)*.

### 3.2.4 Training and mentoring

**Investment in education and training is required in all regions through accessible (practically and financially) fit-for-purpose training packages.** There is a need to broaden core understanding for all those involved in trials of key methodological trial design, implementation and reporting principles (including risk-based proportionate approaches and 'quality by design'), as well as key ethical considerations for clinical trials. This should help to avoid a silo mentality, reduce duplication of effort and minimize misunderstandings about trial applications. Such training should focus on all levels of the clinical trial infrastructure, not only established CTUs; it should be provided to not only trial investigators

but also those in community-based settings (so as to empower local researchers and health professionals), patient advocacy or engagement groups, research coordinators and managers, members of ethics committees and people in regulatory agencies, as well as younger researchers (especially those in low-resource settings).

Robust training and investment in statistical methodology and capacity and clinical data management are central to trials capacity development. They should enable appropriate sample size estimations, favouring fewer, larger, well-designed trials and giving greater clarity as to when small trials may be appropriate for specific situations.

Tailored, specialized training, especially for local clinical trial leadership, is crucial given the current dominance of international trials led from high income countries. Formal and informal peer learning and mentorship systems, allowing smaller centres to benefit from national or regional centres of excellence and junior researchers to learn from more experienced ones, are to be encouraged in order to further enhance the robustness and effectiveness of clinical trials education. Such systems will enable transfer of skills and opportunities for career development, in line with the principles of equitable partnerships.

Another pressing need is promotion of understanding and adoption of innovative trial designs, including adaptive platform and cluster designs.

An internationally-recognized framework for training competency and maturity tools to assess self-development will be vital to enable the continual development and assessment of training needs of all staff involved in clinical research. Some such tools are already available in other contexts. For example, the US Centers for Disease Control and Prevention (CDC) has worked in collaboration with WHO, the Global National Immunization Technical Advisory Groups Network (NITAG GNN) and The Task Force for Global Health to develop a maturity assessment tool for such Technical Advisory Groups *(135, 136)*.

General public understanding of clinical trials could be fostered by encouraging basic clinical trial knowledge to be included as part of national school curriculums.

### 3.2.5 Efficiency

As outlined in sections 1.4, 2.1.8 and 3.1, a move away from traditional risk-averse mentality through adoption of risk-proportionate approaches is integral to improving clinical trial quality and efficiency. This can be motivated through education and appropriate incentives for adopting such methodology.

### 3.2.6 Sustainability

**It is absolutely vital that any investment in the clinical trial ecosystem is done after an assessment of affordability, equity and long-term sustainability of any systems, infrastructure and staffing.** Careful consideration also needs to be given to the environmental impact of clinical trials, with efforts made to foster responsible practices in relation to the climate and environment *(137)*.

### 3.2.7 Innovation

Investment in innovation offers an important opportunity for clinical trials and is increasingly being recognized by multiple stakeholders including academic institutions, regulators, ethics committees, funders and industry. Digital technology, in particular that for building affordable and sustainable electronic health care systems, is needed to improve efficiency and enable research connectivity in the longer term. Where possible, processes should be automated to improve not only the speed but also transparency of clinical trials. Such systems may also improve trial quality by incorporating inbuilt checks for certain variables. Appropriate use of technology enabled by artificial intelligence, such as advanced data analytics, automation and enhanced mobile applications, wearable biosensors and connected devices, offers the potential to improve efficiency and expand the scope of potential outcomes. Search tools and matching services that leverage artificial intelligence may also help to match patients effectively with appropriate clinical trials, a step that could promote health equity and inclusion. As artificial intelligence applications advance rapidly it will be essential for the clinical trial ecosystem to allow for enhancements and efficiencies that this and other technologies will bring. To do so will require an agile approach by researchers and regulators to enable advancements while mitigating risks.

**There is a need to enable wider exploration and adoption of more diverse trial designs (such as platform, adaptive and cluster designs) deployable across a range of settings and decentralized or point-of-care designs which can be embedded in routine care** *(138)*.

The field of pharmacogenomics offers the potential for more personalized care, while modelling techniques or synthetic or data-driven control arms may help to enable clinical trials in certain settings.

Such innovation is vital, but it must ensure that it embraces the key scientific and ethical considerations for clinical trials outlined in Section 2.

### 3.2.8 Transparency

As already discussed in Section 2.3.3, transparency across multiple aspects of clinical trials is imperative to improve efficiency, foster trust and facilitate appropriate data sharing.

