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Feedback form for the public consultation for WHO guidance for global practices for clinical trials

Please note we are providing this word file of the full list of questions to help you plan your online submission – DO NOT make a submission using the word file, the submission should be through the online form. Wherever possible, please coordinate one submission per organization or per institution using the word file to collate input into consolidated submissions through the online form.

Personal information:

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General comments:

Please provide general comments on addressing context-specific issues, considerations, and implications for adapting and implementing the guidance, as well as identifying gaps in the evidence that should be addressed through future research. Please also provide any comments about the strengths of the draft guidance. Feedback to specific content to enhance clarity, address technical errors, and provide any missing information will be in the **suggested amendments**.

This feedback is provided on behalf of the STRIVE research consortium (https://insight.ccbr.umn.edu/i18/). STRIVE (Strategies and Treatments for Respiratory Infections and Viral Emergencies) is a global network of networks formed as a broad international research collaboration in 2022 in the aftermath of the COVID pandemic. STRIVE is primarily funded by the United States National Institutes of Health (NIH) and has developed a master protocol which currently guides 2 multi-site clinical trials. STRIVE is an outgrowth of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership sponsored by NIH, with the infrastructure provided by the ACTIV-3 initiative and sites from ACTIV-1, ACTIV-3, ACTIV-5 and ACTT. STRIVE is aimed at improving the clinical outcomes of patients with acute severe infections while being prepared to respond to infectious disease emergencies, through the rapid implementation of clinical trials designed to inform practice guidelines, public health policy, and the delivery of health care. With 200+ collaborating sites in 40+ countries on all six inhabited continents, and with substantial expertise and experience in conducting RCT's globally to address research questions of public health relevance, STRIVE is an example of an international consortium that can inform considerations to establish a well-functioning global trial ecosystem. Our feedback below reflects wide consultation among the key STRIVE stakeholders.

Some general comments to the draft guidance from WHO:

The document is well-structured and concise. It covers some of the relevant topics required for a much-needed strengthening of the global clinical trials ecosystem, and the specific guidance is largely consistent with STRIVE's perspective on global trials. The WHO is to be complimented for serving a convening role. Nonetheless, we think that the WHO's unique role could be used to further coordinate and advocate for work across governments in support of global clinical trials designed to address global health emergencies.

Some areas could be strengthened:

The definition of the "global clinical trial ecosystem" is critical to the overall message but is underdeveloped. An ecosystem is defined by its relevant actors and the systems in place that mediate their interaction. From our perspective, the critical actors are governments, funders, regulators, ethics

committees, pharmaceutical companies, academic trialists, trial participants, patient advocates, and patients. This guidance document could benefit from describing which aspects of these systems are barriers to preserving human health in the context of an international health emergency.

The WHO has a unique role with regard to defining the conditions of an international health emergency and is therefore uniquely positioned to describe how interactions in the ecosystem should be modified in the context of such an emergency. We observed that the systems for mediating interactions between agencies in the ecosystem were modified during the COVID-19 pandemic, however there is uncertainty as to the extent to which this will occur in the future, and this remains a current barrier to plans for trials during health emergencies. Securing agreements to make such modifications predictable would greatly facilitate planning for and potentially reduce harm from future such emergencies.

The target audience for recommendations on agreed processes is a combination of governments, regulators, and ethics committees. As such, this guidance document could be strengthened by focusing its message on these components of the ecosystem. However, this recommendation should not be construed as recommending reducing the amount of relatively technical material central to proper trial design (e.g., randomization and concurrent controls). Indeed, we applaud WHO for communicating critical aspects of trial design that may be unfamiliar to these actors in this guidance document.

In summary, this document is an important first step towards harmonizing expectations for the design and conduct of international trials in health emergencies. The next steps involve working with governments to coordinate funding and ethical and regulatory review of trials, as well as other aspects of trial conduct, such as international shipment of investigational agents. This will likely involve numerous meetings with members of the ecosystem from enough countries to ensure access to the relevant patient populations. These meetings could benefit from the participation of STRIVE and similar networks.

