

WHO guidance for best practices for clinical trials

DRAFT FOR PUBLIC CONSULTATION

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16 human subjects and CIOMS' International Ethical Guidelines on Health-related Research involving Humans
17 (2016). This document does not supersede any existing guidance; rather it is complementary and intended to
18 support implementation of universal ethical and scientific standards in the context of clinical trials with a
19 focus on under-represented populations.

20 Glossary

21	AVAREF	African Vaccine Regulatory Forum
22	CIOMS	Council for International Organizations of Medical Sciences
23	COVID	coronavirus disease
24	HIC	high-income countries
25	ICTRP	International Clinical Trial Registration Platform
26	ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
27		
28	IRB	institutional review board
29	LMIC	low- and middle-income countries
30	NRA	national regulatory authority
31	R&D	research and development
32	REC	research ethics committee
33	TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
34		

35 Definitions

36 Clinical trial

37 The definition of the term clinical trial for the purposes of this document is a clinical research study that:

- 38 • is interventional, with:
 - 39 ○ one or more intervention arms, pharmacological or nonpharmacological (including, but not
 - 40 limited to, medicines, cells and other biological products, surgical procedures, radiological
 - 41 procedures, devices, behavioural treatments, process-of-care changes and preventive care)
 - 42 ○ at least one control arm
 - 43 ○ prospective assignment to intervention or control;
- 44 • aims to evaluate the effects of the intervention(s) on health-related outcomes;
- 45 • is carried out at any level of the health system, from community to intensive care settings

46 Clinical trial ecosystem

47 The World Health Assembly in resolution WHA75.8 (2022) on Strengthening clinical trials to provide high-
48 quality evidence on health interventions and to improve research quality and coordination¹ requested the
49 Director-General to identify and propose best practices and other measures to strengthen the global clinical
50 trial ecosystem and to review existing guidance and develop new guidance as needed on best practices for
51 clinical trials. However, the resolution does not provide a definition of the clinical trial ecosystem, and
52 currently there is no consensus on what this should be. The Director-General therefore invited inputs on
53 how such an ecosystem should be defined during a public consultation in October–November 2022.
54 Although a universal definition was not established, there were calls to include a holistic view of the
55 ecosystem that included the following elements related to trials:

- 56 • prioritization of trials relevant to all major population groups that they are intended to benefit,
57 with a particular focus on under-represented populations and countries with a high burden of
58 illness
- 59 • trial funding, design, conduct and reporting
- 60 • oversight by regulatory bodies and ethics committees
- 61 • coordination and collaboration
- 62 • liaison with regulatory bodies, health technology assessment authorities and other relevant
63 national authorities
- 64 • the perspective of those conducting systematic reviews, meta-analyses and developing
65 evidence-based guidelines
- 66 • public, patient and community involvement
- 67 • assessment of both pharmacological and nonpharmacological interventions, including
68 behavioural interventions
- 69 • the need for evidence-based decision making to be more culturally embedded in society.

70 These inputs have fed into the guidance presented in this document.

71

72

73 1. Introduction

74 1.1 The importance of clinical trials

75 Clinical research studies of health care interventions broadly fall into two groups: observational studies and
76 clinical trials. Observational studies can be useful for the assessment of large effects (adverse or beneficial)
77 of an intervention or assessing the effects of prolonged exposure to an intervention. However, because of
78 their inherent potential biases, observational studies can be unreliable for determining the effects of many
79 health interventions, especially moderate effects.²

80 This limitation is relevant because most interventions have only modest effects on health and disease, even
81 if they have a large effect on intermediate features (for example, physiological or laboratory tests). However,
82 even modest improvements in health can be important, provided any benefits are not substantially offset by
83 detrimental effects, and therefore it is vital that these modest effects are detected reliably.

84 Clinical trials thus have a **central role in generating the evidence needed to inform the development and**
85 **implementation of health interventions**, because they can reliably determine whether a health intervention
86 has any effect by ensuring that any biases or random errors inherent in the study design are small with
87 respect to the expected treatment effect. The results of such clinical trials and associated meta-analyses
88 have been transformative in advancing global public health.

89 In this context, the phrase “good trials” is taken to mean that the trials are **reliably informative, ethical and**
90 **efficient and answer scientifically important questions relevant to the populations they are intended to**
91 **benefit, with findings generalizable to those populations.**

92

93 1.2 The clinical trials environment: an evolving landscape

94 The clinical trial environment has progressed tremendously since the modern concepts of clinical trials were
95 introduced, with important changes having also taken place in the social, ethical and regulatory environment
96 globally. There is now a broader recognition of the very large health, social and economic returns on
97 investments in research.³ Clinical trials and development of interventions are being supported by industry,
98 non-industry parties (such as academic institutions), and public-private partnerships, sometimes with
99 support from external partners in translational research.

100 There have been revisions of the Declaration of Helsinki,⁴ and development of guidance on clinical trials,
101 notably the CIOMS International ethical guidelines,⁵ ICH clinical trial guidelines⁶ and more recently guidance
102 from the Good Clinical Trials Collaborative,⁷ as well as the creation of guidance by regulators⁸ with new
103 regulatory pathways for approval of products specifically developed for diseases in low- and middle-income
104 countries (LMICs) and public health emergencies.

105 Patient organizations and advocacy groups have come to the fore globally in recent years, raising awareness
106 of the issues affecting patients as well as the role of scientific research in improving their quality of life.

107 All these factors have significantly changed the environment for clinical trials, and the research landscape
108 continues to evolve, with clinical trials in LMICs a particular area of growth. Although early-phase clinical
109 trials are largely still conducted in HICs where adequate testing facilities exist, some Asian and African
110 countries are beginning to conduct such studies. For example, investigational Phase I studies of Ebola virus

disease vaccines were done in HICs, but also in low-resource communities not experiencing an outbreak⁹ and late-stage clinical trials of relevant vaccines are increasingly being conducted in LMICs.¹⁰

[Section A](#) provided high-level guidance in the design and conduct of clinical trials on the key scientific and ethical features that should be universal to all trials (regardless of whether they are set in HICs or LMICs) in order to enable them to produce reliably informative, high-quality evidence, regardless of context. However, for this to be fully translated into improved public health, there also needs to be continued capacity-strengthening and evolution of the global ecosystem for clinical trials. [Section B](#) provides high-level guidance and recommendations on how to do this, through focusing on two main aspects:

(1) [adequate clinical trial infrastructure](#)

(2) [efficient interagency priority setting and collaborative working](#).

[Section C](#) provides high-level guidance highlighting the importance of recruiting diverse populations into clinical trials.

1.3 The problem: paucity of reliable clinical trial evidence

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 well-designed and well-conducted clinical trials**. The reasons may be that clinical trials were never done, or those that were done failed to produce scientifically-robust and clinically-relevant answers or the results were never published. The result can be failure to identify and use effective interventions or the continuing use of ineffective or hazardous interventions. This can lead to research waste, cause unnecessary harm or suffering, and reduce trust in those who develop or use health interventions. The problem is global, affecting high-, middle- and low-income countries, with **some populations particularly under-represented in clinical trials**.

1.3.1 Populations typically under-represented in clinical trials

A lack of funding for clinical trials is particularly prominent in several areas, especially those where the traditional model of development of interventions does not provide incentives for research and development (R&D).¹¹ This includes:

- some LMICs and resource-limited settings;
- those of certain racial or ethnic backgrounds;
- traditionally under-represented populations such as children, pregnant and lactating women and older adults;
- interventions with poor commercial potential, such as lifestyle modifications, in rare diseases, neglected tropical diseases, some epidemic diseases and interventions related to antimicrobial resistance.

1.3.2 Research waste

The need to reduce research waste is a long-recognized global issue affecting clinical trials across the spectrum of the clinical trials ecosystem, with urgency to address this problem having been the focus of much discussion.¹² However, it was particularly highlighted by the research response to the pandemic of

coronavirus disease (COVID-19). WHO's International Clinical Trials Registry Platform (ICTRP)^b recorded more than 18 000 COVID-19-related clinical trials during the pandemic, but of these the vast majority are thought to have contributed little to the evidence base, owing to failure to complete enrolment or through poor design features.¹³ A small proportion, probably less than 10%, were well-designed and well-implemented clinical trials (both publicly and non-publicly funded) and contributed greatly to policy recommendations by WHO and other bodies. In particular, the emergence of large adaptive platform trials¹⁴ with pragmatic features embedded into health systems was pivotal in generating evidence in COVID-19 therapeutics.^{15.16.17}

1.3.3 LMICs /resource-limited settings

The World Bank's bands of income levels are commonly used to classify countries in terms of resources.^c LMICs bear the highest burden of preventable disease globally and, although their burden of disease has decreased since 1990, more efforts are needed to maintain these gains and close the significant remaining gap. Disparities in health outcomes are related to social determinants and structural impediments to fair access to affordable, safe and efficacious interventions and essential health services as well as technology, health workforce, infrastructure and financing. The consequences were particularly highlighted during the COVID-19 pandemic, when gross inequities hindered timely access to medical and other COVID-19 pandemic-related products, notably vaccines,¹⁸ oxygen supplies, personal protective equipment, diagnostics and therapeutics.

LMICs specifically face several 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.¹⁹ Secondly, neonatal, maternal and nutritional diseases are prevalent, and neonatal, under-5 and maternal mortality is high in LMICs. In addition, LMICs have similar rates of noncommunicable diseases to those in upper-middle- and high-income countries (HICs). This means that as the disease burden from communicable diseases in LMICs decreases over time their burden of noncommunicable diseases will become proportionally higher.

However, most research is still conducted in HICs,²⁰ focusing on diseases prevalent in those settings, where a conducive environment, infrastructure and capacity for clinical trials have been built up in past decades to address the health priorities of these countries. In contrast, clinical research and clinical trials in LMICs (where there is limited research capacity and/or commercial viability) has often been focused on observational or implementation studies conducted after the registration or approval of an intervention in HICs, often targeting maternal and child health, infectious disease and nutrition. There is a therefore a pressing need to promote and advance good-quality clinical trials across all phases of research in LMICs and

^b See International Clinical Trials Registry Platform (ICTRP). Geneva: World Health Organization; 2023 (website) (<https://www.who.int/clinical-trials-registry-platform>, accessed 15 June 2023).

^c 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.

low-resource settings, encompassing both communicable and noncommunicable disease in 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.

Furthermore, in the past there have been examples of trials where the disease burden allows for more rapid accrual of endpoints in LMICs or in certain racial and ethnic minority groups, yet these data have been used to file for marketing authorization in HICs or high-resource settings, sometimes leading to availability of interventions in the latter but not the former. Similarly, trials of diagnostics have taken place in LMICs or low-resource settings, the results of which then failed to provide any post-diagnostic support in these settings where there was no capacity or infrastructure to provide treatment and support for the diagnosed condition. These are examples of exploitation and a clear breach of ethical principles, which must be addressed to ensure justice and build trust in research across all communities.

1.3.4 Under-represented populations

Clinical trial cohorts have often lacked diversity, with inadequate representation of certain populations, including:

- pregnant and lactating women
- infants and children
- older adults
- those with multiple comorbidities or disabilities
- those of certain racial or ethnic backgrounds or indigenous populations (with clinical trials often previously over-representing white male participants and those of western European ancestry).