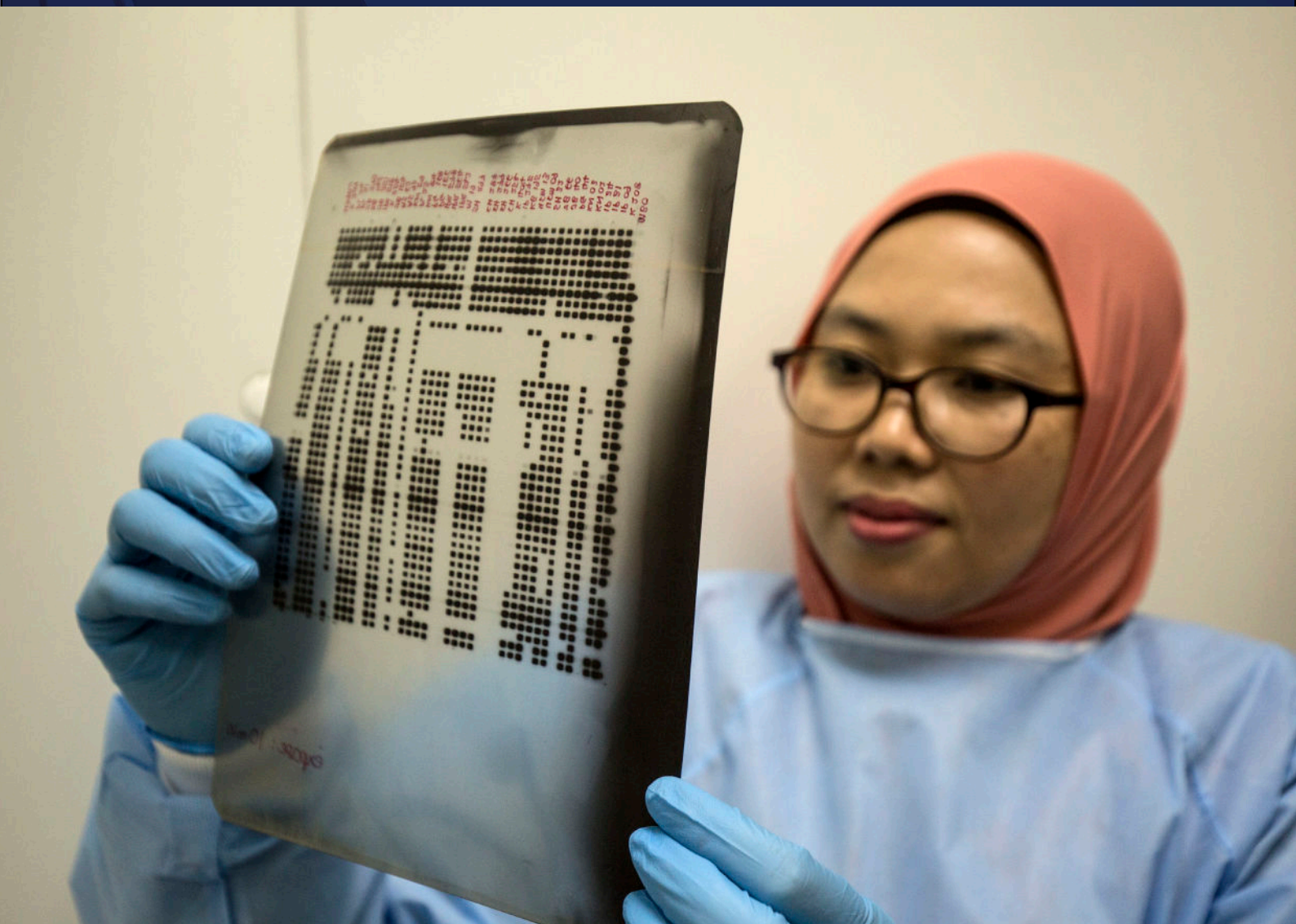
# 4. Conclusion

Lab Technician Babikr processes samples in the laboratory of the Cholera Treatment Centre (CTC) in Gedarif on 23 October 2023.

# 4. Conclusion

**Clinical trials can transform health care and quality of life worldwide.** To fulfil their potential, they need to be reliably informative, ethical and efficient, and answer scientifically important questions relevant to the populations they are intended to benefit. This goal can be attained through identification of relevant research questions, risk-based and proportionate design, conduct, monitoring and audit of clinical trials, and strengthening of the global clinical trial ecosystem. These steps in turn require partnership with patients and their communities, equitable and sustained funding and global collaboration.

# Annexes



A laboratory technologist looks on spoligotyping analysis for tuberculosis cluster investigation at the National TB Reference Laboratory.

# Annex 1. Provisions for rapid funding and approval of good randomized evidence generation in emergencies

Given the possibility of major adverse societal impacts in health emergencies, including fatalities or long-term sequelae in those experiencing infection with a newly emerging disease, it is ethically imperative to ensure that new information is generated during public health emergencies. There may be few or no data on safety and effectiveness of preventive or therapeutic interventions. As underlined in resolution WHA75.8 (2022), clinical trials underpin the generation of reliable information on safety and effectiveness of interventions in both normal times and emergencies.

A key lesson learned from the COVID-19 pandemic is that clinical trial procedures should be developed in normal times in order to enable rapid activation of protocols in emergencies for facilitation of a rapid large-scale response to meet compelling public health needs.

Therefore, one aspect of strengthening of clinical trials ecosystems is inclusion of appropriate provisions that allow for the following activities as soon as a health emergency is declared by WHO or by national authorities:

- rapid agreement on research priorities including those that require clinical trials
- coordination and collaboration of stakeholders to enable the design or activation of pre-existing approved master protocols
- initiation, conduct and reporting of good clinical trials as quickly as possible
- translation of results into policy decision-making by regulators and public health authorities.

These points require those involved in clinical trials to follow good practices for funding and regulatory and ethics procedures in emergencies, including restatement of the provisions in normal times that also apply in emergencies. Key points made in WHA 75.8 in relation to this are outlined below.

## A1.1 Funding of research during public health emergencies

Enacting new funding contracts for researchers amid a health emergency leads to delays in initiation of priority research. It is therefore preferable to have arrangements in place beforehand so that staff can rapidly be redeployed to the conduct of clinical trials and other research in emergencies. Standing network arrangements and previously-agreed master protocols with provisions for emergencies can greatly accelerate timelines.

Funders should encourage use of standardized protocols for data collection that allow for aggregation of data on interventions and outcomes between trials during review of evidence. Clinical trial protocols should be well-designed and well-implemented as outlined in Section 2.

Funders should mandate registration in a publicly-available clinical trial registry within WHO's International Clinical Trials Registry Platform or another registry that meets its standards.

Funders should promote, as appropriate, measures to facilitate the timely reporting of both positive and

negative interpretable clinical trial results in alignment with WHO's joint statement on public disclosure of results from clinical trials including registration of the results on a publicly available clinical trial registry within the International Clinical Trials Registry Platform, and encouraging timely publication of the trial results preferably in an open-access publication.

Funders should promote transparent translation into clinical guidelines, where appropriate, of results from clinical trials, including comparison with existing interventions on effectiveness, based on thorough assessment.

Funders should explore measures during public health emergencies of international concern to encourage researchers to rapidly and responsibly share interpretable results of clinical trials, including negative results, with national regulatory bodies or other appropriate authorities, including WHO for clinical guideline development and Emergency Use Listing, to support rapid regulatory decision-making and emergency adaptation of clinical and public health guidelines as appropriate, and dissemination, including pre-print publication.

## A1.2 Supporting rapid decision-making by regulatory bodies in emergencies

Resolution WHA75.8 (2022) states that Member States should, "in accordance with their national and regional legal and regulatory frameworks and contexts and, as appropriate, … support new and existing mechanisms to facilitate rapid regulatory decision-making during public health emergencies of international concern, so that:

(a) safe, ethical, well-designed clinical trials can be approved and progress quickly;

(b) data from clinical trials can be assessed rapidly, for example through the WHO Emergency Use Listing procedure, and health interventions deemed safe and effective can be swiftly authorized."Regulatory bodies, whether those focusing on research ethics or marketing authorization of medicines and health products, can only respond quickly in emergencies if they have adequate resources and capacity. Therefore, it is essential that resources are provided for trained personnel in regulatory bodies, including those concerned with research ethics. This area is sometimes neglected in considerations of strengthening research capacity.

Member States should have a process for rapid review by NRAs, RECs or IRBs of submissions of clinical trials in the context of health emergencies. Clinical trials judged to be a national priority should be reviewed and approved by a single REC or IRB in a country, avoiding excessive parallel reviews by many RECs or IRBs in the same country, and the rapid review process should provide guidance on which single REC or IRB will provide oversight in the country.

## A1.3 Detailed guidance was published by WHO, as part of the R&DBlueprint activities, in 2020 on rapid review of research by ethics committees, sharing of results *(118)*

During public health emergencies of international concern, further measures should be explored to encourage researchers to expedite fast and responsible sharing of interpretable results of clinical trials (for example, through pre-print publication) with national regulatory bodies or other appropriate authorities, including WHO for clinical guideline development and Emergency Use Listing. This in turn will support rapid regulatory decision-making and emergency adaptation of clinical and public health guidelines as appropriate.