We now remark on a number of more specific areas:

Section 1.3.4 calls for increased involvement of pregnant and lactating women in trials. We agree with this point, in particular in situations where novel interventions are relevant to study in this population because of increased vulnerability to adverse serious outcomes (e.g., influenza and COVID-19). However, what is not recognized in the document is that a key reason for lack of data in this area is that regulatory authorities have very strict views on allowing pregnant and lactating women into trials. For example, pregnant women were not allowed to participate in trials assessing human antibodies to treat COVID-19 before teratogenic tests had been completed. During an infectious emergency, there is often the need to study novel agents, and not allowing pregnant women into such trials clearly leaves them at a disadvantage, is inconsistent with the autonomy of these women, and is ultimately inconsistent with the consent process. We call for discussions including experts and the child-bearing community on how to handle this dilemma in situations of infectious emergencies.

Section 1.4.1 points to the need of being able to identify a relevant research question. We agree the principles mentioned but request further clarity on how to reach consensus on this among the key stakeholders – principally, governments and funders.

We strongly agree with the sentiment mentioned in section 1.4.2 to ensure that oversight of trials by authorities should be proportional and focused on key aspects of conduct of the trial (i.e., consent, and appropriate reporting of data related to the key research question). Emphasis should be placed on those components of research activity that are critical to trial integrity, safety and outcome, as opposed to time spent on activities that have little bearing. This emphasis should be stronger developed within the document.

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Section 1.4.3 is short, lacks detailed content and appears almost as an afterthought. How to strengthen the global trial ecosystem is obviously the central component of the report.

We agree with the recognition of ICH guidelines when conducting trials aimed for review by regulatory authorities.

Please provide general comments for Section A: Key scientific and ethical considerations for good clinical trials.

This section would benefit from defining the principal aims of a trial. Many aspects of trial design, regulatory oversight and reporting of findings will depend on these aims. For example, some trials aim to inform regulatory authorities' decision on whether to licence a novel drug. Others aim to evaluate drugs already approved for routine use for other conditions. Yet other trials may address strategic questions for how to optimize the use of a drug known to be effective for a given condition (e.g., should be early or later in course of the disease).. The latter two categories may or may not involve a regulatory evaluation. For example, the label for dexamethasone does not include COVID-19, but the drug is often used for these patients.

Section 2.1.3 - adequate sample size. For clarity: "random errors must be small by comparison with the clinically meaningful effect sizes. Also, the clinically meaningful effect size may be smaller than the expected effect size, the sample size of the trial allows to have adequate power to detect." Also "Adjusting for pre-randomization covariates that are predictive of the outcome can also be an effective strategy for reducing the magnitude of random errors."

Section 2.1.4 - blinding and use of placebo/control. We agree with the principles stated here. Of note, some have stated the opinion that appropriate controls are not ethically acceptable – if the condition under study has a high fatality rate. For example, during the Ebola and Mpox epidemics, but also during the COVID-19 pandemic, this view was articulated, and trials designed accordingly. Trials of novel compounds were done (and some are still ongoing) without having a contemporarily identified control group. If no appropriate control group is included as part of trial design, possible benefit, or harm, from the intervention can't be assessed. Our view – consistent with the text of the draft document – is that it is both ethically acceptable and actually strongly encouraged to design trials evaluating novel interventions with a placebo/control group (e.g., randomize to active or placebo on top of whatever interventions that are considered as standard-of-care for that condition). Such trials clearly must be monitored during their conduct by a DMC in order to identify safety and efficacy signals. This is also true for conditions without any standard-of-care interventions other than supportive care. Adhering to these principles will accelerate the possibilities of identifying standard-of-care interventions, and hence further advance better care. Conversely, lack of adherence to these principles will do the opposite.

Section 2.15 – adherence to allocated intervention. The statements made (that lack of adherence/cross over within a trial reduces the chance of detecting a possible benefit from an intervention) are true if the goal of the study is to detect the pharmacological effect of an intervention. We recommend increasing the sample size if adherence is an issue since the impact of lack of adherence is to reduce the magnitude of the effect size. However, from a pragmatic point of view, lack of adherence to allocated treatment arm may be informative for ultimate decision making.