Pregnant and lactating women have typically been excluded from clinical trials by default, while infants and children are often not considered early enough in clinical development programmes, which is a particular challenge for LMICs where the paediatric age group represents a large proportion of the population. From a population health perspective, older adults are a crucial group as they often carry a significant burden of disease and in whom any absolute effects of an intervention may be particularly large. For example, whereas relative protective effects may be higher for certain interventions (such as vaccines) in young healthy adults, the absolute benefits will often be much higher in older adults given their higher rates of events and case fatality for many conditions. Despite this, older adults are often excluded from clinical trials.

Lack of appropriate inclusion and diversity in clinical trials therefore means that trial results may be less generalizable to groups who would potentially benefit from the findings. This weakness has **impeded the quality of available evidence for decision-making, leaving huge uncertainties related to care and inequitable access to interventions**, sometimes most affecting the groups with the highest burden from a particular disease or condition or groups that make up most of the world's population.

The issue of under-representation can also apply to how results of clinical trials are reported. For example, age, sex and ethnicity were all associated with mortality from COVID-19, and sex and gender can have implications for vaccine efficacy, rendering inclusive participation and comprehensive reporting of outcomes important in COVID-19 trials. However, only a minority of COVID-19 vaccine trials reported primary outcomes disaggregated by sex.²¹ This fact mirrors a trend seen in published national health statistics

reports, with many countries not including disaggregated data²² despite guidelines for disaggregation being in place.²³ However, it is important to remember that findings for subgroups need appropriate interpretation, particularly where numbers are small.

1.4 Steps required to facilitate good clinical trials and reduce waste

1.4.1 Identification of a relevant research question

A key prerequisite for conducting a good clinical trial is **research priority setting** through identification of an important and relevant research question. Clinical trials should principally **focus on public health and disease areas of current 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 take into account epidemiological trends so as 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 addressed. This can be facilitated by conducting systematic reviews 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 guiding the selection of interventions and outcome measures. By conducting a systematic review researchers can prevent unnecessary duplication and minimize research waste.²⁴

1.4.2 Proportionate design and conduct of clinical trials

One area identified as a potential barrier to clinical trials has been **overinterpretation of existing regulations and guidance for clinical trials**. This in turn has often led to **excessive bureaucracy** which, although well-intended, has also typically 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. 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 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 such as collecting and filing documents, the length of clinical trial protocols and other documentation.²⁵ Crucially, **trial processes should be proportionate to their context and any associated risks, with efficient implementation**. 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.

1.4.3 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.

1.4.4 Diversity and inclusion; representation of under-represented populations

To maximize the potential of clinical trials it is vital to ensure that they are inclusive with a diverse range of trial participants, including those traditionally under-represented by evidence from clinical trials, including those in LMICs and resource-limited settings, pregnant and lactating women, infants and children, older adults, people with comorbidities and those from under-represented racial and ethnic backgrounds.

1.5 Aims of this guidance

This guidance updates and adapts WHO's previous work on research capacity²⁶ for the context of clinical trials as framed in resolution WHA75.8 (2022). It aims to address the issues outlined above, **improve efficiency and minimize research waste**, both in normal times and in time of emergency or pandemics. These themes are described in three sections as follows:

- [Section A](#) provides high-level guidance for **clinical trial design and conduct** 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;
- [Section B](#) provides high-level **guidance and recommendations on best practices for the strengthening of the ecosystem** for clinical trials, including enabling actions;
- [Section C](#) provides high-level guidance on **how clinical trials can better address evidence needs in under-represented subpopulations**, in particular, **pregnant and lactating women and infants and children**.

These sections are followed by a presentation of recommendations for Member States, research funders and researchers.

1.6 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 in which randomization is used 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, for example:

- **any design for a clinical trial**: including comparisons of two or more interventions (one of which may be to provide no additional active intervention beyond usual practice/standard care); blinded or not; parallel, cluster, crossover or other design;
- **any health intervention**: including (but not limited to) pharmaceutical and biological therapies; use of medical devices; surgical procedures; vaccination; nutritional measures; cognitive, behavioural and psychological interventions; physical therapy interventions; digital and public health approaches;

- **any purpose:** including (but not limited to) guidelines processes; recommendations for clinical practice or public health strategies; health technology assessments – there is some relevance to regulatory submissions noting the central role of the guidance issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which this document does not replace;
- **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 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; trial sponsors (both academic 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, while complying with universal scientific and ethical standards.

For clinical trials designed to support submission to regulatory authorities concerned with medicinal products, trial sponsors should continue to refer to the ICH guidelines, in particular ICH E6 on good clinical practice,²⁷ ICH E8 on general considerations for clinical studies²⁸ 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 not restricted to medicinal products.

2. Section A: Key scientific and ethical considerations for good clinical trials

The following points, taken together, capture the necessary qualities of a well-designed, well-implemented and clinically-relevant trial. 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, any 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.

This process requires the combination of:

- **randomization without foreknowledge of intervention allocation:** as a result, any differences in health outcomes between the groups are due either to the effect of the study intervention or to the play of chance;
- **adequate sample size:** to reduce the impact of *random errors* (that is, the play of chance) on the results;
- **unbiased assessment of outcomes:** that is, not influenced by knowledge of intervention allocation;
- **intention-to-treat analyses:** to compare outcomes according to which intervention arm participants were allocated to and **without emphasis on data-derived subgroups.**

Good clinical trials should include the following 12 features.

2.1.1 Appropriate trial population

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

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. In particular, children, pregnant and lactating women should as a norm be eligible for trial enrolment unless a valid justification is provided for their exclusion (see [Section C](#)).

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 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.

2.1.2 Robust intervention allocation

Key message: Randomization requires generation of an unpredictable allocation schedule with concealment of to which intervention 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^{d29} (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 has been 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).

2.1.3 Adequate size

Key message: A clinical trial should be sufficiently large 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, then, in addition to randomization (to minimize biases), 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 (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).³⁰

There are some scenarios for which it is inappropriate or challenging to randomize sufficiently large numbers of participants, such as trials assessing interventions for rare diseases.^e For such trials, it may be helpful to contribute to a broader collaboration to conduct them or to select a clinically relevant outcome for which the effect size is expected to be larger (for example, a physiological or imaging biomarker). It may be possible to reduce the impact of random errors through the statistical analyses that are done or by making assessments at a time when the effects of the intervention are expected to be greatest.

2.1.4 Blinding and masking of allocated trial intervention

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 or by ensuring that those individuals or systems responsible for assessing participant outcomes are unaware of the intervention allocation.

^d Cluster randomized clinical trials can be used in many settings, both HICs and LMICs. They are further discussed in [Section C](#) in relation to the latter.

^e As also referred to in ICH Harmonised Tripartite Guideline E9: Statistical principles for clinical trial – scientific guideline.

Why this is important: In some 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. These consequences are particularly important for trials in which blinding of the allocated intervention is neither feasible nor desirable. 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, blinded or masked outcome assessment should still be pursued (see the section on [ascertainment of outcomes](#) below).

2.1.5 Adherence to allocated trial intervention

Key message: Efforts should be made to facilitate and encourage adherence to the allocated intervention(s).

Why this is important: 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 the false conclusion is more likely that there is no meaningful difference between the interventions when in fact there is one). Although there can be valid scenarios where 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.

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: 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

Key message: The outcomes that are assessed in a clinical trial need to be relevant to the question being addressed. These may include physiological measures, symptom scores, participant-reported outcomes, functional status, clinical events, or use of health care services. The way in which these are assessed should

435 be sufficiently robust and interpretable (for example, having been used in previous well-conducted trials or
436 validated in a relevant context, particularly for surrogate outcomes). Use of standardized core outcomes
437 should be considered, particularly in the context of the results of a clinical trial being potentially relevant for
438 inclusion in later meta-analyses.^f

439 *Why this is important:* The ways by which the consequences of the randomized intervention are measured
440 should be sensitive to the expected effects of the intervention and appropriate to the study question, and in
441 general should be applicable and clinically or scientifically meaningful for the relevant population. The choice
442 of outcomes may vary depending on the extent of prior knowledge of the effects of the intervention (for
443 instance, early trials may assess the effects on imaging and laboratory markers whereas later trials study the
444 effects on clinical outcomes). It is rarely possible or desirable to assess the full range of potential outcomes
445 in a single trial. Instead, there should be a focus on providing a robust answer to the specific, well-
446 formulated question.

447 **2.1.8 Proportionate, efficient and reliable capture of data**

448 *Key messages:* Data collection should focus on those aspects needed for assessment and interpretation of
449 the trial results as specified in the protocol and should not be excessive. The extent to which information (for
450 example, on participant characteristics, concomitant treatments, clinical events and laboratory markers) is
451 detected and recorded, and the means and level of detail to which this is done, should be tailored to each
452 clinical trial. This should take into account what is needed to answer the trial question and the level of
453 existing knowledge about the background health condition and the intervention being studied. The choice of
454 approach to data collection may also be influenced by considerations such as its suitability, availability and
455 usability as well as the extent to which such information is sufficiently accurate, comprehensive, detailed and
456 timely.

457 Tools and methods for data collection, storage, exchange and access should enable the trial to be conducted
458 as designed, support privacy and security, and enable reliable and consistent analyses. Digital technology
459 and routine collection of health care data can provide alternative or complementary means to record
460 information about participants and their health at study entry, during the intervention and follow-up period,
461 and for many years beyond, where available and appropriate.

462 *Why this is important:* The volume, nature and level of detail of data collection should be balanced against its
463 potential value. Disproportionate data collection wastes time and resource. It places an unnecessary burden
464 on trial participants and staff, distracts attention from those aspects of the trial that have greatest
465 consequence for the participants, and reduces the scale (number of participants and duration of follow-up)
466 of what is achievable with available resources. In some trials, it may be appropriate to measure some
467 features (for example, intermediary biomarkers) in a subset of participants, chosen on the basis of baseline
468 characteristics or random selection, or at a limited number of timepoints. The choice of method used for

^f There are several such initiatives (see for instance the COMET Initiative [website] (<https://www.comet-initiative.org>, accessed 16 June 2023)), some designed to address specific disease areas such as chronic kidney and cardiovascular disease (see The SONG Initiative: standardised outcomes in nephrology [website] (<https://songinitiative.org>, accessed 16 June 2023) and Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B et al. 2017 Cardiovascular and stroke endpoint definitions for clinical trials. *Circulation* 2018; 137(9):961-972 (<https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.117.033502>, accessed 16 June 2023)).

data collection can have an important bearing on trial reliability and feasibility. Use of data standards[§] can help to ensure data quality and data integrity. 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 reducing 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 be the same in all randomized groups. These measures include the frequency and intensity of assessments. 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: Trial results should be analysed in accordance with the protocol and statistical analysis plan, which should be developed and clearly specified before the study results become known (that is, before conduct of any unblinded analyses on study outcomes), with the primary analysis focusing on the key question that the trial intends to address. Any analyses conducted after the initial results are known should be clearly identified as such. 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 pre-specified or are multiple in number (whether pre-specified 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.

Why this is important: The strength of a clinical trial 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,

[§] For example, the Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM) [website] (<https://www.cdisc.org/standards>, accessed 16 June 2023).

507 bias can be inadvertently introduced by the post-randomization removal of certain individuals from analyses
508 (such as those who are found later not to meet the eligibility criteria, who do not adhere to their allocated
509 study treatment or who commence an active intervention having been allocated to a control group).

510 Additional analyses can also be reported; for example, when the frequency of a specific side effect is being
511 described, it may be justifiable to record its incidence only among those who received the active
512 intervention, because randomized comparisons may not be needed to assess large effects. However, in
513 assessing moderate effects of the treatment, “on-treatment” or “per protocol” analyses can be misleading,
514 and intention-to-treat analyses are generally more trustworthy for assessing whether there is any real
515 difference between the allocated trial interventions in their effects. Additional analyses may be needed to
516 explore the impact of the treatment on any safety signals.