# Annex 2. Recommendations for Member States, research funders and researchers

These recommendations relate to clinical trials for any disease or health condition and for any purpose (see section on Scope). The recommendations[1] listed below are all aimed at enabling reliably-informative, locally-relevant clinical research in all settings (including resource-limited settings), with fair sharing of responsibilities, burdens and benefits. They have been grouped by target audiences, being split into high-level and topic-specific recommendations. Although the recommendations for the reader's own group will be of primary interest to them, those for the other groups can facilitate understanding of the other stakeholders' perspectives and thus promote successful collaborative working.

## A2.1 High-level recommendations

### A2.1.1 For Member States and regulatory authorities

The target audiences could include relevant ministries (such as those concerned with health or science), authorities in charge of regulating health products and bodies in charge of scientific and ethical review of research protocols.

Should Member States and regulatory authorities want to take measures to create a conducive research environment, they should consider some or all of the recommended actions listed below:

(a) invest in a sustainable research environment in terms of general infrastructure, security, health systems infrastructure, equipment and human resources, and support the establishment or maintenance of centres and networks to conduct clinical research;

(b) seek to improve efficiency in regulatory authorities and ethics committees for oversight of clinical trials, to streamline procedures wherever possible and appropriate, and to adopt a proportionate approach balancing rigour of review with risks posed by the proposed research;

(c) create incentives and opportunities for engaging and training new researchers and for setting up and maintaining research sites, and inform local researchers of options where funding for clinical research can be obtained;

(d) clarify regulatory requirements, avoiding legal uncertainties, and harmonize them with those of other countries; identify unnecessary obstacles and reduce bureaucracy; shorten ethics and regulatory review timelines; and rely on the decisions of other authorities wherever possible;

(e) establish and enforce effective regulations for ethical review; ensure appropriate protection – which does not mean exclusion – of under-represented people and those in vulnerable situations in research so that these populations are not precluded from potential access to safe and effective interventions;

(f) support the establishment of platforms for researchers to engage with patient representatives and communities, for example community advisory boards; and request and consider formal communication plans as part of applications for clinical studies;

1 Adapted from CIOMS' guidance (Clinical research in resource-limited settings. Geneva: Council for International Organizations of Medical Sciences; 2021 (https://cioms.ch/wp-content/uploads/2021/06/CIOMS_ClinicalResearch_RLS.pdf, accessed 5 June 2024).

(g) invest in constructive dialogue with stakeholders, including patients and communities, on research priorities and methods to generate relevant evidence, including members of under-represented populations such as children; and link research findings with implementation, as appropriate, in national health systems to advance delivery of evidence-based health care.

### A2.1.2 For researchers

These could include researchers from academic institutions, the health care industry, contract research organizations and noncommercial entities.

Domestic and international researchers have the responsibility to act accountably and transparently and to build public trust in the value of clinical research for the populations in which it is conducted. Therefore, they should:

(a) understand and respect the local context, for example, social and cultural aspects, health systems, laboratory equipment and facilities, assay technologies, scientific and administrative capacities, as well as the local epidemiology and genetics of diseases of the population;

(b) aim to build sustainable research capacity in resource-limited settings;

(c) ensure a focus on the key features for well-designed and well-implemented trials as outlined in Section 2 of this document;

(d) engage local study participants and communities throughout the research, from an early stage of study design, to ensure that the research addresses questions meaningful to them and adheres to high ethical standards (thus helping to generate relevant findings and facilitate their translation into health benefits, thereby justifying the burdens of the study on the local population) and not divert resources from already-overstretched local health care systems;

(e) plan in advance how to communicate and engage, throughout all phases of the clinical research, with community stakeholders such as participants, participants' partners and families, community, traditional and religious leaders, or advisory boards; and be transparent about the aims and interests of all parties involved;

(f) ensure that any clinical research project has scientifically-justified research questions, with study designs and data-collection methods that are sufficiently efficient and robust to generate high-quality evidence and, where relevant, contribute to systematic reviews that underpin policies and guidelines;

(g) where feasible, integrate trial activities into the work of points of care to simplify trial conduct;

(h) consider the use of innovative, adaptive study designs and novel digital technologies, for example trial-at-home, electronic health records and artificial intelligence where such methods decrease complexity and burden for participants and support generation of reliable evidence;

(i) invest in integrity of scientific data, transparency and confidentiality of personal data at all phases of the planning, conduct and implementation of the study, including dissemination of study results and reporting, with due consideration given to relevant guidelines;

(j) ensure appropriate inclusion of members of under-represented populations such as children, pregnant and lactating women and older people;

(k) access or conduct a review of data and literature on the proposed research topic for data relevant to the planned research setting, so that any new research builds on existing knowledge. Capacities for synthesis of evidence are an essential aspect of research, for use before and after completion of the research study.

### A2.1.3 For international organizations and funders

Organizations that initiate and/or fund research have a significant influence in shaping policies and practices. They should also monitor the financial resources disbursed and ensure effective budget management and, where necessary, build capacity to do so. These groups are urged to synergize their resources and to support building and maintaining clinical research capacity through the following recommended strategies:

(a) prioritize research that answers important questions definitively and is relevant for the specific setting and the health care systems of the communities involved;

(b) support policies and multifunctional coalitions (including public–private partnerships or product development partnerships) that facilitate a conducive environment for investing and participating in reliably-informative local clinical research;

(c) support the establishment and maintenance of functional, efficient and effective multicountry systems and coalitions for ethical and regulatory oversight of clinical research;

(d) educate, empower and support patient organizations and communities to foster an understanding of the value of clinical research;

(e) make agreements strongly encouraging open collaboration and data sharing through information technology and electronic health records, avoiding fragmentation of research efforts and capacity, and support dissemination of study information and results.

## A2.2 Topic-specific recommendations

In this section, the symbols denote the following groups:

Member States and regulatory authorities

Researchers

Funders

### A2.2.1 Creating an enabling environment for clinical trials

| | |
|---|---|
|  | Member States are encouraged to create an enabling environment for health research, including clinical trials, and appreciate the benefits that this will bring to the quality of the health systems and practitioners and the health (and economic status) of the people they serve. |
|  | Funders and researchers should work with Member State authorities to facilitate public engagement and public understanding of the value of research for health, including clinical trials. |
|  | International agencies and non-State actors providing aid in conflict areas should be open to the need to conduct or facilitate research benefiting people affected by conflict and discrimination, while staying impartial and being careful to support and not undermine relevant local health initiatives. |
|  | The global community should develop and test new models that could be used successfully in the fight against corruption in global health, and funders should support this effort. |
|  | All stakeholders should actively reduce unnecessary bureaucracy, ensure transparency—by means that include the disclosure of conflicts of interest—and accountability in their operations, and build capacity for management and accounting where necessary. |
|  | Health ministries should aim to strengthen regulatory processes and improve efficiency, by means that include allocating adequate funding, and clarifying legal uncertainties. Clinical trial agreements, uniform shared templates for material/data transfer agreements and other mechanisms enabling researchers to achieve the study objectives within agreed timelines, while respecting national guidelines, should be encouraged. |
|  | Researchers should improve their communication with local communities, including policy-makers and clinicians, about the potential benefits of clinical research. |