Section 2.1.6 – lost-to-follow-up. We agree with the statements made but think it would be relevant to emphasize that in a situation in which the stated principles are not adhered to, the ability to interpret the results of the trial is compromised.

Section 2.1.7 – outcome in trial. Although the stated principles are reasonable, we suggest to further expand on this section. We suggest that the key principle is that trials aimed to improve public health

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should study outcomes that actually are important and relevant to improve public health. We recognise the dilemma – trials powered to assess whether a prioritized intervention being studied actually affect a serious clinical outcome typically requires a much larger sample size than a trial using a laboratory defined outcome. If a laboratory outcome is to be used, demonstrating surrogacy of that outcome is critical and established criteria are available for such demonstration.

While relying on precedent to define a good outcome may make planning and regulatory review more straightforward, it may have the consequence of discouraging innovation, and it leaves the qualities of a good outcome unspecified/vague. It would be more helpful if the qualities of a good outcome were enumerated, i.e., clinically relevant / interpretable, patient-centric, objective, and statistically efficient/feasible. These qualities are at odds at times, and it can be difficult to find an outcome that satisfies all qualities. In this case one often needs to make a hard, pragmatic decisions. WHO should encourage regulators to embrace this thinking rather than relying exclusively on precedent.

Selection of the relevant primary endpoint in trials among hospitalized patients during the COVID-19 pandemic provides a good example. Ordinal scales at days 7 or 14 were advocated initially but dropped because they did not capture the total disease course, including rehospitalizations and deaths after day 14. Subsequently, favoured endpoints were composite primary endpoints that either encapsulated clinical disease progression (death or possible progression to COVID-ARDS), or time to recovery. Prevention of death is an obvious relevant and ascertainable outcome in populations at high risk. However, in lower risk populations, the ideal intervention should both prevent disease progression and accelerate recovery; only focusing on a progression endpoint typically makes sample sizes to achieve adequate power extraordinarily large. Novel endpoints were subsequently developed for such situations. However, not all regulators have accepted these novel endpoints, rather many have insisted to focus on 'death' being the gold standard endpoint for COVID-19. As the pandemic/epidemic evolved and deaths became less frequent, even in high-risk populations, trials with mortality endpoints became futile.

Section 2.1.9 – ascertainment of outcome. We agree with statements made but would suggest emphasizing that outcomes defined based on objective parameters only attenuate/preclude the potential biases of adjudication.

Section 2.1.10 – statistical analyses. We suggest emphasizing the following: there can be strong rationale for allowing modified ITT (mITT) analyses, namely when the modifications improve the potential for treatment differences without risking selection biases. For example, when there is delay between randomization and the initiation of the intervention, it may be quite reasonable to exclude persons who clinically deteriorate and cannot initiate the intervention or exclude those who withdraw consent during this short gap, or persons for whom the study drug is never delivered in a remote trial due to a courier mistake. Such exclusions are reasonable if there is not plausible way the exclusion mechanism is associated with the allocation, such as the use of blinding of treatment assignment. This guidance is too dogmatic about using ITT. There are situations where mITT is advantageous and does not compromise the internal validity of the clinical trial, but the rationale for exclusions needs to be clearly described and follow-up for excluded participants should continue when feasible with ITT as a sensitivity analysis. A fully developed statistical analysis plan determined by the trial steering committee should define these analyses *a priori.*

The document emphasizes caution in the interpretation of analyses of subgroups. We agree with that, but also finds it of relevance to do so in relation to secondary outcomes, as there are multiple comparisons at play, and these outcomes may have (much) lower power than the primary outcome.

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Section 2.1.12 – interim monitoring of trials. In situations in which the DMC recommends ceasing enrolment, it would be helpful to be more specific that enrolment into the trial may cease, but follow-up would continue on persons previously enrolled.

The plan for interim monitoring should also be nimble and allow for modifications to the timing and content of reviews, e.g., by using an error-spending approach to efficacy monitoring. Such flexibility is sometimes discouraged by regulators and much of the pharmaceutical industry operates under the assumption of fixed monitoring times. This rigidity of approach should be modified.