517 One of the most important sources of bias in the analysis is undue concentration on just part of the evidence
518 (such as selective emphasis on the result in one subgroup out of many or in a subgroup that is defined after
519 consideration of the data). Apparent differences between the therapeutic effects in different subgroups of
520 study participants can often be produced solely by the play of chance. Subgroups therefore need to be
521 relevant, pre-specified and limited in number. Analysis of results in subgroups determined by characteristics
522 observed after randomization should be avoided because, if the recorded value of some feature is (or could
523 be) affected by the trial intervention, then comparisons within subgroups that are defined by that factor
524 might be biased. It is important to interpret results in specific subgroups (for example men and women)
525 cautiously and consider whether they are consistent with the overall result. Failure to do so can lead to
526 people in those subgroups being treated inappropriately (given an intervention that is ineffective or harmful)
527 or untreated inappropriately (not being given an intervention that would benefit them) when there is no
528 good evidence that the effect varies between them.

529 **2.1.11 Assessing beneficial and harmful effects of the intervention**

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

535 *Why this is important:* Not every health event that happens in a trial is caused by one of the interventions;
536 individuals involved in a trial may suffer health events that have nothing to do with the trial or the
537 interventions being studied. (The less healthy the participants in the trial, the more likely that any health
538 event is related to factors other than the intervention.)

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

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 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 DMC provides a robust means to evaluate safety and efficacy data from an ongoing trial, including 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 DMC 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 DMC can promote transparency, and facilitate DMCs to operate more effectively. Some trials may not require a DMC (for example, if the trial is short-term and would not be modified regardless of interim data).

A 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 the randomized intervention group. 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^h combine the search for answers to important questions with scientific validity and appropriate protection and respect for all involved, particularly participants. Independent review of

^h The CIOMS International Ethical Guidelines for Health-related Research Involving Humans (Fourth Edition. Geneva: Switzerland: Council for International Organizations of Medical Sciences; 2016

586 proposals for new research, through an institutional review board (IRB), research ethics committee (REC) or
587 equivalent is an important governance tool and can help to ensure appropriate steps are taken to protect
588 the rights and welfare of participants.

589 **2.2.1 Appropriate communication with participants**

590 *Key message:* At all stages of a clinical trial (before, during and after), relevant, easily-understandable
591 information should be shared with trial participants (or, where applicable, their legal representatives), with a
592 careful balance of the duty to inform against the risk of information saturation and account being taken of
593 the clinical context. Information should be provided in a clear manner and in suitable languages and formats
594 for the intended audiences.ⁱ

595 *Why this is important:* Providing timely and relevant information to participants during a trial facilitates
596 ethical research with benefits to both the participants and the quality of the trial results. It is essential that
597 potential or recruited trial participants are appropriately informed but presenting excessive or exhaustive
598 detail can work against this objective by overwhelming, confusing or disconcerting potential participants.
599 Care should be taken to communicate effectively and enable relevant discussion. The exact approach may be
600 influenced by the context of the research, including clinical, cultural or other issues.

601 **2.2.2 Relevant consent**

602 *Key messages:* The trial consent process should clearly explain to potential trial participants (or, where
603 applicable, their legal representatives) the reasons why the trial is being done, the questions it is seeking to
604 answer, what is involved for them, and the potential benefits and risks of participation. The extent, nature
605 and timing of information provided before and during the informed consent process should be guided by the
606 level of additional risks and commitment that participation in the trial would involve in the context of the
607 usual clinical care or circumstances that the same individuals would normally receive. The information
608 provided should prioritize the needs and expectations of the prospective participant rather than those of the
609 organization or individuals conducting the trial. Consent information should be widely accessible and readily
610 understandable (for example, with respect to readability), avoid legalistic or other technical language, and be
611 as succinct as possible.³¹ Approaches to obtaining and maintaining ongoing consent and communication
612 should be relevant to the trial it relates to, with due consideration given to cultural and community contexts.
613 Development of consent processes should give due consideration to potential wider future use of data. The
614 wording of consent forms should facilitate optimal use of data where possible through inclusion of text that
615 allows for appropriate and relevant future application of data or use of biological samples in research.

616 *Why this is important:* Consent is valid if it is informed, voluntary and competently given before entry into a
617 trial. There are some situations in which an individual cannot give informed consent (for example, for infants
618 or individuals lacking mental capacity) or it is not practical to do so because of the urgency of the medical
619 situation (for example, in cases of trauma or medical emergencies). Such situations should not automatically
620 preclude the conduct of clinical trials (which may be the only way to provide reliable information on how
621 best to manage such health issues) but appropriate safeguards should be put in place to maintain the rights
622 of the individuals who participate. For some trials and in some individual situations, explicit consent may be

(<https://cioms.ch/shop/product/international-ethical-guidelines-for-health-related-research-involving-humans/>,
accessed 16 June 2023)) provide detailed commentary on how universal ethical principles, as outlined in the World
Medical Association's Declaration of Helsinki, should be applied with a particular focus on resource-limited settings.

ⁱ Including provision for those who have impaired sight or hearing and those who are illiterate, where applicable.

623 modified or waived^j by the overseeing ethics committee or IRB. In such cases, there should be minimal
624 additional risks and burdens to participation in comparison to the usual care a prospective participant might
625 receive outside the trial. Data from clinical trials should be used to maximal efficiency to minimize potential
626 research waste.

627 **2.2.3 Changing consent**

628 *Key message:* Participants should be free to stop or change the nature of their participation without affecting
629 the usual care received, and efforts should be made to determine the intended meaning of such individual
630 decisions.

631 *Why this is important:* The term “withdrawal” can mean different things to different people, ranging from
632 participants wanting to stop receiving the study intervention, to stopping attending study visits in person
633 (but perhaps be happy to be contacted or for information about their health outcomes to be collected from
634 their regular doctors or from routine health data systems), to their biological samples no longer being
635 assayed or stored or their data no longer being processed or shared. Therefore, it is clearer to avoid the term
636 and instead clarify with the participant(s) what level of participation they want to have and what they want
637 to cease. If this is not properly explored and the withdrawal is interpreted with prejudice to mean complete
638 removal from the study, trial participants may be unnecessarily and inadvertently lost to full or partial
639 follow-up, with possible implications for the reliability of trial findings, and may miss out on aspects of the
640 RCT that matter to them (such as attendance at study visits or being informed about progress and results of
641 the study).

642 **2.2.4 Implications of changing consent**

643 *Key message:* The rights of an individual participant to withdraw consent for use of trial data and samples
644 that have already been collected should be balanced with scientific and ethical requirements.

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

651 **2.2.5 Managing the safety of individual participants in the clinical trial**

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

^j For these exceptional situations, see Guideline 10 of CIOMS’ Revised International Guidelines for Ethical Health-related Human Research (2016).

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

670 **2.2.6 Communication of new information relevant to the intervention**

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

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

685
686

687 **2.3 Good clinical trials are collaborative and transparent**

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

693 **2.3.1 Working in partnership with people and communities**

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

696 *Why this is important:* The early involvement of a diverse range of patients and relevant members of the
697 public can play a key role in: refining and prioritizing research questions; assessing and increasing the
698 acceptability and feasibility of the trial; selecting trial intervention and outcomes that are relevant and
699 meaningful to the intended population; developing the trial design and procedures; optimizing the nature
700 and delivery of information; and encouraging dialogue about access to health care interventions that prove
701 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. Good Participatory Practice guidelines have been developed, by WHO and others,^{32,33} that provide detailed guidance on working in partnership with stakeholders and communities. All relevant stakeholders should have the opportunity to learn, raise concerns and provide input into planning and implementation.³⁴ To ensure broad representation, efforts should be made to ensure appropriate diversity in any such patient and public involvement.

2.3.2 Collaboration among organizations

Key message: It is important that interactions between individuals in different organizations involved in the 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 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:

- (a) Clinical trials should be registered from the outset on a publicly-available registry of clinical trials.^k
- (b) Making other information about a trial (including its protocol and other documentation such as the statistical analysis plan) publicly available is strongly encouraged.
- (c) Once the trial is completed, reports should be publicly available in a timely manner (typically within 12 months³⁵) and should describe the study design, methods and results in a clear and transparent manner, regardless of the trial's findings,³⁶ preferably in open-access publications.³⁷
- (d) 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 than reporting results to the clinical and scientific community.
- (e) Data sharing should be enabled at a suitable time,³⁸ if ethical, feasible and scientifically appropriate.
- (f) There should also be transparency regarding trial funding, approval processes and any relevant conflicts of interest.

Why this is important: Transparency and sharing of knowledge about health care interventions helps to generate further knowledge, build and maintain trust and gives confidence to both those involved in the trial and those who are not. 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.

^k WHO's International Clinical Trial Registry Platform (www.who.int/ictvp) provides global standards for trial registration.

740 **2.4 Good clinical trials are designed to be feasible for their context**

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

744 **2.4.1 Setting and context**

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

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

755 **2.4.2 Use of existing resources**

756 *Key messages:* Clinical trials should be tailored to be practicable given the available infrastructure in relevant
757 settings. This planning includes making optimal use of pre-existing resources and facilities, including using
758 any expertise, skills, professional standards and quality oversight mechanisms associated with routine health
759 care practice.

760 All individuals involved in performing a trial should be qualified by education, training or experience to
761 perform their respective task(s), but it should be recognized that there are many aspects of conducting a
762 clinical trial that are in line with routine care and therefore may not require additional training, procedures
763 or checks.

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

770 **2.5 Good clinical trials manage quality effectively and efficiently**

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

773 **2.5.1 Good governance**

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

776 *Why this is important:* Effective and efficient governance (for example, through a trial steering committee)
777 helps to maintain the scientific and ethical integrity of a trial and to provide advice on appropriate courses of

778 action. It should be structured to enable effective responses to issues that may arise, particularly when
779 multiple organizations are involved, and enable reasonably consistent implementation across the trial.

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

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

790 **2.5.2 Protecting trial integrity**

791 *Key message:* The integrity of the results of a clinical trial should be protected by ensuring that decisions
792 about its design, delivery and analysis are not influenced by premature access to unblinded information
793 about the emerging results.

794 *Why this is important:* Interim data provide an unreliable and biased assessment of the overall benefit-to-
795 risk profile of the trial interventions. Prejudgment based on overinterpretation of interim data can affect
796 recruitment, delivery of interventions and follow-up, risking the ability of the trial to achieve its goals.³⁹

797 **2.5.3 Planning for success and focusing on issues that matter**

798 *Key messages:* Good quality should be prospectively built into the design and delivery of clinical trials, rather
799 than relying on retrospectively trying to detect issues after they have occurred (when often they cannot be
800 rectified). Such trials should be described in a well-articulated, concise and operationally-viable protocol
801 which is tailored to be practicable given the available infrastructure in relevant settings.