### A2.2.2 Building research infrastructure and capacity

| | |
|---|---|
|  | Member States, international organizations and sponsors should support the development of local research career structures as well as training schemes in research ethics, research methodology, statistical analysis, research practice and clinical data management. |
|  | Member States, international organizations and sponsors should invest in creating and maintaining local laboratory infrastructure and sample storage resources and associated staff capacity to support clinical trials wherever possible. Participation in external quality assurance schemes should be encouraged and supported. |
|  | Researchers and funders should aim to work together and share their experiences, methods and resources. |
|  | Regulatory authorities, funders and researchers should collaborate to establish or maintain existing clinical research networks. |

### A2.2.3 Building research infrastructure and capacity

Regulatory authorities should consider WHO's guidance on the high-level principles and considerations for good reliance practices in the regulation of medical products, especially those in resource-limited settings.

Regulatory authorities should only require local clinical trials or set other special requirements if they are scientifically justified.

Member States and funders should allocate greater financial and human resources for training and continuous education about the key scientific and ethical considerations for good clinical trials.

### A2.2.4 Building research infrastructure and capacity

Good clinical trials apply standards that are based on key scientific and ethical principles and focused on issues that materially matter to the well-being of trial participants and the reliability of trial results. Risk-based proportionate approaches should be adopted (see Section 2).

### A2.2.5 Protecting research participants

Researchers should allocate adequate time and resources for measures and materials to obtain properly informed consent. Consent information should be as succinct as possible. Innovative options for obtaining informed consent using new technologies, such as audiovisual models to ensure better understanding, or electronic consent should be considered where appropriate. At all stages of a clinical trial, relevant and easily understandable information should be shared with trial participants, with careful balancing of the duty to inform against the risk of information saturation and taking account of the clinical context. Information should be provided in a clear manner and in suitable languages and formats for the intended audiences and avoid legalistic or other technical language.

Patients and communities should be engaged to help to provide valuable contributions to the design and execution of clinical trials and interpretation of their results and hence enable effective measures to protect research participants' rights.

### A2.2.6 Avoiding exploitative research

The priority-setting exercise for clinical research should involve relevant local bodies, patients and the public and should take into account under-represented groups and people in vulnerable situations. Before approving the study, local authorities may want to negotiate with the sponsors about how the benefits will be shared with the local population.

Ethical review should consider whether sufficient resources are available at the study site to avoid any negative impact on routine patient care.

| | |
|---|---|
|  | Research projects initiated by sponsors in HICs should be approved by a REC in the host country as well the REC in the high-income setting. |
|  | Measures should be taken to oppose double standards in research and support long-term equitable research relationships between partners in LMICs and HICs. |

### A2.2.7 Ethical review and capacity-building

| | |
|---|---|
|  | Member States should consider setting up national ethics committees to promote consistency and avoid unnecessary duplication of work in regions where several RECs exist. Regions or countries should consider having joint RECs or common reviews for multicentre research. |
|  | Member States, international organizations and sponsors of research projects should invest in capacity-building for RECs in resource-limited settings, including training in scientific research and the key scientific and ethical considerations for good clinical trials (as described in Section 2), training for expedited and rapid reviews, and proportionate risk-based monitoring and evaluation. |
|  | Review by an REC should be based on the protocol and complete, up-to-date supporting information and should include a determination of whether the proposed clinical study is scientifically sound, justified, proportionate and risk-based. |
|  | RECs should examine their internal processes to reduce unnecessary bureaucracy, streamline their functions and harmonize processes with those of other RECs in the country or region. Regional or national forums, databases or registries should be encouraged to allow for communication and coordination between RECs. |
|  | Ethics committees should be empowered to function independently of any institutional, external pressure or conflict of interest and to take unbiased decisions. |
|  | International initiatives to strengthen ethical review, including those of WHO, should be supported. |
|  | International organizations, sponsors and funders should make efforts to reduce the language barrier in capacity-building by providing documents and organizing events in languages other than English. |

### A2.2.8 Participant and community engagement

| | |
|---|---|
|  | Where necessary, researchers should educate community representatives about what a clinical trial is, how it differs from routine health care and the specific protections provided for trial participants. |
|  | Researchers should develop formal plans on how they will communicate with participants and the local community throughout the clinical trial in a meaningful way. |
|  | Communities in resource-limited settings should be empowered to negotiate for fair benefits of clinical research. This activity will require support by an effective, independent local REC. |

## A2.2.9 Conceptualizing and designing research

| | |
|---|---|
|  | Funders and institutions conducting research should recognize the value of information about the study population and its importance for assessment of the potential impact and benefit of health research. Community engagement may provide access to valuable information. |
|  | Research to address the health needs of children and women, including pregnant and lactating women, should be viewed as the norm unless there is valid justification to exclude them. |
|  | Efforts should be made to ensure that clinical trials recruit as diverse and inclusive populations as possible. |
|  | Both industry-sponsored and academic research in resource-limited settings should focus on relevant research questions that will help to address a clear health need |
|  | Researchers should consider the use of adaptive study designs and data collection, where possible and appropriate. |
|  | As a rule, to minimize the burden on the local infrastructure and population, data collection should focus on those variables that provide needed scientific information for the study. |
|  | Research protocols should be adapted as much as possible to local clinical practice and cultural/social considerations, for example regarding frequency of visits and sampling. |
|  | Member States, international organizations and sponsors should support education on research methodology and study designs in resource-limited settings, as well as building the necessary infrastructure. |

## A2.2.10 Responsible information sharing

| | |
|---|---|
|  | Researchers should minimize the risk of re-identification of individual participants from any data that may be shared outside the study and should make both the plans for data-sharing and any risk of data identification clear to study participants as part of seeking informed consent. |
|  | Academic research institutions and hospitals should support appropriate management, analysis and publication of clinical research data and results, seeking support for writing and translation where necessary. |
|  | Funders are encouraged to accommodate the costs of data-related activities when funding clinical research. |
|  | Funders and sponsors are encouraged to allocate dedicated human resources for communicating objective, validated information and research results to participants, communities, clinicians and policy-makers before, during and after research, as well as to the media and the general public. |

### A2.2.11 Under-represented populations: women of child-bearing age

| | |
|---|---|
|  | More research should be conducted to address the needs of women of child-bearing age, including pregnant and lactating women. CIOMS' ethical guidelines issued in 2016 *(14)* make a compelling case for inclusion of women in research, including pregnant and lactating women. The fact that a population is physiologically different should never be a reason to exclude it from participation in clinical research where the results may be beneficial to that population, so long as everyone involved in the research is aware of the risks involved and appropriate safeguards and protective health measures are in place. |
|  | Researchers and ethics committees should ensure that the cultural context is respected when studies are conducted in women of child-bearing age, including pregnant and lactating women. |
|  | The establishment and use of pregnancy registries in LMICs should be considered. |