Situations may arise where the DMC and one or more regulatory bodies come to different sets of conclusions. This section should outline such a scenario and describe how such situations are best resolved. Whereas the DMC has access to the totality of intermediate data within the trial, regulatory authorities often only have access to reported serious adverse events (sometimes across multiple trials). In particular, in trials assessing interventions in high-risk populations, balancing possible safety signals against progression of underlying disease(s) does require a broad perspective. We advise that the WHO recommend that in such circumstances, the DMC and regulatory authority(ies) have conversations on best path forward of the trial, while ensuring that the trial's integrity is best preserved.

Section 2.2-2.6 – good trial practise that respects participants rights and wellbeing, are collaborative, are feasible, manage quality effectively and efficiently.
There should be much more emphasis on capacity building for RECs, and DMCs, and community engagement. In the pandemic the various PPI groups, for example, the one created at one of the largest Clinical Trials Units in the UK to help with the pandemic work, could not work at the pace required to have any meaningful input.

Section 2.2.6, includes extensive discussion of timeliness, but this needs definition. We would suggest emphasizing that use of a central trial database, real-time data collection, and clearly laid out statistical analysis plan at the onset of the trial, are the optimal means to ensure swift trial oversight by the DMC and in case of unblinding of the results, rapid communication of findings made. The STRIVE consortium has a great deal of experience with this approach with rapid publication of findings at the conclusion of the trial.

In this section, there is no mentioning of access post-trial in LMICs settings to IMPs proven to be 'successful' in trials conducted in those locations. Is that intentional?

Finally, there are many opportunities to improve clinical site monitoring. The focus needs to be on verification of critical elements of informed consent, eligibility, and ascertainment of the primary outcome. This is especially true in the context of an international health emergency.

Please provide general comments for Section B: Guidance on strengthening the clinical trial ecosystem.

Section 3.1.1 - what is the definition of a 'well-functioning' clinical research institution, and who decides on whether this is true or not for a given institution?

Section 3.1.2 - in this section WHO states quite clearly that WHO can't support countries to develop clinical trial infrastructure. But what the document does not describe is which agencies are identified as having funding responsibilities. A global trial ecosystem will only function if there is dedicated funding to develop it.

Section 3.2.1 – it is stated that "WHO has a key role in developing global health research priorities". While this may be an accurate description of WHO's perception, it does not fully recognize the interests of all ecosystem members. The track-record indicates that WHO should not lead the conduct

of trials but leave this to professionally led consortia developed for this purpose. Conversely, WHO's role is to convene stakeholders to reach a consensus on what those priorities are. Having 'dry runs' of how to reach quick consensus is encouraged if this process is to work quickly and efficiently in situations of an emergency.

Of note, there is no mention of the importance of access to healthcare, and how this needs to be strengthened in order to facilitate clinical research.

Section 3.2.2. The ambition of having a cooperative REC/regulatory approval system would be the ideal scenario. Most recently, the International Coalition of Medicines Regulatory Authorities has served a convening role in relation to immunobridging for authorization of COVID-19 vaccines. Also, the EU launched the CTIS platform for this purpose. However, the workload required to submit a trial for regulatory review using this platform is extensive, as each member state may have specific requirements for their review. Agreement among governments to harmonize is the obvious key.

It is also recognised that approval process in some countries outside the USA and EU is accelerated for trials already approved by the US FDA or the EU EMA. The issue here is obviously that the launch of trials outside of the US and EU are delayed; a clearly unintended consequence of doing submissions in series (i.e., first in US and/or EU and then elsewhere) as opposed to in parallel across the globe. More international coordination could greatly accelerate the initiation of trials in the countries in which the health emergency started, thereby reducing the global impact of such emergencies.

It should also be recognized in the document that regulatory approval time has slowed considerably post pandemic. There is no recognition of this in the document, and consequently no suggestion of what to do to remedy the situation. In STRIVE, we are developing a contingency plan for how to optimize timely launch and conduct trials with a global reach within this consortium of 40+ countries.

Please provide general comments for Section C: Addressing under-represented subpopulations.