802 *Why this is important:* Rather than trying to avoid all possible issues, the aim should be to identify the key
803 issues that would have a meaningful impact on participant well-being and safety or on decision-making
804 based on the trial results. Specific attention should be focused on identifying sources of systematic errors
805 that may introduce bias. Efforts can then be focused on eliminating, mitigating and monitoring those issues.
806 Such an assessment should consider the context of the clinical trial and what is additional or special about it
807 by comparison with routine care. Broadly, these considerations come under four headings:

- 808 (a) *factors associated with the intervention* (for example, known and potential adverse effects;
809 comorbidities or concomitant medications that might impact safety; special requirements for
810 administering the intervention)
- 811 (b) *factors associated with evaluations required to answer the study objective that would not be expected in*
812 *usual care* (for example, additional invasive investigations)
- 813 (c) *resource implications* (for example, need for specialist imaging or laboratory assays; unfamiliar or novel
814 procedures requiring additional training)
- 815 (d) *ethical and privacy implications* (for example, access to medical records and sharing of health
816 information with pharmaceutical companies, researchers, or regulators).

817 Such an assessment process can then be used to guide the development of approaches to mitigate errors,
818 such as improving trial design or implementing standard operating procedures, protocol-specific training and
819 tailored trial monitoring. Trial processes that add scientific or ethical value to clinical trials should be
820 prioritized, and those that do not, or where the additional complexity outweighs the benefit, should be
821 avoided.

822 **2.5.4 Monitoring, auditing and inspection of study quality**

823 *Key message:* The nature and frequency of any trial monitoring, auditing and inspection activities should be
824 proportionate to any identified risks to study quality.

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

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

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

844

3. Section B: Guidance on strengthening the clinical trial ecosystem

3.1 Adequate clinical trial infrastructure

Key message: Efficient high-quality clinical trials require adequate infrastructure, both in terms of [physical infrastructure](#) and [trial personnel](#). Where possible, this should involve **use and optimization of pre-existing resources and facilities**, including those associated with routine health care practice. Appropriate development and enhancement of such infrastructure facilitate future research.

Why this is important: As outlined in [Section A](#), it should be recognized that, even though some investment in clinical trial infrastructure may be required, many aspects of performing a clinical trial are in line with routine care and therefore may not require additional facilities, training, procedures or checks. Where additional training is required, it is generally preferable to train or mentor the existing local health workforce, wherever possible, rather than staff that work on research in isolation, and ensure health researchers are well integrated into the health system. Such an approach minimizes research waste, improves quality and helps to ensure that the clinical trial results are generalizable.

It is also increasingly recognized that the capacity-building involved in designing and running many clinical trials represents 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 or improve regular medical care when the initial studies are completed. It is often through participation in well-designed, responsible trials that local medical doctors and other health care professionals are introduced to the principles of evidence-based medicine and then go on to apply them in their own practice.

3.1.1 Physical infrastructure

The physical infrastructure typically includes **laboratories** (a core need for many types of clinical trial, depending on the intervention) and well-functioning **clinical research institutions**. These can be established within government bodies, academic institutions, or the private sector.

At lower-capacity levels, every country should work to establish at least one well-functioning clinical research institution, whereas at higher-capacity levels, health research institutions often expand with specializations in certain thematic areas or types of health research such as biomedical science, implementation science and behavioural science. It is essential that at least some of these clinical research institutions include a focus on conduct and governance of clinical trials and that they can work with or develop additional clinical research sites within relevant communities to respond to public health needs.

3.1.2 Clinical trial personnel

Although WHO does not currently have a maturity-level system to provide support to countries in further developing clinical trial infrastructure (as exists for national regulatory systems and research ethics systems), but the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases framework for clinical research competency⁴⁰ lists all the competencies that should be demonstrated by a clinical research team to undertake a successful study. The framework can be applied to any research study,

885 regardless of the size of the team, place, disease focus and type of research.¹ Together with its supporting
886 tools, the framework is also intended to be used to help to plan staffing requirements for a study, carry out
887 appraisals of staff, guide career development and create educational curricula for research staff. These areas
888 are summarized as below, with four main competency domains (see also Figure 1):

- 889 • **Scientific thinking**
 - 890 ○ design and planning of research
 - 891 ○ protocol operationalization
 - 892 ○ interpretation of study results
- 893 • **Ethics, quality and risk management**
 - 894 ○ safeguards
 - 895 ○ quality assurance
 - 896 ○ regulations and governance
- 897 • **Study and site management**
 - 898 ○ oversight
 - 899 ○ study communications
 - 900 ○ staff management
 - 901 ○ resources management
- 902 • **Research operations**
 - 903 ○ data flow
 - 904 ○ clinical and laboratory operations
 - 905 ○ interactions with the public/participants.

¹ Not all competencies are required in every unit as some elements, such as creation and maintenance of the trial database, may be located and performed at a central coordination unit.

Figure 1. TDR Global Competency Framework for Clinical Research (reproduced with permission)



(Acronyms. 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).

3.2 Efficient interagency priority setting and collaborative working

Key messages: Efficient high-quality clinical trials require all parties involved to engage proactively in research-priority setting and to foster relevant and proportionate approaches to the funding and approval of such trials. Collaboration and communication between such parties are vital. Adequate funding and training of staff in all agencies concerned with clinical trials are as essential as funding of clinical trials and research institutions. (see an example in Box 1).

Why this is important: Reliably informative, high-quality clinical trials that address relevant questions can only be enabled if all relevant parties understand, engage and adopt risk-based proportionate approaches, work together to agree on research priorities, and communicate and collaborate effectively to reduce research waste. To achieve this goal requires investment in the training of such staff, with a focus on the key scientific and ethical principles described in [Section A](#).

Relevant parties include:

- national authorities concerned with health research, such as regulatory authorities
- ethics bodies (research ethics committees [RECs] or institutional review boards [IRBs])
- funders
- health technology assessment bodies and guideline makers.

Particular topics for consideration and action include:

- [research priority setting and funding](#)
- [research approval processes](#)
- [clinical research networks](#)
- [translating research evidence into practice](#)
- [use of standards to facilitate data sharing and meta-analyses](#)
- [use of benchmarking tools](#).

These aspects are expanded upon in the following subsections 3.2.1–3.2.6.

Box 1: A model for national authorities to collaboratively prioritise, fund and support high impact clinical trials for vulnerable populations

The COVID-19 pandemic, as well as other epidemic crises such as those of Ebola or Zika virus disease, necessitated the swift mobilization of research funds, prioritization of clinical inquiries, and implementation of multicentre, multicountry trials. The HIV pandemic also facilitated significant international research collaborations, albeit at a slower pace. Although these endeavours achieved notable successes, they were not without inefficiencies. Additionally, vulnerable populations, including pregnant and lactating women, newborns and children, were often overlooked or included belatedly in these research initiatives, resulting in growing inequities and limited access to medical innovations, particularly in LMICs.

Of equal concern are health crises occurring outside the context of emergencies, which fail to capture the attention and commitment of funders, despite their profound impact on survival and lifelong health. A prime example is the childhood obesity pandemic. Globally, the prevalence of overweight and obesity among children and adolescents aged 5–19 years has dramatically risen from a mere 4% in 1975 to more than 18% in 2016. LMICs face similar challenges as high-income settings. Failing to prevent obesity carries lifelong consequences for affected children and imposes substantial economic and resource burdens on health systems and national economies. This situation highlights the need for coordinated and efficient mobilization of research efforts to guide public health action, not solely limited to infectious disease outbreaks.

The Healthy Life Trajectories Initiative (HeLTI) serves as an exemplar of how national authorities can collectively respond to a high-impact, common challenge and generate evidence and operational insights to inform child health policies and programs. 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 HeLTI consortium, research teams harmonized research questions, interventions and data and biospecimen collection. In the future, pooled analyses will amplify the findings from individual trials and complement the lessons learned during implementation. By April 2023, recruitment had been completed in one country, nearly completed in a second country and was progressing well in the remaining two settings. Initial findings will be reported in 2024.

HeLTI embodies how national authorities and funders, with technical support from WHO, can effectively target and drive high-quality research aligned with country needs, adhering to scientific standards that inform critical areas of public health policy for vulnerable populations. It provides a roadmap for optimizing research investments, enabling research prioritization, and facilitating appropriate national and international resource mobilization.

Source: WHO Department of Maternal, Newborn, Child and Adolescent Health and Ageing.

3.2.1 Research priority setting and funding

Research programmes and their funding should be **informed by national, regional and global health research priorities**, and there should be mechanisms to update priorities quickly as new health problems emerge. **Appropriate collaboration and coordination between all concerned parties can facilitate research priority setting, minimize unnecessary duplication, improve efficiency and hence reduce waste.**

It can be particularly beneficial for national regulatory authorities (NRAs) to maintain active links with other national and international clinical research networks in this context.

WHO has a key role in developing global health research priorities and has issued guidance for their development.⁴¹ Regional health priorities are also often set by regional organizations in liaison with WHO, and, where such organizations become involved in clinical research, efficiency should be an explicit goal. 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 medical or health research authorities. Conversely, where clinical trials are aligned with global priorities, NRAs have some responsibility to avoid unnecessary bureaucracy or inefficiencies in approval processes. Equally, it is also important to recognize that not all research in resource-limited settings has added value. Increasingly, regulatory authorities require local clinical trials as a condition for registration of medicines and health products, even if they have already been registered in other jurisdictions. Local trials for registration purposes and other special regulatory requirements should only be imposed if there is a solid scientific rationale and should not be undertaken as a mere formality.

Health research funders should also ensure that funding is efficiently aligned with national, regional and global priorities, and liaise with each other to ensure that:

- calls for funding are coordinated and collectively address agreed priorities in an efficient manner
- information is shared to avoid unhelpful duplication and enhance synergies
- grant funding is transparent, for instance being accessible through research investment portals (such as the global observatory on health R&D); transparency can also decrease inequities in LMICs by revealing how much funding is apportioned to HICs compared with that to LMICs.

Models for coordination of funders are available in different disease areas.^m

Rapid priority setting is vital in public health emergencies, as referred to in resolution WHA75.8 (2022). 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](#) further details specific considerations in times of public health emergencies.

Research funders should also take action to increase the quality of evidence from clinical trials, for example providing incentives, focusing resources on trials that will inform policy and improve health outcomes, and encouraging trial protocols to be well-designed and well-implemented, as outlined in [Section A](#), as opposed to a principal focus on the amount of output generated.

3.2.2 Research approval processes

For research priority setting to achieve its goal, **trial authorization processes also need to be proportionate with risk-based flexibilities to allow for the rapid initiation and conduct of agreed priority trials.**

In each country it should be clear which parties take responsibility for reviewing and approving clinical trials and overseeing the conduct of IRBs or RECs. **Interagency coordination models can substantially minimize unnecessary duplication and improve efficiency** by facilitating communication and coordination between bodies regulating clinical trials and giving ethics approval, for instance by identifying a single IRB or REC for priority multicentre trials and coordinating review where many approval bodies are required to consider a single clinical trial. WHO encourages such regulatory harmonization and good reliance procedures,⁴² with good practice being for regulatory authorities to take into account and give significant weight to work performed by other regulators, as appropriate.

The Health Research Authority in the United Kingdom of Great Britain and Northern Ireland is an example of a national strategic research oversight body which promotes coordinated and coherent approaches to research review by regulators and ethics committees, with its Integrated Research Application System being a single system for applying for the permissions and approvals for research on health and social care/community care in the country.⁴³ Given that clinical trials are highly important to evaluate not only

^m Examples include: the [Global Alliance for Chronic Diseases](#), which brings together major international research funding agencies specifically to address the growing burden of noncommunicable diseases in LMICs and vulnerable populations in HICs; the Joint Programming Initiative on Antimicrobial Resistance; the Global Research Collaboration for Infectious Disease Preparedness (and its GloPID-R Funders Living Roadmap for Clinical Trial Coordination – see <https://www.glopid-r.org/launch-of-a-new-tool-for-funders-living-roadmap-will-support-stronger-coordination-of-clinical-trial-responses-to-epidemics-and-pandemics/>, accessed 3 July 2023); and the European & Developing Countries Clinical Trials Partnership (see <https://www.edctp.org>), which funds clinical research for medical tools to detect, treat and prevent poverty-related infectious diseases in sub-Saharan Africa.