### A2.2.12 Under-represented populations: children

| | |
|---|---|
|  | Clinical trials in children should be considered from the outset at all stages of clinical development. |
|  | Clinical studies in children are needed across the spectrum of health care settings, including hospitals and communities, including those in remote areas. |
|  | More pharmacokinetic and pharmacodynamic studies and pharmaceutical formulation studies should be conducted to support the development of safe and effective medicines for children. |
|  | Member States and funders should support initiatives to strengthen regulatory expertise for paediatric medicines as well as academic expertise in and capability for conducting paediatric clinical trials. |

### A2.2.13 Under-represented populations: the elderly and very elderly

| | |
|---|---|
|  | Clinical trials in the elderly and very elderly should be considered from the outset at all stages of clinical development. |
|  | Clinical studies in the elderly and very elderly are needed across the spectrum of health care settings, including hospitals and communities, including those in remote areas. |
|  | More pharmacokinetic and pharmacodynamic studies and pharmaceutical formulation studies should be conducted to support the development of safe and effective medicines for the elderly and very elderly. |
|  | Member States and funders should support initiatives to strengthen regulatory expertise for medicines for the elderly and very elderly as well as academic expertise in and capability for conducting clinical trials in the elderly and very elderly. |

# References


1. Council for International Organizations of Medical Sciences (CIOMS). (https://cioms.ch/; accessed 07 February 2024).
2. Good Clinical Trials Collaborative. (https://www.goodtrials.org/; accesssed 07 February 2024).
3. Resolution WHA75.8. Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination. In: Seventy-fifth World Health Assembly, Geneva, 22-28 May 2022. Resolutions and decisions, annexes. Geneva: World Health Organization; 2022 (WHA75/2022/REC/1 (https://apps.who.int/gb/ebwha/pdf_files/WHA75-REC1/A75_REC1_Interactive_en.pdf#page=5; accessed 07 February 2024).
4. The WHO strategy on research for health. Geneva: World Health Organization. 2012. (https://apps.who.int/iris/handle/10665/77935; accessed 07 February 2024).
5. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). (https://www.ich.org/; accessed 31 July 2024)
6. ICH Harmonised Guideline. General Considerations for Clinical Studies E8(R1). Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2021 (https://database.ich.org/sites/default/files/ICH_E8-R1_Guideline_Step4_2021_1006.pdf; accessed 07 February 2024).
7. ICH Harmonised Guideline. Good Clinical Practice (GCP) E6(R3). Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2023 (https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf, accessed 07 February 2024).
8. ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9. Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 1998 (https://database.ich.org/sites/default/files/E9_Guideline.pdf; accessed 07 February 2024).
9. ICH Harmonised Guideline. Addendum on Estimands and Sensitivity Analysis in Clincial Trials E9(R1). Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2019 (https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf; accessed 07 February 2024).
10. Clinical research in resources-limited settings. A consensus by a CIOMS Working Group. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2021. (https://cioms.ch/publications/product/clinical-research-in-low-resource-settings/; accessed 07 February 2024).
11. Good Clinical Trials Collaborative. Guidance for Good Randomized Clinical Trials. 2022. (https://www.goodtrials.org/the-guidance/guidance-overview/; accessed 07 February 2024).
12. WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects. Ferney-Voltaire, France: World Medical Association; 2022 [website] (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/; accessed 07 February 2024).
13. WMA Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks. World Medical Association; 2016. (https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-considerations-regarding-health-databases-and-biobanks/; accessed 07 February 2024).
14. International Ethical Guidelines for Health-related Research involving Humans. Geneva: Council for International Organizations of Medical Sciences; 2016. (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf; accessed 07 February 2024). .
15. J. Woodcock, L. M. LaVange, Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med 377, 62-70 (2017).
16. J. J. H. Park et al., Randomised trials at the level of the individual. Lancet Glob Health 9, e691-e700 (2021).
17. Clinical Trials Transformation Initiative. Master Protocol Studies. (https://ctti-clinicaltrials.org/our-work/novel-clinical-trial-designs/master-protocol-studies/; accessed 07 February 2024).
18. U.S. Food and Drug Administration. Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry. 2022. (https://www.fda.gov/media/120721/download; accessed 07 February 2024).

19. Decentralized Clinical Trials for Drugs, Biological Products, and Devices Guidance for Industry, Investigators, and Other Stakeholders. Draft Guidance. U.S. Department of Health and Human Services Food and Drug Administration 2023. (https://www.fda.gov/media/167696/download; accessed 07 February 2024).

20. R. M. Califf, P. Cavazzoni, J. Woodcock, Benefits of Streamlined Point-of-Care Trial Designs: Lessons Learned From the UK RECOVERY Study. JAMA Intern Med 182, 1243-1244 (2022).

21. Firth, John D., and others, 'Large-scale randomized evidence: Trials and meta-analyses of trials', in John Firth, Christopher Conlon, and Timothy Cox (eds), Oxford Textbook of Medicine, 6 edn (Oxford, 2020; online edn, Oxford Academic, 1 Jan. 2020). (https://doi.org/10.1093/med/9780198746690.003.0010; accessed 07 February 2024).

22. R. Collins, S. MacMahon, Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. Lancet 357, 373-380 (2001).

23. S. MacMahon, R. Collins, Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. Lancet 357, 455-462 (2001).

24. L. Bowman et al., Understanding the use of observational and randomized data in cardiovascular medicine. Eur Heart J 41, 2571-2578 (2020).

25. R. Collins, L. Bowman, M. Landray, R. Peto, The Magic of Randomization versus the Myth of Real-World Evidence. N Engl J Med 382, 674-678 (2020).

26. U.S. Food and Drug Administration. Real-World Evidence. (https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence; accessed 07 February 2024).

27. U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program. 2018. (https://www.fda.gov/media/120060/download?attachment; accessed 07 February 2024).

28. Clinical Trials Transformation Initiative. Real-World Data. (https://ctti-clinicaltrials.org/our-work/novel-clinical-trial-designs/real-world-data/; accessed 07 February 2024).

29. R. E. Sherman et al., Real-World Evidence - What Is It and What Can It Tell Us? N Engl J Med 375, 2293-2297 (2016).

30. European Medicines Agency. Engagment Framework: EMA and patients, consumers and their organisations. 2022. (https://www.ema.europa.eu/system/files/documents/other/updated_engagement_framework_-_ema_and_patients_consumers_and_their_organisations_2022-en.pdf; accessed 07 February 2024).