We agree with the principles of attempting to ensure that as diverse populations as possible are included in trials. This will optimize the generalizability of the findings obtained. But equally important, this will ensure that diverse countries are involved with generating trial data and consequently in how trials are designed and conducted, and findings interpreted. This involvement will be a central part of improving global public health. And this certainly includes populations living in LMICs.

In relation to pregnant women – we kindly refer to general comments above and will not repeat them here.

Please provide general comments for ANNEX 1: Provisions for rapid funding and approval of good randomized evidence generation in emergencies.

STRIVE is created to respond to the emergencies described in this appendix. The rationale for forming STRIVE was – as also outlined in this document – that few global trial infrastructures existed prior to the pandemic and as a result, research efforts during the pandemic were uncoordinated.

As described above, STRIVE is developing a contingency plan that outlines the tasks for designing, and conducting trials, and what aspects are potential bottlenecks for rapid conduct. It is clear that some of the bottlenecks are intrinsic to the consortium (i.e., tasks we are in control of completing), whereas others require involvement of a third party for their completion (e.g., regulatory or ethics authorities in participating countries, shipment of study drug to trial site pharmacy, seeking approval from institution leadership where the 200+ sites are located across the world, etc). We expect that this detailed and specific outline will facilitate a discussion within the consortium but also with each of the relevant third

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parties – as well as doing dry runs of completion of relevant tasks - in order to optimize STRIVE's ability to implement trials quickly and seamlessly. This work could greatly benefit from WHO efforts at international coordination, thereby rapidly implementing trials, finding safe and effective treatments, and ending pandemics more rapidly. Our trial oversight committee (called the Executive Committee) is important to anchor the key stakeholders that support STRIVE. However, equally important is to have a priori agreement with funders, the pharmaceutical and diagnostic industry, on decision making in case of an emergency.

Please provide general comments for ANNEX 2: Recommendations for Member States, research funders and researchers.

Suggested amendments (maximum 30 amendments):

Amendment 1

Please indicate the line number the suggested amendment starts	**54**
Amendments	Suggest add words in bold Although a universal definition was not established ***and remains undefined*** Also suggest to add: ***Efforts to clearly define the parameters of a global clinical trial ecosystem should continue with the aim of ensuring all stakeholders have a clear understanding of remit.***
Please provide the rationale for the suggested amendments	The definition of global trials eco-system remains unclear. Consequently, various stakeholders' input are listed as generic and this central concept to the document remains ill defined. Efforts should be made to agree on a definition of the concept outlined in resolution 75:8 to ensure that all stakeholders involved have the same understanding when talking about this.

Amendment 2

Please indicate the line number the suggested amendment starts	**138**
Amendments	Add bullet point – **rural and remote settings in HIC**
Please provide the rationale for the suggested amendments	Under-represented populations also include those in HIC who do not typically have access to major research centres

Amendment 3

[redacted]

Please indicate the line number the suggested amendment starts	**197**
Amendments	Add sentence: **A well-functioning global clinical trial eco-system which includes and involves funders and Industry can help to ensure that equity in access, including access of post-trial IMP in LMIC, is achieved**
Please provide the rationale for the suggested amendments	Document does not currently include reference to this issue

Amendment 4

Please indicate the line number the suggested amendment starts	**259 (1.4.3)**
Amendments	Section 1.4.3 Suggest to expand this section with a definition of global clinical trial ecosystem and bullet point list of critical elements required - including not least the role of regulatory authorities in streamlining the implementation of global clinical trials in an emergency
Please provide the rationale for the suggested amendments	Currently this section lacks detail and could benefit from more clearly articulating components

Amendment 5

Please indicate the line number the suggested amendment starts	**268 (1.4.4)**
Amendments	Add statement: **Reporting of diversity and inclusion parameters relating to trial populations is essential to ensure trial representativeness**
Please provide the rationale for the suggested amendments	Ensuring reporting is made mandatory will allow monitoring of diversity and inclusion and trial representation