1031 medical products but also nonpharmacological interventions (for example, behavioural interventions and
1032 their application to health outcomes in many areas including but not restricted to mental health), pooling
1033 expertise into a single national authority can maximize use of resources.

1034
1035 Other operationally-effective models for coordinated review of clinical trials authorization include the
1036 African Vaccine Regulators Forum (AVAREF).⁴⁴ This network has a joint review procedure that is endorsed by
1037 the countries on the continent. It provides a platform for parallel review of multicountry clinical trial
1038 applications by NRAs, national RECs and all relevant local RECs and IRBs, enabling all parties involved in
1039 oversight of a trial to provide coordinated reviews to trial sponsors with agreed timeframes for clinical trial
1040 approval by all such involved oversight bodies. However, further work is needed to develop better
1041 coordination mechanisms focusing on RECs, as, in most regions, regulatory harmonization between NRAs is
1042 more advanced than coordination between RECs at the time of writing. AVAREF's strategy allows its
1043 Secretariat to support research and development in all countries on the African continent, as well
1044 strengthening the capacity of clinical trial oversight.

1045
1046 The International Coalition of Medicines Regulatory Authorities⁴⁵ is exploring several approaches to
1047 harmonization and collaborative assessments between agencies with the aim of streamlining and improving
1048 efficiency and coordination of procedures for multicountry trials, without undermining their quality, safety
1049 or ethical aspects. Such models need to be developed further, which requires investment in infrastructure at
1050 national, regional and global levels.

1051
1052 As highlighted in resolution WHA75.8 (2022), rapid review of clinical trials submissions and decision-making
1053 by NRAs, RECs and IRBs in public health emergencies of international concern is of particular importance. In
1054 2020, WHO published detailed guidance on rapid review of research by RECs during public health
1055 emergencies.⁴⁶

1056
1057 The AVAREF model has successfully been used in such an emergency context. In 2020, based on lessons
1058 learned during the Ebola virus disease outbreaks and the possible need to initiate clinical trials urgently
1059 during an ongoing epidemic, AVAREF published a guidance document on strategy and guidance for
1060 emergency preparedness.⁴⁷ This provision was later successfully used for one of the largest multicountry
1061 clinical trials in Africa, involving 13 countries and several sponsors. With this emergency provision, three
1062 options are now available for AVAREF joint reviews, with the timelines reflecting the public health impact of
1063 the investigational product based on selection criteria.

1064
1065 A key lesson learned from the COVID-19 pandemic is that specific procedures should be developed in normal
1066 times that will allow rapid activation of protocols in emergencies to facilitate a rapid, large-scale response to
1067 meet compelling public health needs, whether these are related to endemic or epidemic diseases. Wherever
1068 possible, pre-positioning and prior approval of master protocols can further accelerate the response when
1069 emergencies occur.⁴⁸ It should be noted, however, that regulatory bodies, including ethics committees, can
1070 only respond quickly in emergencies if they have adequate resources and capacity. Therefore, it is essential
1071 that resources are provided for training personnel in proportionate regulatory processes and research ethics
1072 in normal times. This area is sometimes neglected in considerations of research capacity strengthening but it
1073 is vitally important.

1074
1075 [Annex 1](#) further details specific considerations in times of public health emergency.

1076 **3.2.3 Clinical research networks**

1077 Clinical research networks can play a crucial role in enabling coordination between parties, accelerating the
1078 generation of high-quality evidence and reducing waste. Numerous such networks were identified through
1079 the public consultation that the WHO Secretariat held in late 2022. WHO's African Region has been the focus
1080 of major networking and strengthening of research capacity, but major gaps in networks were identified in
1081 part of Latin America, the Caribbean, eastern Europe, WHO's Eastern Mediterranean Region and parts of
1082 Asia.

1083 Member States are encouraged to consider developing platforms to facilitate collaboration among
1084 researchers in their countries, each maintaining a database of all clinical research institutions so that
1085 researchers who want to partner with a particular institution would know what capacities exist in the
1086 country.

1087 **3.2.4 Translating research evidence into practice**

1088 Health technology assessment agencies and national bodies that develop health guidelines represent a vital
1089 group that should be engaged throughout the clinical trial process. Building in the perspectives of those
1090 entities (for example, by seeking their views on relevant trial outcomes) through collaboration, those
1091 designing and approving trials can help to ensure that the formulation of recommendations in guidelines or
1092 other policy documents is based on mutually-agreed priorities and robust evidence. **(see an example in Box**
1093 **2).** Crucially, this approach can facilitate translation of clinical trial results into practice and hence public
1094 health benefits. However, even where there are strong recommendations for or against particular
1095 interventions based on high-quality randomized data, practice is not always based on such robust evidence.
1096 An example of this lack of linkage was observed during the COVID-19 pandemic, when some countries
1097 witnessed widespread use of interventions for which there was no supportive evidence and when there was
1098 strong evidence that interventions were not beneficial (such as, the use of hydroxychloroquine for treatment
1099 of COVID-19). Use should be, therefore, made of the extensive resources on evidence-informed decision-
1100 making, such as the WHO's Evidence-informed Policy Network,⁴⁹ which provides guidance on translation of
1101 knowledge to health policy-making.

1102 Box 2: Clinical trial processes as part of a cycle rather than a linear pathway: the example of antenatal
1103 glucocorticoids.

1104 Research should begin and end with a comprehensive review of existing evidence to address knowledge
1105 gaps and incorporate new findings into the evidence base. When clinical trials commence by involving
1106 relevant stakeholders in prioritizing research questions, it ensures the relevance of the study to those who
1107 need to support the implementation of effective and safe interventions.

1108 During the development of WHO guidelines, a research gap and the need for investigation were identified
1109 regarding the safety and efficacy of antenatal glucocorticoids in preventing preterm infant mortality in
1110 resource-limited settings.ⁱ These interventions were long recommended in high-income settings, but
1111 conflicting results from a large-scale implementation research conducted in six resource-limited countries
1112 introduced significant uncertainty about the role and potential harm of this intervention in such settings. To
1113 address this research question, a group of stakeholders prioritized it and implemented a well-designed

randomized trial in several countries in Asia and Africa.ⁱⁱ Great care was taken during the trial's design stage to address scientific and ethical considerations.

The trial results were consistent with a meta-analysis of trials conducted in high-income settings,ⁱⁱⁱ indicating that antenatal glucocorticoids reduce preterm infant mortality in both resource-limited and high-income settings. Following best practices, WHO's guidelines were updated to incorporate the trial results and any other recent evidence into the global evidence base,ⁱⁱⁱ enabling the formulation of global recommendations on the use of antenatal glucocorticoids to prevent preterm infant mortality.^{iv} This trial exemplifies 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.

Sources:

ⁱ WHO recommendations on interventions to improve preterm birth outcomes. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1&isAllowed=y, accessed 6 July 2023).

ⁱⁱ 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).

ⁱⁱⁱ 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).

^{iv} WHO recommendations on antenatal corticosteroids for improving preterm birth outcomes. Geneva: World Health Organization; 2022 (<https://www.who.int/publications/i/item/9789240057296>, accessed 6 July 2023).

3.2.5 Use of standards to facilitate data sharing and meta-analyses

Use of data standards and/or standardized data protocols can allow for collection of data that enables better amalgamation of datasets for meta-analyses after appropriate removal of identifiers and anonymization. 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.⁵⁰

3.2.6 Use of benchmarking tools

The WHO Global Benchmarking Tool for evaluation of national regulatory systems for medicinal products⁵¹ provides a maturity-level framework for Member States to improve the functioning of their national regulatory systems, including those for oversight of clinical trials. More recently the WHO Secretariat is piloting 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.⁵² Note that the scope of the latter ethics document is broader in that it is not restricted to medicinal products. Sometimes, guidance intended for application to clinical trials of medicinal products, such as ICH guidance documents, is applied outside its scope, thereby raising concerns of a lack of proportionality in requirements.

1153 [Annex 2](#) summarizes recommendations for the different parties involved in clinical trials, which include
1154 aspects of efficient interagency priority setting and collaborative working.

1155

DRAFT

4. Section C: Addressing under-represented subpopulations

Key message: Strenuous efforts need to be made to recruit diverse populations into clinical trials.

Why this is important: Inclusive eligibility criteria increase the relevance of the findings to all potential groups who may benefit from an intervention, and hence increases accessibility to interventions.

As outlined in the [Introduction](#), a lack of appropriate clinical trials has been particularly prominent in certain population types including:

- people in LMICs and resource-limited settings
- children and infants
- pregnant and lactating women
- elderly people
- people with health conditions, comorbidities or disabilities
- people of certain racial or ethnic backgrounds or indigenous populations.

LMICs bear the highest burden of preventable disease globally. There is, therefore, a pressing need to promote and advance good-clinical trials across all phases of research in LMICs and low-resource settings, encompassing both communicable and noncommunicable diseases to address the substantial morbidity and mortality risks affecting people in those settings. However, the design of such trials needs to take into consideration the typically-limited research capacity in these settings.

One reason for exclusion of children and pregnant and lactating women was that they were seen as physiologically-special populations. However, beyond these physiological differences, there are many circumstances that can marginalize potential research participants in different and overlapping ways. Unnecessary research with people in vulnerable situations (or indeed any people) should be avoided, but it is a matter of basic equity and justice that, unless there is a good medical or scientific justification for doing otherwise, the default position should be that all people are afforded the opportunity to be included in research to ensure that they equally benefit from scientific advancement and interventions that are proven to be equally safe and efficacious.

For all under-represented populations, people involved in research must find ways to include as broad and varied population as possible in clinical trials through appropriate patient, public and community engagement while safeguarding participants' rights and welfare, and to find practical ways to do this. As one example, WHO has created a framework for meaningful engagement of people living with noncommunicable diseases and mental health and neurological conditions.⁵³

Exclusion of certain groups on the basis that a trial may not have adequate power to detect subgroup-specific effects is inappropriate. As described in [Section A](#), when interpreting trial results for specific subgroups (for example, men and women), it is more important to consider whether they are consistent with the overall trial result. Clinical trials with different eligibility criteria that involve large numbers of many different types of patients can also be combined in meta-analyses of individual participant data, and hence can provide reliable information about treatment effects that can be widely generalized to different circumstances.

In particular, in recent years there have been moves to expand inclusion of groups in LMICs and resource-limited settings and to change from exclusion to inclusion of children, infants and pregnant and lactating women in clinical trials. These groups are discussed further below.