31. U.S. Food and Drug Administration. FDA Patient Engagement Partnerships. (https://www.fda.gov/patients/learn-about-fda-patient-engagement/fda-patient-engagement-partnerships; accessed 07 February 2024).

32. U.S. Food and Drug Administration. Patient Engagement Cluster. (https://www.fda.gov/patients/learn-about-fda-patient-engagement/patient-engagement-cluster; accessed 07 February 2024).

33. U.S. Food and Drug Administration. Patient Engagement in the Design and Conduct of Medical Device Clinical Studies Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. 2022. (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-engagement-design-and-conduct-medical-device-clinical-studies; accesssed 07 February 2024).

34. WHO, R&D Blueprint. Good Participatory Practice (GPP) for COVID-19 clinical trials: a toolbox. Geneva: World Health Organization (https://cdn.who.int/media/docs/default-source/science-division/research/blueprint-good-participatory-practice-for-covid-19-clinical-trials---a-toolbox.pdf?sfvrsn=ba08094c_10; accessed 07 February 2024).

35. D. Haerry et al., EUPATI and Patients in Medicines Research and Development: Guidance for Patient Involvement in Regulatory Processes. Front Med (Lausanne) 5, 230 (2018).

36. A. Hunter et al., EUPATI Guidance for Patient Involvement in Medicines Research and Development: Health Technology Assessment. Front Med (Lausanne) 5, 231 (2018).

37. I. Klingmann et al., EUPATI and Patients in Medicines Research and Development: Guidance for Patient Involvement in Ethical Review of Clinical Trials. Front Med (Lausanne) 5, 251 (2018).

38. The James Lind Alliance. Priority Setting Partnerships. (https://www.jla.nihr.ac.uk/; accessed 07 February 2024).

39. J. J. H. Park et al., Urgently seeking efficiency and sustainability of clinical trials in global health. Lancet Glob Health 9, e681-e690 (2021).

40. The World Bank. Data. Population ages 0-14 years (% of total population) (https://data.worldbank.org/indicator/SP.POP.0014.TO.ZS?contextual%20=max&end=2021&locations=XM&most_recent_value_desc=true&start=1960&view=chart; accessed 31 July 2024).

41. M. J. Page et al., The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. J Clin Epidemiol 134, 178-189 (2021).

42. I. Chalmers, P. Glasziou, Avoidable waste in the production and reporting of research evidence. Lancet 374, 86-89 (2009).

43. M. J. Grainger, F. C. Bolam, G. B. Stewart, E. B. Nilsen, Evidence synthesis for tackling research waste. Nat Ecol Evol 4, 495-497 (2020).

44. World Health Organization. International Clinical Trials Registry Platform (ICTRP) ; ICTRP Registry Network; Primary Registries (https://www.who.int/clinical-trials-registry-platform/network/primary-registries; accessed 22 February 2024).

45. ClinicalTrials.gov. U.S. Department of Health and Human Services, National Institutes of Health, National Library of Medicine, and National Center for Biotechnology Information. (https://clinicaltrials.gov/; accessed 26 April 2024).

46. Landray MJ, Grandinetti C, Kramer JM, Morrison BW, Ball L, Sherman RE. Clinical Trials: Rethinking How We Ensure Quality. Drug Information Journal. 2012;46(6):657-660. doi:10.1177/0092861512464372.

47. U.S. Food and Drug Administration. Enhancing the Diversity of Clinical Trial Populations - Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry. 2020. (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial; accessed 07 February 2024).

48. U.S. Food and Drug Administration. Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry. Draft Guidance. 2022. (https://www.fda.gov/media/157635/download; accessed 07 February 2024).

49. National Institute for Health and Care Research. Improving inclusion of under-served groups in clinical research: Guidance from INCLUDE project. 2022. (https://www.nihr.ac.uk/documents/improving-inclusion-of-under-served-groups-in-clinical-research-guidance-from-include-project/25435; accessed 07 February 2024).

50. WHO framework for meaningful engagement of people living with noncommunicable diseases, and mental health and neurological conditions. Geneva: World Health Organization; 2023 (https://www.who.int/publications/i/item/9789240073074, accessed 07 February 2024).

51. D. M. Gray, 2nd, T. S. Nolan, J. Gregory, J. J. Joseph, Diversity in clinical trials: an opportunity and imperative for community engagement. Lancet Gastroenterol Hepatol 6, 605-607 (2021).

52. N. Vousden et al., Facilitating participation in clinical trials during pregnancy. BMJ 380, e071278 (2023).

53. C. B. Krubiner et al., Pregnant women & vaccines against emerging epidemic threats: Ethics guidance for preparedness, research, and response. Vaccine 39, 85-120 (2021).

54. A. D. Lyerly et al., Ending the evidence gap for pregnancy, HIV and co-infections: ethics guidance from the PHASES project. J Int AIDS Soc 24, e25846 (2021).

55. ICH Final Concept Paper. E21: Inclusion of Pregnant and Breast-feeding Individuals in Clinical Trials. 2023. (https://database.ich.org/sites/default/files/ICH_E21_Final_Concept_Paper_2023_1106_MCApproved.pdf; accessed 22 February 2024).

56. ICH Harmonised Guideline. Addendum to ICHE11: Clinical Investigation of Medicinal Products in the Pediatric Population E11(R1). Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2017. (https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf; accessed 07 February 2024).

57. Sixty-ninth World Health Assembly. Promoting innovation and access to quality, safe, efficacious and affordable medicines for children. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/252800; accessed 07 February 2024).

58. Roadmap towards ending TB in children and adolescents, 2nd ed. Geneva: World Health Organization; 2018 (https://iris.who.int/handle/10665/275422; accessed 07 February 2024).

59. High-Level Dialogue to Assess Progress on and Intensify Commitment To Scaling Up Prevention, Diagnosis and Treatment of Paediatric HIV and TB. 2022, Vatican City State. (https://www.paediatrichivactionplan.org/_files/ugd/38bdff_e6a43bd0240440c5bfa9c488326ccbb8.pdf; accessed 07 February 2024).

60. WHO and other stakeholders join forces to accelerate access to effective paediatric HIV and tuberculosis diagnostics and medicines. News item. Geneva: World Health Organization; 2020 (https://www.who.int/news/item/20-11-2020-accelerate-access-to-effective-paediatric-hiv-and-tuberculosis-diagnostics-and-medicines; accessed 31 July 2024).

61. Global Accelerator for Paediatric Formulations Network (GAP-f).Geneva: World Health Organization; 2023 (https://www.who.int/initiatives/gap-f; accessed 31 July 2024).

62. U.S. Food and Drug Administration. Pediatric Research Equity Act (PREA). (https://www.fda.gov/drugs/development-resources/pediatric-research-equity-act-prea#:~:text=PREA%20gives%20FDA%20the%20authority,pediatric%20labeling%20for%20the%20product; accessed 07 February 2024).