Amendment 6

Please indicate the line number the suggested amendment starts	**342 (Section 2.1)**
Amendments	Suggest to add '**Defining principal aims of trial'** as one of the key features of a good clinical trial ***Key messages*: Appropriate definition of the key aims of a clinical trial will help guide many aspects of the trial design including appropriate eligibility criteria, choice of outcome, degree of regulatory oversight required and reporting of the findings.** ***Why this is important*: Clinical trials cover a wide range of situations and questions. Some of these may relate to licensing of novel investigational agents whilst others may evaluate strategic questions using already licensed produce. Requirements for study procedures including reporting, data collection and regulatory involvement are linked to the overall study aims which must be clearly determined at the onset**

[redacted]

Please provide the rationale for the suggested amendments	Appropriate definition of aims of trial not currently mentioned

Amendment 7

Please indicate the line number the suggested amendment starts	**337**
Amendments	Expand sentence **"**should not be unnecessarily restrictive**, and where possible harmonised across multiple studies**
Please provide the rationale for the suggested amendments	Highlights importance of harmonisation to allow cross study comparison and generalisability

Amendment 8

Please indicate the line number the suggested amendment starts	**377**
Amendments	Adapt sentence: "random errors must be small by comparison with **the clinically meaningful effect sizes. Also, the clinically meaningful effect size may be smaller than the expected effect size that the sample size of the trial allows to have adequate power to detect.**"
Please provide the rationale for the suggested amendments	Clarity

Amendment 9

Please indicate the line number the suggested amendment starts	**381**
Amendments	Add sentence **"Adjusting for pre-randomization covariates that are predictive of the outcome can also be an effective strategy for reducing the impact of random errors.**
Please provide the rationale for the suggested amendments	Clarity

Amendment 10

Please indicate the line number the suggested amendment starts	**428**
Amendments	Add words "…of the intervention**, thus compromising the ability to interpret the results of the trial.**
Please provide the rationale for the suggested amendments	Emphasis

[redacted]

Amendment 11

Please indicate the line number the suggested amendment starts	**446**
Amendments	Suggest to add: **However, it should also be recognised that relying exclusively on precedent in choice of outcome may limit innovation in defining the most important outcomes that can improve public health. Instead, the qualities of a good outcome which include being clinically relevant / interpretable, patient-centric, objective, and statistically efficient/feasible should all be taken into consideration and the most appropriate outcome chosen and justified.**
Please provide the rationale for the suggested amendments	Inflexibility in only using precedent to define what is a good outcome may result in impractical studies with sample sizes that are not feasible to achieve. Regulatory bodies should be encouraged to view the evolving ecosystem of a pandemic with flexibility

Amendment 12

Please indicate the line number the suggested amendment starts	**487**
Amendments	Add sentence: **Outcomes defined based on objective parameters help attenuate the potential biases of adjudication.**
Please provide the rationale for the suggested amendments	Emphasis

Amendment 13

Please indicate the line number the suggested amendment starts	**510**
Amendments	Add following paragraph: **Strong rationale can be made for allowing modified ITT (mITT) analyses, namely when the modifications improve the potential for treatment differences without risking selection biases. For example, when there is down-time between randomization and the initiation of the intervention, it may be quite reasonable to exclude persons who clinically deteriorate and cannot initiate the intervention or exclude those who withdraw consent during this short gap, or persons for whom the study drug is never delivered in a remote trial due to a courier mistake. Such exclusions are reasonable if there is no plausible way the exclusion mechanism is associated with the allocation. The rationale for exclusions needs to be clearly described and follow-up for excluded participants should continue when feasible with ITT as a sensitivity analysis. A fully developed statistical analysis plan determined by the trial steering committee should define these analyses *a priori*.**

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Please provide the rationale for the suggested amendments	This guidance is too dogmatic about using ITT. There are situations where mITT is advantageous and does not compromise the internal validity of the clinical trial,

Amendment 14

Please indicate the line number the suggested amendment starts	**576**
Amendments	Add following sentence: **In situations in which the DMC recommends ceasing enrolment into the trial, follow-up should continue on persons previously enrolled.**
Please provide the rationale for the suggested amendments	Clarity

Amendment 15

Please indicate the line number the suggested amendment starts	**576**
Amendments	Add following sentence: **In the event that a trial DMC and regulatory authority(ies) have differing opinions on the implications of data being reviewed respectively by both bodies, a collaborative approach is suggested, whereby conversations on best path forward for the trial take place, while ensuring that the trials integrity is best preserved**.
Please provide the rationale for the suggested amendments	Situations may arise where the DMC and one or more regulatory bodies come to different sets of conclusions, in this case a harmonised approach is supported