4.1 Enabling clinical trials in resource-limited settings

Measures to enable clinical trials in resource-limited settings are outlined in [Section B](#) and [Annex 2](#). In addition, cluster randomized clinical trials are a specific type of trial which, if robustly designed and conducted, can be useful in determining which interventions might be useful for public health or clinical care. Cluster randomized clinical trials can be used in numerous settings in both HICs and LMICs, but are in particular increasing in popularity in LMICs or resource-limited settings, as many of their design features lend themselves well to priority areas of research in these environments. In cluster trials, the intervention is randomly allocated to whole groups of people or organizations, such as communities, hospitals, clinics or schools, instead of to individuals. This approach can be especially relevant in health system research where interventions often involve changes to the way health care is delivered or organized rather than specific treatments or medications for individual patients. In addition, cluster randomized clinical trials can provide information about the implementation of the intervention (for example, how it was delivered or the extent to which it was adopted by each group). They do, however, have some key methodological considerations that should be taken into account in their design and analysis, and recently there have been substantial efforts towards unifying and improving the standards of the design, analysis and interpretation of the results of cluster trials.²⁹ Alternatives, such as stepped-wedge or cluster-paired designs, have also been designed and may require smaller sample sizes than traditional cluster randomized trials. These designs may also be particularly useful in LMICs, where resources for recruitment and follow-up may be limited.

4.2 Enabling clinical trials in pregnant and lactating women

Inclusion of pregnant and lactating women in clinical trials, after a robust benefit–risk assessment, can ensure that they have the possibility to benefit from potentially life-saving therapies. This trend must be extended so that such women potentially benefit from a reliable knowledge base to make treatment decisions about other interventions.

Trials of therapeutic interventions in pregnant and lactating women can be considered in two different groups, with different implications for assessment of their benefits and risks:

(a) **trials of interventions where there is pre-existing evidence of use, and safety of use, in pregnancy**

Such trials include, for example, instances when the same intervention has been used for a different clinical indication in pregnant and lactating women, or when evidence exists concerning use of an intervention in the same or a similar class. Assessment of benefits may include consideration of the severity of the condition for pregnant and lactating women, their potential for improved health outcomes, and the consequent improved outcomes for their pregnancy and infants. Assessment of risks should encompass previous evidence of use of the same or similar interventions in pregnancy and subsequent outcomes of pregnancy and for infants. Reassuring pre-existing information concerning use in pregnancy and lactation favours inclusion of pregnant and lactating women in a trial and will ensure they are able to access therapies. For example, a new inactivated vaccine would benefit from a wealth of safety information on the safety of use of inactivated vaccines in pregnant women.

(b) **trials of novel interventions where there is no pre-existing evidence of use of the same, or similar, interventions in pregnancy**

A benefit–risk assessment should be undertaken that should include consideration of the severity of maternal disease and pre-existing reproductive toxicology studies. Where maternal disease is severe and maternal and pregnancy outcomes are poor and reproductive toxicology studies are reassuring, benefit to women is likely to outweigh any potential risk. If the potential for benefit is unclear, independent

1239 assessment by an organization or individuals with expertise in maternal-fetal medicine may be helpful to
1240 inform decisions concerning the inclusion of pregnant and lactating women.

1241 In several therapeutic areas, practical ways to accelerate investigation of new medicines and vaccines in
1242 pregnant and lactating women have already been explored, charting a path for collaboration across
1243 stakeholders to potentially replicate in other disease areas.^{54,55,56}

1244 **4.3 Enabling paediatric clinical trials**

1245 Although much progress has been made for paediatric medicines in the past 20 years, additional efforts
1246 need to be made to give children access to the same quality of health interventions as for adults globally, for
1247 which the relevant dosing, safety and efficacy have been demonstrated.

1248 Children should not be an afterthought in the development programme, but should be considered from the
1249 onset in terms of planning and collecting data throughout the clinical development of interventions. Children
1250 should be included as early as possible in clinical trials of interventions of potential benefit to them, with
1251 collection of data (for example, pharmacokinetic data and relevant biomarkers) planned in advance in order
1252 to better inform the demonstration of safety and efficacy in the paediatric population.

1253 The use of existing knowledge and available efficacy and safety data in adults and older paediatric age
1254 groups is essential for the better design of a development programme for a paediatric medicine. Wherever
1255 possible, extrapolation of adult efficacy and safety data to children should be considered. Modelling and
1256 simulation are also tools that can help to avoid unnecessary paediatric studies and to ensure that
1257 appropriate data are generated from the smallest number of paediatric patients.

1258 Historically, enrolment of children in clinical trials was done in an age-stratified way, enrolling adolescents
1259 and older children first, leaving the inclusion of younger patients last and resulting in long delays in collecting
1260 relevant efficacy and safety data. Current thinking is to encourage age-agnostic trial enrolment and use of
1261 standardized weight band dosing for children, with parallel enrolment of all children across those weight
1262 bands encouraged as much as possible.

1263 Optimizing trial design to enable rapid enrolment and generation of appropriate evidence in a difficult-to-
1264 study population is also very important. In this context, it is important to integrate regulatory requirements,
1265 including pharmacokinetic and safety evaluations, into broader efficacy studies conducted in children
1266 (including neonates) with the greatest burden of disease in LMICs. Targeting studies to priority research
1267 questions and leveraging approaches such as platform trials to increase efficiency in paediatric studies that
1268 present challenges with enrolment of children (such as neonatal sepsis) are of particular importance for this
1269 population.

1270 Another essential aspect of paediatric clinical development is the development of appropriate paediatric
1271 formulations. Gaps in evidence for the safe and efficacious administration of a medicinal product in children
1272 should be identified as early as possible in the development of trials, including those for the conduct of
1273 paediatric clinical studies. For oral forms, consideration should be given to formulations that are palatable
1274 and to flexibility in dosing according to different weights, for example scored dispersible tablets.
1275 Consideration should be given also to stability of formulations that are suitable for packaging, storage,
1276 distribution and use in LMICs.

1277 In May 2016, the Sixty-ninth World Health Assembly adopted resolution WHA69.20 on promoting innovation
1278 and access to quality, safe, efficacious and affordable medicines for children.⁵⁷ This area of work is also a
1279 feature of WHO's Roadmap towards ending tuberculosis in children and adolescents (2018)⁵⁸ which led
1280 WHO and other stakeholders to join forces to accelerate access to effective paediatric diagnostics and

1281 medicines for HIV infection and tuberculosis.⁵⁹ Following adoption of resolution WHA69.20, the Global
1282 Accelerator for Paediatric Formulations Network (GAP-f) was created to build on and formalize the model
1283 developed within the HIV community to provide a sustainable mechanism to ensure that safer, more
1284 effective and more durable paediatric formulations are developed and made available to children against an
1285 accelerated timeline.⁶⁰ Broadly speaking, WHO's process involves:

- 1286 • prioritizing the most-needed paediatric formulations, which should be evaluated in children relating
1287 to a specific disease or a condition;
- 1288 • engaging with product developers and regulatory processes so that formulations receive licensure
1289 for use in children;
- 1290 • coordinating efforts to introduce new, adapted formulations into health systems.

1291 Such global initiatives offer platforms for continuous engagement and collaborations across stakeholders
1292 including policy-makers, those in research networks and industry, regulators and members of civil society.

1293

1294

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:

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

Here good practices are discussed for funding, regulatory and ethics procedures in emergencies, including restatement of the provisions in normal times that also apply in emergencies.

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 A](#).

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.

1335 Funders should promote transparent translation into clinical guidelines, where appropriate, of results from
1336 clinical trials, including comparison with existing interventions on effectiveness, based on thorough
1337 assessment.

1338 Funders should explore measures during public health emergencies of international concern to encourage
1339 researchers to rapidly and responsibly share interpretable results of clinical trials, including negative results,
1340 with national regulatory bodies or other appropriate authorities, including WHO for clinical guideline
1341 development and Emergency Use Listing, to support rapid regulatory decision-making and emergency
1342 adaptation of clinical and public health guidelines as appropriate, and dissemination, including pre-print
1343 publication.

1344 **2. Supporting rapid decision-making by regulatory bodies in emergencies**

1345 Resolution WHA75.8 (2022) states that Member States should, “in accordance with their national and
1346 regional legal and regulatory frameworks and contexts and, as appropriate, ... support new and existing
1347 mechanisms to facilitate rapid regulatory decision-making during public health emergencies of international
1348 concern, so that:

1349 (a) safe, ethical, well-designed clinical trials can be approved and progress quickly;

1350 (b) data from clinical trials can be assessed rapidly, for example through the WHO Emergency Use
1351 Listing procedure, and health interventions deemed safe and effective can be swiftly authorized.”

1352 Regulatory bodies, whether those focusing on research ethics or marketing authorization of medicines and
1353 health products, can only respond quickly in emergencies if they have adequate resources and capacity.
1354 Therefore, it is essential that resources are provided for trained personnel in regulatory bodies, including
1355 those concerned with research ethics. This area is sometimes neglected in considerations of strengthening
1356 research capacity.

1357 Member States should have a process for rapid review by NRAs, RECs or IRBs of submissions of clinical trials
1358 in the context of health emergencies. Clinical trials judged to be a national priority should be reviewed and
1359 approved by a single REC or IRB in a country, avoiding excessive parallel reviews by many RECs or IRBs in the
1360 same country, and the rapid review process should provide guidance on which single REC or IRB will provide
1361 oversight in the country.

1362 Detailed guidance was published by WHO, as part of the R&D Blueprint activities, in 2020 on rapid review of
1363 research by ethics committees.⁴⁶

1364 **3. Sharing of results**

1365 During public health emergencies of international concern, further measures should be explored to
1366 encourage researchers to expedite fast and responsible sharing of interpretable results of clinical trials (for
1367 example, through pre-print publication) with national regulatory bodies or other appropriate authorities,
1368 including WHO for clinical guideline development and Emergency Use Listing. This in turn will support rapid
1369 regulatory decision-making and emergency adaptation of clinical and public health guidelines as appropriate.

Recommendations for Member States, research funders and researchers

The recommendationsⁿ 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 more 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.

1. High-level recommendations

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 where practicable; 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 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;
- (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

ⁿ 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 18 June 2023).)

populations such as children; link research findings with implementation, as appropriate, in national health systems to advance delivery of evidence-based health care.

1.2 For researchers

This could include researchers from academic institutions, the health care industry, contract research organizations and non-commercial 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 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 A](#) 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 (this will help to generate relevant findings and facilitate their translation into health benefits, thereby justifying the burdens of the study for 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; 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 efficient and robust enough 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.

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) support policies and multifunctional coalitions that facilitate a conducive environment for investing and participating in reliably-informative local clinical research;
- (b) support the establishment and maintenance of functional, efficient and effective multicountry systems and coalitions for ethical and regulatory oversight of clinical research;
- (c) prioritize research that answers important questions definitively and is relevant for the specific setting and the health care systems of the communities involved;
- (d) educate, empower and support patient organizations and communities to foster an understanding of the value of clinical research;
- (e) make agreements mandating open collaboration and data sharing through information technology and electronic health records, avoiding fragmentation of research efforts and capacity; support dissemination of study information and results.

2. Topic-specific recommendations

In this section, the arrows denote the following groups:

- *For Member States and regulatory authorities*
- ▷ *For researchers*
- *For funders*

2.1 Creating an enabling environment for clinical trials — Recommendations

- Member States are encouraged to create an enabling environment for health research, including clinical trials, and appreciate the benefits 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 investigators 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 benefits of clinical research.

2.2 Building research infrastructure and capacity — Recommendations

▶ *For Member States and regulatory authorities*

▷ *For researchers*

➤ *For funders*

▶▷▶ 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, analysis and research practice.

▶▷▶ Member States, international organizations and sponsors should invest in creating and maintaining local laboratory infrastructure, resources and staff capacity to support clinical trials wherever possible. Participation in external quality assurance schemes should be encouraged and supported.

▷▶ Where appropriate, it is important to conduct or identify a systematic review of existing evidence before initiating new research, particularly in the context of a clinical trial. This ensures that the planned study effectively addresses a specific gap in the available evidence

▷▶ Researchers and funders should consider working together and sharing their experiences, methods and resources.