63. EU Paediatric Regulation. (https://www.ema.europa.eu/en/human-regulatory-overview/paediatric-medicines-overview/paediatric-regulation#:~:text=The%20Paediatric%20Regulation%20came%20into%20force%20in%20the,17%20years.%20Human%20Regulatory%20and%20procedural%20guidance%20Paediatrics; accessed 30 July 2024).

64. Global Network for Women's and Children's Health Research (Global Network). (https://globalnetwork.azurewebsites.net/; accessed 07 February 2024).

65. J. A. Cook et al., DELTA(2) guidance on choosing the target difference and undertaking and reporting the sample size calculation for a randomised controlled trial. BMJ 363, k3750 (2018).

66. Jeff A. Sloan, Amylou Dueck, Rui Qin, Wenting Wu, Pamela J. Atherton, Paul Novotny, Heshan Liu, Kelli N. Burger, Angelina D. Tan, Daniel Szydlo, Victor M. Johnson, Sara J. Felten, Xinghua Zhao, Brent Diekmann, Quality of Life: The Assessment, Analysis, and Interpretation of Patient-Reported Outcomes by Fayers, P. M. and Machin, D., Biometrics, Volume 64, Issue 3, September 2008, Page 996, (https://doi.org/10.1111/j.1541-0420.2008.01082_11.x; accessed 01 August 2024).

67. W. S. Weintraub, T. F. Luscher, S. Pocock, The perils of surrogate endpoints. Eur Heart J 36, 2212-2218 (2015).

68. International Consortium for Health Outcomes Measurement (ICHOM). (https://www.ichom.org/; accessed 08 February 2024).

69. Core Outcome Measures in Effectiveness Trials (COMET). (https://www.comet-initiative.org/; accessed 08 February 2024).

70. K. A. Hicks et al., 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol 71, 1021-1034 (2018).

71. Standardised Outcomes in Nephrology (SONG). (https://songinitiative.org/; accessed 08 February 2024).

72. International Alliance of Mental Health Research Funders (IAMHRF). (https://iamhrf.org/projects/driving-adoption-common-measures; accessed 08 February 2024).

73. Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM). (https://www.cdisc.org/standards/foundational/sdtm; accessed 31 July 2024).

74. S. Heidari et al., WHO's adoption of SAGER guidelines and GATHER: setting standards for better science with sex and gender in mind. Lancet 403, 226-228 (2024).

75. J. A. Sterne, G. Davey Smith, Sifting the evidence-what's wrong with significance tests? BMJ 322, 226-231 (2001).

76. S. Greenland et al., Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol 31, 337-350 (2016).

77. Wasserstein, Ronald L., Allen L. Schirm, and Nicole A. Lazar. 'Moving to a World Beyond "p < 0.05"'. The American Statistician 73, no. sup1 (2019): 1–19. (https://doi.org/10.1080/00031305.2019.1583913; accessed 01 August 2024).

78. Wasserstein, Ronald L., and Nicole A. Lazar. 'The ASA Statement on P-Values: Context, Process, and Purpose'. The American Statistician 70, no. 2 (2016): 129–33. (https://doi.org/10.1080/00031305.2016.1154108; accessed 01 August 2024).

79. G. H. Guyatt et al., GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336, 924-926 (2008).

80. U.S. Food and Drug Administration. Use of Electronic Informed Consent in Clinical Investigations - Questions and Answers Guidance for Institutional Review Boards, Investigators, and Sponsors. 2016. (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-informed-consent-clinical-investigations-questions-and-answers; accessed 08 February 2024).

81. J. C. Crocker et al., Impact of patient and public involvement on enrolment and retention in clinical trials: systematic review and meta-analysis. BMJ 363, k4738 (2018).

82. World Health Organization 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 08 February 2024).

83. K. F. Schulz, D. G. Altman, D. Moher, C. Group, CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 63, 834-840 (2010).

84. A. M. Manyara et al., Reporting of surrogate endpoints in randomised controlled trial reports (CONSORT-Surrogate): extension checklist with explanation and elaboration. BMJ 386, e078524 (2024).

85. Sharing and reuse of health-related data for research purposes: WHO policy and implementation guidance. Geneva: World Health Organization; 2022. (https://www.who.int/publications/i/item/9789240044968; accessed 07 February 2024).

86. World Health Organization. International Clinical Trials Registry Platform (ICTRP). (https://www.who.int/clinical-trials-registry-platform; accessed 07 February 2024).

87. T. R. Fleming et al., Maintaining confidentiality of interim data to enhance trial integrity and credibility. Clin Trials 5, 157-167 (2008).

88. ESSENCE and UKCDR Good Practice Document. 2022. Four Approaches to Supporting Equitable Research Partnerships. (https://tdr.who.int/publications/m/item/four-approaches-to-supporting-equitable-research-partnerships; accessed 27 April 2024).

89. A systematic approach for undertaking a research priority-setting exercise: guidance for WHO staff. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240009622; accessed 08 February 2024). .

90. World Health Organization. WHO Council on the Economics of Health For All. (https://www.who.int/groups/who-council-on-the-economics-of-health-for-all; accessed 07 February 2024).

91. World Health Organization. Health for All: Transforming economies to deliver what matters. Final report 2023. (https://www.who.int/publications/m/item/health-for-all--transforming-economies-to-deliver-what-matters; accessed 07 February 2024).

92. GloPID-R Funders Living Roadmap for Clinical Trial Coordination. 2023. (www.glopid-r.org/wp-content/uploads/2023/05/glopid-r-funders-living-roadmap-for-clinical-trial-coordination.pdf; accessed 27 April 2024).

93. Global Alliance for Chronic Diseases (GACD). (https://www.gacd.org/; accessed 07 February 2024).

94. Joint Programming Initiative on Antimicrobial Resistance (JPIAMR). (https://www.jpiamr.eu/; accessed 07 February 2024).

95. Global Research Collaboration for Infectious Disease Preparedness (GloPID-R). (https://www.glopid-r.org/; accessed 07 February 2024).

96. European & Developing Countries Clinical Trials Partnership (EDCTP). (https://www.edctp.org/; accessed 07 February 2024).

97. Ensuring Value In Research (EViR). (https://evir.org/; accessed 07 February 2024). .

98. Innovative Medicines Initiative. (https://www.imi.europa.eu/about-imi; accessed 28 February 2024).

99. WHO Global Observatory on Health Research and Development. (https://www.who.int/observatories/global-observatory-on-health-research-and-development#:~:text=Global%20Observatory%20on%20Health%20R%26D%20The%20Global%20Observatory,R%26D%20and%20decision-making%20related%20to%3A%20health%20R%26D%20gaps; accessed 01 August 2024).

100. The TRUST Code – A Global Code of Conduct for Equitable Research Partnerships, DOI: 10.48508/GCC/2018.05. (https://www.globalcodeofconduct.org/wp-content/uploads/2023/06/The_TRUST_Code.pdf; accessed 07 February 2024).