Amendment 16

Please indicate the line number the suggested amendment starts	**821**
Amendments	Add following sentences: **The use of a central trial database, real-time data collection, and a clearly laid out statistical analysis plan at the onset of the trial, are optimal means to ensure swift trial oversight by the DMC and in case of unblinding of the results rapid communication of findings made.**
Please provide the rationale for the suggested amendments	Highlights aspects to improve trials feasibility and importance of forward planning

Amendment 17

Please indicate the line number the suggested amendment starts	**824**

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Amendments	Add sentence: **The burden of unnecessary monitoring on sites and trial staff should not be under-estimated, particularly during a pandemic. Remote monitoring should be considered where appropriate as well as trial staff training, free access to online resources and capacity building during periods of relative quiescence**
Please provide the rationale for the suggested amendments	Monitoring of sites involved in trials (and most especially in pandemic situations which present an extra set of challenges) is the bane of everyone's lives. Important to emphasise capacity strengthening and remote monitoring.

Amendment 18

Please indicate the line number the suggested amendment starts	**870**
Amendments	Provide sentence on what WHO considers to be a well-functioning clinical research institution. If it is those core competencies set out in Fig 1 then this should be specified
Please provide the rationale for the suggested amendments	This is not currently specified

Amendment 19

Please indicate the line number the suggested amendment starts	**1049**
Amendments	Expand sentence: 'Such models need to be developed further, **as workload required to submit trials using these platforms are extensive, particularly when each member state has specific requirements for their review. Further investment in infrastructure at the national, regional and global levels is required**
Please provide the rationale for the suggested amendments	Although there are advances in streamlining these processes across countries, current models are still far from ideal and greater engagement and funding from governments is required

Amendment 20

Please indicate the line number the suggested amendment starts	**1082**
Amendments	Add sentence: '**Established and evolving global clinical research networks are critical to the conduct and generation of high-quality clinical research. However, they are only part of the global trial ecosystem, and their efficient functioning relies on other parties, including regulatory agencies, to facilitate timely and efficient passage of clinical trials through the system. All stakeholders should strive to work together on a global level to ensure procedures are in place so that quick consensus can be achieved in state of emergency**"
Please provide the rationale for the suggested amendments	This document should highlight to third parties the importance of timely review and passage of documents. Currently regulatory bodies have returned to pre-pandemic state and there is no clear remedy to this. WHO can play a major part in convening working parties and advocating for the importance of this concept

[redacted]

Amendment 21

Please indicate the line number the suggested amendment starts	**1640**
Amendments	Add the following dot point: **Representatives from the child-bearing community should be embedded in decision making on how to conduct research in women of child-bearing age**
Please provide the rationale for the suggested amendments	Emphasis on community involvement

Amendment 22

Please indicate the line number the suggested amendment starts	**1432**
Amendments	Add the following words: "Consider the use of innovative adaptive study designs, **novel point of care diagnostics** and digital technologies….."
Please provide the rationale for the suggested amendments	Novel diagnostics esp at POC may play critical part in simplifying clinical trials infrastructure

Amendment 23

Please indicate the line number the suggested amendment starts	**1361**
Amendments	Add the following sentences **"In addition to improving rapid decision making at the national level, efforts must be made to encourage international dialogue and agreement, particularly in the areas of regulatory approval and ethical reviews. Enhancement of these processes across borders are essential to facilitate the conduct of global clinical trials, particularly in times of emergency. In between emergency periods and as part of preparedness, planning should be ongoing to ensure that processes are worked through, and solutions reached, prior to future states of crisis"**
Please provide the rationale for the suggested amendments	It is essential to advocate for international parties to work together to find solutions to these complex issues. Failure to do so will inevitably lead us to similar situations as were observed in the COVID-19 pandemic and prevent true global equity in clinical trial conduct and access.

Please copy the above form if you wish to suggest more amendments.

Thank you for your participation in the public consultation.