▶▷▶ Regulatory authorities, funders and researchers should collaborate to establish or maintain existing clinical research networks.

2.3 Regulatory capacity, coordination and reliance — Recommendations

▶ *For Member States and regulatory authorities*

▷ *For researchers*

➤ *For funders*

▶ Regulatory authorities in resource-limited settings should compare and as far as possible align their practices with those in neighbouring countries, and should engage with more experienced authorities to share information and resources.

▶ Regulatory authorities should consider WHO's guidance on the high-level principles and considerations for good reliance practices in the regulation of medical products⁴², especially those in resource-constrained 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 resource support for training and continuous education in the key scientific and ethical considerations for good clinical trials.

2.4 Implementing standards — Recommendations

▶ *For Member States and regulatory authorities*

▷ *For researchers*

➤ *For funders*

1523 ►►► Good clinical trials apply standards that are based on key scientific and ethical principles and focused
1524 on issues that materially matter to the well-being of trial participants and the reliability of trial
1525 results. Risk-based proportionate approaches should be adopted, as outlined in this document.

1526 **2.5 Protecting research participants— Recommendations**

1527 ► *For Member States and regulatory authorities*

1528 ▷ *For researchers*

1529 ➤ *For funders*

1530 ▷ Researchers should allocate adequate time and resources for measures and materials to obtain
1531 properly informed consent. If written informed consent is appropriate, forms should be as concise as
1532 possible. Innovative options for obtaining informed consent using new technologies, such as
1533 audiovisual models to ensure better understanding, should be considered where appropriate. At all
1534 stages of a clinical trial, relevant, easily understandable information should be shared with trial
1535 participants, with careful balancing of the duty to inform against the risk of information saturation
1536 and taking account of the clinical context. Information should be provided in a clear manner and in
1537 suitable languages and formats for the intended audiences.

1538 ►►► Patients and communities should be engaged to help to provide valuable contributions to the design
1539 and execution of clinical trials and interpretation of their results, and hence enable effective
1540 measures to protect research participants' rights.

1541 **2.6 Avoiding exploitative research — Recommendations**

1542 ► *For Member States and regulatory authorities*

1543 ▷ *For researchers*

1544 ➤ *For funders*

1545 ► The priority-setting exercise for clinical research should involve relevant local bodies, patients and
1546 the public and should take into account under-represented groups and people in vulnerable
1547 situations. Before approving the study, local authorities may want to negotiate with the sponsors
1548 about how the benefits will be shared with the local population.

1550 ► Ethical review should consider whether sufficient resources are available at the study site to avoid
1551 any negative impact on routine patient care.

1552 ►►► Research projects initiated by sponsors in HICs should be approved by a REC in the host country as
1553 well the REC in the high-income setting.

1554 ►►► Measures should be taken to oppose double standards in research and support long-term equitable
1555 research relationships between partners in LMICs and HICs.[°]

1556 **2.7 Ethical review and capacity-building — Recommendations**

1557 ► *For Member States and regulatory authorities*

1558 ▷ *For researchers*

1559 ➤ *For funders*

[°] For example, as outlined in the TRUST Project's Global Code of Conduct for Research in Resource Poor Settings (TRUST. [website] (<https://www.globalcodeofconduct.org/wp-content/uploads/2018/05/Global-Code-of-Conduct-Brochure.pdf>, accessed 19 June 2023).)

- ▶ 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 on scientific research and the key scientific and ethical considerations for good clinical trials as outlined in [Section A](#), training for expedited and rapid reviews, and elements of follow-up, risk-based proportionate 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,⁶¹ 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.

2.8 Participant and community engagement — Recommendations

- ▶ *For Member States and regulatory authorities*
- ▷ *For researchers*
- *For funders*
- ▷ Where necessary, researchers should educate community representatives on knowledge 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 or study continuum in a meaningful way.
- ▶▶ Communities in resource-limited settings should be empowered to negotiate for fair benefits of clinical research. This will require support by an effective, independent local REC.

2.9 Conceptualizing and designing research — Recommendations

- ▶ *For Member States and regulatory authorities*
- ▷ *For researchers*
- *For funders*
- ▷ 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.

- 1601 ▷ Efforts should be made for clinical trials to include as diverse and inclusive a trial population as
1602 feasible.
- 1603 ►▷ Research to address the health needs of children and women, including pregnant and lactating
1604 women, should be viewed as the norm unless there is valid justification to exclude them.
- 1605 ►▷ Efforts should be made to ensure that clinical trials recruit as diverse and inclusive populations as
1606 possible.
- 1607 ►▷ Both industry-sponsored and academic research in resource-limited settings should focus on
1608 relevant research questions that will help to achieve a clear health benefit.
- 1609 ▷ Researchers should consider the use of adaptive study designs and data collection, where possible
1610 and appropriate.
- 1611 ▷ As a rule, to minimize the burden on the local infrastructure and population, data collection should
1612 focus on those variables that provide needed scientific information for the study.
- 1613 ▷ Research protocols should be adapted as much as possible to local clinical practice and
1614 cultural/social considerations, for example regarding frequency of visits and sampling.
- 1615 ►▷ Member States, international organizations and sponsors should support education on research
1616 methodology and study designs in resource-limited settings, as well as building the necessary
1617 infrastructure.
- 1618 **2.10 Responsible information-sharing — Recommendations**
- 1619 ► *For Member States and regulatory authorities*
- 1620 ▷ *For researchers*
- 1621 ► *For funders*
- 1622 ▷ Researchers should minimize the risk of re-identification of individual participants from any data that
1623 may be shared outside the study and should make both the plans for data-sharing and any risk of
1624 data identification clear to study participants as part of seeking informed consent.
- 1625 ►▷ Academic research institutions and hospitals should support appropriate management, analysis and
1626 publication of clinical research data and results, seeking support for writing and translation where
1627 necessary.
- 1628 ► Funders are encouraged to accommodate the costs of data-related activities when funding clinical
1629 research.
- 1630 ►► Funders and sponsors are encouraged to allocate dedicated human resources for communicating
1631 objective, validated information and research results to participants, communities, clinicians and
1632 policy-makers before, during and after research, as well as to the media and the general public.
- 1633 **2.11 Underserved populations: women of child-bearing age — Recommendations**
- 1634 ► *For Member States and regulatory authorities*
- 1635 ▷ *For researchers*
- 1636 ► *For funders*
- 1637 ►▷ More research should be conducted to address the needs of women of child-bearing age, including
1638 pregnant and lactating women.

- 1639 ►▷ Researchers and ethics committees should ensure that the cultural context is respected when
1640 studies are conducted in women of child-bearing age, including pregnant and lactating women.
- 1641 ►▷► The establishment and use of pregnancy registries in LMICs should be encouraged.
- 1642 **2.12 Under-represented populations: children — Recommendations**
- 1643 ► *For Member States and regulatory authorities*
- 1644 ▷ *For researchers*
- 1645 ► *For funders*
- 1646 ►▷► Clinical studies in children in resource-limited settings are needed in not only hospitals but also
1647 communities, including those in remote areas.
- 1648 ▷► More pharmacokinetic and pharmacodynamic studies and pharmaceutical formulation studies
1649 should be conducted to support the development of safe and effective medicines for children.
- 1650 ►► Member States and funders should support initiatives to strengthen regulatory expertise for
1651 paediatric medicines as well as academic expertise in and capability for conducting paediatric clinical
1652 trials.

- ¹ 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 15 June 2023)).
- ² See Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence, *New Engl J Med* 2020; 382:674-678 (<https://www.nejm.org/doi/full/10.1056/NEJMs1901642>); Califf RM, Hernandez AF, Landray M. Weighing the benefits and risks of proliferating observational treatment assessments: observational cacophony, randomized harmony. *JAMA* 2020; 324(7):625-626 (<https://jamanetwork.com/journals/jama/article-abstract/2769139>); Bowman L, Baras A, Bombien R, Califf RM, Chen ZhM, Gale CP et al. Understanding the use of observational and randomized data in cardiovascular medicine. *Eur Heart J* 2020; 41(27):2571-2578 Appropriate use of randomised and observational evidence (<https://doi.org/10.1093/eurheartj/ehaa020>, accessed 19 June 2023); Bowman L, Weidinger F, Albert MA, Fry ETA, Pinto FJ, the Clinical Trial Expert Group, ESC Patient Forum. Randomized trials fit for the 21st century: a joint opinion from the European Society of Cardiology, American Heart Association, American College of Cardiology, and the World Heart Federation. *Circulation*. 2023; 147:925-929 (<https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.122.063378>).
- ³ WHO Council on the Economics of Health For All. Geneva: World Health Organization [website] (<https://www.who.int/groups/who-council-on-the-economics-of-health-for-all> and WHO report on Macroeconomics and Health: Investing in Health for Economic Development, accessed 17 June 2023).
- ⁴ 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 17 June 2023).
- ⁵ CIOMS. 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 17 June 2023).
- ⁶ ICH official website (<https://www.ich.org>, accessed 17 June 2023).
- ⁷ Good Clinical Trials Collaborative. Guidance for good randomized clinical trials. 2022 [website] (<https://www.goodtrials.org/the-guidance/guidance-overview/>, accessed 17 June 2023).
- ⁸ USFDA. Clinical trials guidance documents. [website] United States Food & Drug Administration; 2023 (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trials-guidance-documents>, accessed 17 June 2023).
- ⁹ Agnandji ST, Huttner A, Zinser ME, Njuguna P, Dhalke C, Fernandes F et al. Phase 1 trials of rVSVS Ebola vaccine in Africa and Europe. *N Engl J Med* 2016; 374:1647-1660 (<https://www.nejm.org/doi/full/10.1056/nejmoa1502924>, accessed 20 June 2023).
- ¹⁰ Grenham A, Villafana T. Vaccine development and trials in low and lower-middle-income countries: key issues, advances and future opportunities. *Hum Vaccin Immunotherapy* 2017; 13(9):2192-2199 doi: [10.1080/21645515.2017.1356495](https://doi.org/10.1080/21645515.2017.1356495) (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5617553/>, accessed 20 June 2023).
- ¹¹ Swaminathan S, Pécoul B, Abdullah H, Christou C, Gray G, Usselmuiden C et al. Reboot biomedical R&D in the global public interest. *Nature (London)* 2022; 602:207-210 doi: <https://doi.org/10.1038/d41586-022-00324-y> (<https://www.nature.com/articles/d41586-022-00324-y>, accessed 15 June 2023).
- ¹² Research: increasing value, reducing waste. 2014. *The Lancet* (<https://www.thelancet.com/series/research>, accessed 15 June 2023). See also Gold SM, Landray MJ, Medhurst N, Otte C. Fast tracking informative clinical trials: lessons for mental health. *The Lancet Psychiatry* 2023; 10(6):376-378 ([https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366\(23\)00115-3/fulltext](https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(23)00115-3/fulltext), accessed 16 June 2023).
- ¹³ Bugin K, Woodcock J. Trends in COVID-19 therapeutic clinical trials. *Nat Rev Drug Discov* 2021; 20:254-255 doi: <https://doi.org/10.1038/d41573-021-00037-3> (<https://www.nature.com/articles/d41573-021-00037-3>, accessed 15 June 2023); Park JJH, Mogg R, Smith GE, Makimuli-Mpungu E, Jehan F, Rayner CR et al. How COVID-19 has fundamentally changed clinical research in global health. *The Lancet Global Health* 2021; 9(5):E711-E720 ([https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(20\)30542-8/fulltext#%20](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30542-8/fulltext#%20), accessed 16 June 2023).