101. World Health Organization. Evidence, policy, impact: WHO guide for evidence-informed decision-making. 2022. (https://www.who.int/publications/i/item/9789240039872; accessed 28 February 2024).

102. WHO recommendations on interventions to improve preterm birth outcomes. World Health Organization. 2015. (https://iris.who.int/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1; accessed 01 August 2024).

103. WHO recommendations on antenatal corticosteroids for improving preterm birth outcomes. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240057296; accessed 08 February 2024).

104. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD004454. DOI: 10.1002/14651858.CD004454.pub3 (accessed 6 July 2023).

105. McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews 2020, Issue 12. Art. No.: CD004454. DOI: 10.1002/14651858.CD004454.pub4 (accessed 6 July 2023).

106. World Health Organization. 2021. WHO Global Benchmarking Tool (GBT)for evaluation of national regulatory systems of medical products: revision VI. World Health Organization. https://iris.who.int/handle/10665/341243.

107. WHO tool for benchmarking ethics oversight of health-related research with human participants (draft version for piloting). Geneva: World Health Organization; 2022 [website] (https://www.who.int/publications/i/item/9789240076426; accessed 08 February 2024).

108. Pan American Health Organization; Regional Office for the Americas of the World Health Organization. Tool for the accreditation of research ethics committees. 2023. (https://www.paho.org/en/documents/tool-accreditation-research-ethics-committees; accessed 22 February 2023).

109. European Medicines Agency. Clinical Trials Information System. (https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/clinical-trials-human-medicines/clinical-trials-information-system; accessed 08 February 2024).

110. Accelerating Clinical Trials in the EU (ACT EU): for better clinical trials that address patients' needs. 2022. (https://www.ema.europa.eu/en/news/accelerating-clinical-trials-eu-act-eu-better-clinical-trials-address-patients-needs; accessed 08 February 2024).

111. NHS Health Research Authoirty Integrated Research Application System. (https://www.hra.nhs.uk/about-us/committees-and-services/integrated-research-application-system/ and https://www.myresearchproject.org.uk/; accessed 08 February 2024).

112. WHO African Vaccine Regulatory Forum (AVAREF). (https://www.afro.who.int/health-topics/immunization/avaref; accessed 31 July 2024).

113. The SIDCER-FERCAP Foundation. (https://www.sidcer-fercap.org/pages/home.php; acccessed 31 July 2024).

114. United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases. (https://tdr.who.int/; accesssed 31 July 2024).

115. International Coalition of Medicines Regulatory Authorities (ICMRA). (https://icmra.info/drupal/en/home; accessed 01 August 2024).

116. World Health Organization. Guidance for research ethics committees for rapid review of research during public health emergencies. 2002. (https://www.who.int/publications/i/item/9789240006218; accessed 28 February 2024).

117. African Vaccine Regulatory Forum (AVAREF) Strategy and Guidance for Emergency Preparedness. 2020 (https://www.afro.who.int/sites/default/files/2020-05/AVAREF_Guidance_Emergency_Preparedness_May2020.pdf; accessed 31 July 2024).

118. World Health Organization R&D Blueprint for Epidemics. Geneva: World Health Organization. (https://www.who.int/teams/blueprint/who-r-and-d-blueprint-for-epidemics; accessed 08 February 2024).

119. Preparing U.S. Clinical Trials Infrastructure for Emergencies. (https://www.whitehouse.gov/ostp/news-updates/2023/01/06/preparing-u-s-clinical-trials-infrastructure-for-emergencies-a-white-house-virtual-roundtable-discussion/; accessed 08 February 2024).

120. G7 100 Days Mission to respond to future pandemic threats. UK 2021. (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/992762/100_Days_Mission_to_respond_to_future_pandemic_threats__3_.pdf; accessed 08 February 2024).

121. Healthy Life Trajectories Initiative (HeLTI). (https://helti.org/; accessed 08 February 2024).

122. S. T. Agnandji et al., Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe. N Engl J Med 374, 1647-1660 (2016).

123. A. Grenham, T. Villafana, Vaccine development and trials in low and lower-middle income countries: Key issues, advances and future opportunities. Hum Vaccin Immunother 13, 2192-2199 (2017).

124. The Global Health Network Global Health Training Centre. TDR Global Competency Framework for Clinical Research. (https://globalhealthtrainingcentre.tghn.org/pds/core-competency-framework/; accessed 08 February 2024).

125. Using the TDR Global Competency Framework for Clinical Research: A set of tools to help develop clinical researchers. Competency Dictionary. (https://media.tghn.org/medialibrary/2016/11/TDR_Framework_Competency_Dictionary.pdf; accessed 08 February 2024).

126. The European Clinical Research Infrastructure Network (ECRIN). (https://ecrin.org/; accessed 08 February 2024).

127. National Institute for Health and Care Research's Clinical Research Network (NIHR CRN). (https://www.nihr.ac.uk/explore-nihr/support/clinical-research-network.htm; accessed 07 February 2024).

128. Accelerating Clinical Trials (ACT). (https://act-aec.ca/; accessed 08 February 2024). .

129. Clinical Research Initiative for Global Health (CRIGH). (https://crigh.org/; accessed 08 February 2024).

130. The Global Health Network (TGHN). (https://tghn.org/; accessed 07 February 2024).

131. ARO Alliance for ASEAN and East Asia (ARISE). (https://arise.ncgm.go.jp/en/; accessed 08 February 2024).

132. Indian Clinical Trial And Education Network (INTENT). (https://main.icmr.nic.in/content/indian-clinical-trial-and-education-network-intent; accessed 08 February 2024).

133. African Union-European Union Innovation Agenda. 2023. (https://research-and-innovation.ec.europa.eu/document/download/c9c4eb8e-df0f-41e7-a322-891786fef29b_en?filename=ec_rtd_au-eu-innovation-agenda-final-version.pdf; accessed 08 February 2024).

134. A. W. Chan et al., SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 158, 200-207 (2013).

135. World Health Organization. National Immunization Technical Advisory Groups (NITAGs). (https://www.who.int/europe/groups/national-immunization-technical-advisory-groups; accessed 31 July 2024).

136. National Immunization Technical Advisory Group (NITAG) Maturity Assessment Tool (NMAT). (https://www.nitag-resource.org/external/nmat/index.html#/; accessed 08 February 2024).

137. The Academy of Medical Sciences. Enabling greener biomedical research. (https://acmedsci.ac.uk/file-download/61695123; accessed 29 February 2024).

138. E. Vayena, A. Blasimme, J. Sugarman, Decentralised clinical trials: ethical opportunities and challenges. Lancet Digit Health 5, e390-e394 (2023).

Science Division
Department of Research for Health (RFH)
World Health Organization
20, Avenue Appia
1211 Geneva 27
Switzerland
Email: wha758@who.int

9789240097711