- 14 Park JJH, Ford N, Xavier D, Ashorn P, Grais RF, Bhutta ZA et al. Randomised trials at the level of the individual. *The Lancet Glob Health* 2021; 9(5):E691-E700 ([https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(20\)30540-4/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30540-4/fulltext), access 3 July 2023).
- 15 University of Oxford. RECOVERY – Randomised Evaluation of COVID-19 Therapy [website] (<https://www.recoverytrial.net/>, accessed 15 June 2023).
- 16 World Health Organization. WHO COVID-19 Solidarity Therapeutics Trial [website] (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments>, accessed 15 June 2023).
- 17 REMAP-CAP - A randomised, embedded, multi-factorial, adaptive platform trial for community-acquired pneumonia (website) (<https://www.remapcap.org/>, accessed 15 June 2023).
- 18 Yamey G, Garcia P, Hassan F, Mao Wenhui, McDade KK, Pai M, et al. It is not too late to achieve COVID-19 vaccine equity. *BMJ* 2022; 376 doi: <https://doi.org/10.1136/bmj-2022-070650> (<https://www.bmj.com/content/376/bmj-2022-070650>, accessed 15 June 2023).
- 19 The World Bank. Data. Population ages 0-14 years (% of total population) (Webpage) (https://data.worldbank.org/indicator/SP.POP.0014.TO.ZS?contextual=max&end=2021&locations=XM&most_recent_value_desc=true&start=1960&view=chart, accessed 15 June 2023).
- 20 Park JJH, Grais RF, Taljaard M, Nakimuli-Mpungu E, Jehan F, Nachega JB et al. Urgently seeking efficiency and sustainability of clinical trials in global health. *The Lancet Global Health* 2021; 9(5):E681-E690 ([https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(20\)30539-8/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30539-8/fulltext), accessed 16 June 2023).
- 21 Heidar S, Palmer-Ross A, Goodman T. A systematic review of the sex and gender reporting in COVID-19 clinical trials. *Vaccines (Basel)* 20 (21; 9(11):1322 doi: 10.3390/vaccines 9111322 (<https://pubmed.ncbi.nlm.nih.gov/34835253/>, accessed 15 June 2023).
- 22 World Health Organization. SCORE for health data technical package: global report on health data systems and capacity, 2020 [website] (<https://www.who.int/publications/i/item/9789240018709>, accessed 15 June 2023).
- 23 Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. *Res Integr Peer Rev* 2016; 1:2 doi: <https://doi.org/10.1186/s41073-016-0007-6> (<https://pubmed.ncbi.nlm.nih.gov/29451543/>, accessed 15 June 2023).
- 24 Clarke M, Hopewell S, Chalmers I. Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report. *J R Soc Med*. 2007 Apr;100(4):187-90. doi: 10.1177/014107680710011415 (<https://pubmed.ncbi.nlm.nih.gov/17404342/>, accessed 15 June 2023).
- 25 Califf RM, Cavazzoni P, Woodcock J. Benefits of streamlined point-of-care trial designs: lessons learned from the UK RECOVERY Study. *JAMA Intern Med*. 2022;182(12):1243–1244. doi:10.1001/jamainternmed.2022.4810 (<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2797846>, accessed 16 June 2023).
- 26 World Health Organization. (2012). The WHO strategy on research for health. Geneva: World Health Organization (<https://apps.who.int/iris/handle/10665/77935>, accessed 15 June 2023).
- 27 ICH-E6 Good clinical practice. Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2016 (https://database.ich.org/sites/default/files/ICH_E6-R3_GCP-Principles_Draft_2021_0419.pdf, accessed 3 July 2023).
- 28 ICH. 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 3 July 2023).
- 29 Dron L, Taljaard M, Cheung YB, Grais R, Ford N Thorlund K et al. The role and challenges of cluster randomised trials for global health. *The Lancet Global Health* 2021; 9(5): E701-E710 ([https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(20\)30541-6/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30541-6/fulltext), accessed 16 June 2023).
- 30 Cook J A, Julious S A, Sones W, Hampson L V, Hewitt C, Berlin J A et al. DELTA² guidance on choosing the target difference and undertaking and reporting the sample size calculation for a randomised controlled trial *BMJ* 2018; 363 :k3750 doi:10.1136/bmj.k3750 (<https://www.bmj.com/content/363/bmj.k3750>, accessed 16 June 2023).
- 31 CTTI. Informed consent [website] (<https://ctti-clinicaltrials.org/our-work/ethics-and-human-research-protection/informed-consent/>, accessed 16 June 2023).
- 32 WHO. Good Participatory Practice (GPP) with trial populations for the Solidarity Trial Vaccines (STV) An international randomised trial of candidate vaccines against COVID-19. Geneva: World Health Organization [website] (stv-gpp-handbook-v1.1-eng.pdf ([who.int](http://stv-gpp-handbook-v1.1-eng.pdf)), accessed 17 June 2023).

- ³³ AVAC, UNAIDS. Good Participatory Practice: Guidelines for biomedical HIV prevention trials, second edition. Geneva: Joint United Nations Programme on HIV/AIDS; 2011 (<https://www.vac.org/good-participatory-practice>, accessed 17 June 2023).
- ³⁴ WHO, R&D Blueprint. Good Participatory Practice (GPP) for COVID-19 clinical trials: a toolbox. Geneva: World Health Organization [website] (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 17 June 2023).
- ³⁵ WHO. Joint statement on public disclosure of results from clinical trials. Geneva: World Health Organization; 2017 [website] (<https://www.who.int/news/item/18-05-2017-joint-statement-on-registration>, accessed 17 June 2023).
- ³⁶ For links to Schulz KF, Altman DG, Moher D for the CONSORT Group. CONSORT 2010 Statement: update guidelines for reporting parallel group randomized trials, which was published simultaneously in nine journals, see the Equator Network link [website] (<https://www.equator-network.org/reporting-guidelines/consort/>, accessed 17 June 2023).
- ³⁷ WHO Policy on open access. Geneva: World Health Organization [website] (<https://www.who.int/about/policies/publishing/open-access>, accessed 17 June 2023).
- ³⁸ See WHO's policy brief: [Sharing and reuse of health-related data for research purposes: WHO policy and implementation guidance link](#). Geneva: World Health Organization; 2022 (<https://www.who.int/publications/i/item/9789240044968>, accessed 3 July 2023).
- ³⁹ Fleming TR, Sharples K, McCall J, Moore A, Rodgers A, Stewart R. Maintaining confidentiality of interim data to enhance trials integrity and credibility. Clin Trials 2008; 5(2):157-167 (https://journals.sagepub.com/doi/10.1177/1740774508089459?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed, accessed 3 July 2023).
- ⁴⁰ Global Health Training Centre. Research competencies. [website] (<https://globalhealthtrainingcentre.tghn.org/pds/core-competency-framework/>, accessed 17 June 2023).
- ⁴¹ WHO. A systematic approach for undertaking a research priority-setting exercise: guidance for WHO staff. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/334408>, accessed 17 June 2023).
- ⁴² WHO. WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. WHO Technical Report Series, No. 1033. Geneva: World Health Organization; 2021, Annex 10: Good reliance practices in the regulation of medical products: high level principles and considerations (<https://apps.who.int/iris/handle/10665/340323>, accessed 17 June 2023).
- ⁴³ See Health Research Authority. HRA approval. 2021 [website] (<https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/hra-approval/>, accessed 17 June 2023); and Integrated Research Application System. HRA and MCRW approval. 2023 [website] (<https://www.myresearchproject.org.uk/help/hlphraapproval.aspx>, accessed 17 June 2023).
- ⁴⁴ WHO. The African Vaccine Regulatory Forum. Brazzaville: Regional Office of the World Health Organization [website] (<https://www.afro.who.int/health-topics/immunization/avaref/overview>, accessed 18 June 2023).
- ⁴⁵ International Coalition of Medicines Regulatory Authorities. 2023 [website] (<https://www.icmra.info/drupal/en/home>, accessed 18 June 2023).
- ⁴⁶ WHO. Guidance for research ethics committees for rapid review of research during public health emergencies. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/332206>, accessed 18 June 2023).
- ⁴⁷ AVAREF. African Vaccine Regulatory Forum (AVAREF) Strategy and Guidance for Emergency Preparedness. 2020 [website] (https://www.afro.who.int/sites/default/files/2020-05/AVAREF_Guidance_Emergency_Preparedness_May2020.pdf, accessed 18 June 2023).
- ⁴⁸ Dean NE, Gsell PS, Brookmeyer R, Crawford FW, Donnelly CA, Ellenberg SS et al. Creating a framework for conducting randomized clinical trials during disease outbreaks. N Engl J Med 2020; 382:1366-1369 doi: 10.1056/NEJMs1905390 (<https://www.nejm.org/doi/10.1056/NEJMs1905390>, accessed 18 June 2023).
- ⁴⁹ WHO. EVIPNet: Evidence-informed Policy Network. [website] (<https://www.who.int/initiatives/evidence-informed-policy-network>, accessed 18 June 2023).
- ⁵⁰ WHO. Sharing and reuse of health-related data for research purposes: WHO policy and implementation guidance. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/handle/10665/352859>, accessed 18 June 2023).
- ⁵¹ WHO. WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory system of medical products: revision VI. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/341243>, accessed 18 June 2023).

- ⁵² WHO. 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/m/item/who-tool-for-benchmarking-ethics-oversight-of-health-related-research-with-human-participants>, accessed 18 June 2023).
- ⁵³ WHO. 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 19 June 2023).
- ⁵⁴ Vousden N, Haynes R, Findlay S, Horby P, Landray M, Chappell L et al. Facilitating participation in clinical trials during pregnancy *BMJ* 2023; 380 :e071278 doi:10.1136/bmj-2022-071278 (<https://www.bmj.com/content/380/bmj-2022-071278>, accessed 19 June 2023).
- ⁵⁵ Krubiner CB, Faden RR, Karron RA, Little MO, Lyerly AD, Abramson JS et al. PREVENT Working Group. Pregnant women & vaccines against emerging epidemic threats: Ethics guidance for preparedness, research, and response. *Vaccine*. 2021 Jan 3;39(1):85-120. doi: 10.1016/j.vaccine.2019.01.011 (<https://pubmed.ncbi.nlm.nih.gov/31060949/>, accessed 19 June 2023).
- ⁵⁶ Lyerly AD, Beigi R, Bekker L-G, Chi BBH, Cohn SE, Diallo DD et al. Ending the evidence gap for pregnancy, HIV and co-infections: ethics guidance from the PHASES project. *J Internat AIDS Soc* 2021; 24(12):e25846 (<https://doi.org/10.1002/jia2.25846>, accessed 19 June 2023).
- 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 19 June 2023).
- ⁵⁸ WHO. Roadmap towards ending TB in children and adolescents, 2nd ed. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/handle/10665/275422>, accessed 20 June 2023).
- ⁵⁹ WHO. 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 19 June 2023).
- ⁶⁰ WHO. Global Accelerator for Paediatric Formulations Network (GAP-f). [website] Geneva: World Health Organization; 2023 (<https://www.who.int/initiatives/gap-f>, accessed 19 June 2023).
- ⁶¹ See WHO. WHO Global Health Ethics. [website] Geneva: World Health Organization (https://www.who.int/health-topics/ethics-and-health#tab=tab_1, accessed 19 June 2023).