**FPM** Public consultation for WHO guidance for global practices for clinical trials

**Guidance:** Please respond to each question to the best of your knowledge within this document. **Please provide your name alongside your comments.** The completed document will then be circulated to the FPM PCG and any pertinent internal stakeholders (other contributors) for review.

**From:** World Health Organisation (WHO)

**Deadline:** **11:59 PM (****GMT) 15th September 2023**

[**Consultation Description:**](https://www.who.int/news-room/articles-detail/public-consultation-on-who-guidance-for-best-practices-for-clinical-trials)

In May 2022, the Seventy-fifth World Health Assembly adopted a resolution on *Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination,* in which one action requested of the Director-General was to develop WHO guidance on best practices for clinical trials. Please see action 2 under section “Requests the Director-General” at the end of WHA 75.8 resolution [here](https://apps.who.int/gb/ebwha/pdf_files/WHA75/A75_R8-en.pdf). WHO is launching a public consultation on draft guidance developed in line with this request.

We aim to obtain input from all relevant stakeholders, spanning all diseases and health conditions during this consultation, so that these inputs can be taken into account in revision of this draft, following advice from the WHO Technical Advisory Group established to support this process.

Important stakeholder groups for this technical guidance include, (but are not restricted to): public sector researchers, private sector entities engaged in clinical trials, national health authorities or research councils involved in health research, clinical trial registries, research ethics bodies, national or transnational medicinal product regulatory authorities, decision-making bodies making use of evidence such as guidelines developers, and health technology assessment bodies, healthcare practitioners, patient engagement and community engagement entities, and professional associations in disciplines for whom clinical trials of health interventions are relevant. There may also be some relevance to medical journals.

We would like to receive your overall comments on what the [draft guidance](https://cdn.who.int/media/docs/default-source/research-for-health/2023-07_who-guidance-for-best-practices-for-clinical-trials_draft-for-public-consultation.pdf?sfvrsn=7a5c9fa5_4) does well and less well at the moment, as well as comments on the sections of the document and line by line if desired. Please review the request for guidance development in WHA resolution 75.8 before providing comments. Please use the online form accessible through the following [link](https://extranet.who.int/dataformv3/index.php/465963?lang=en.) to provide inputs.

**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**.

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| In section 1.1, the importance of clinical trials, the text implies that more clinical trials and fewer observational studies should be conducted. The latter has been considered complementary to clinical trials. In addition, there are now many pragmatic trials emerging. Oddly, the word pragmatic appears only once in the document (line 155). FPM believes that conducting good trials is important, but it does not mean that real-world studies should not be conducted. Also, the words “umbrella” and “basket” do not appear in the document despite these novel trial designs being adopted by many.    The points regarding the burden of disease and representation of populations in LMICs vs HICs are well made, but there is a futility aspect here. For example, in COVID studies, if LMICs do not have the infrastructure to support any intervention, the utility of the intervention will not be able to be rolled out. This may be in clinical infrastructure, cold chain, or any other aspect, even beyond the simple economics of being able to afford the intervention.    There is a need to invest in infrastructure locally and widely before trying to implement an HIC model of studies into LMICs. For this reason, the priority should be to adapt trials and prioritise those that have relevance to the specific ability to implement any intervention that can lead to real-life improvements, given the environmental challenges of working in an LMIC.    There are also under-representation issues, as described. This is not only ethnic, gender and age-related but also related to applicability and implementation. The ability to utilise any intervention, even biologically valid, may limit its utility. Thus, an approach to identify interventions that can be impactful incrementally may be more useful than looking for LMIC additions to standard studies.    On study designs, the point on COVID study design, underpowering and futility is also well made. A sensible proposition would be a way to provide protocol skeletons or frameworks, plus the ability for pooled data from centres working within these frameworks. WHO, regulators and ethics committees should be more strongly aligned to reject underpowered, poorly designed studies that will either directly cause harm or indirectly through their failure and opportunity cost.    The concept of continuous study and evaluation (in a well-controlled manner) will not be sufficiently established to allow current Phase 2/3.  Lines 178 – 188 – FPM agrees with these.  Lines – 190 – 197 – FPM agrees with these.  Lines 216 – 220 – FPM agrees with these.  Lines 251 – 258 – FPM strongly supports these. |

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

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| The comments here are all sensible and standard practice in GCP, so these standards are essential to enshrine more widely in non-GxP studies. This affords the participants sufficient protection while raising standards overall.    The comment that studies should be able to allow the elimination of uncertainties is different from the likelihood of outcomes. Some confounders affect this, as well as the fact that even the best studies do not provide a clear answer at times. A study should not be seen in isolation. It should be seen in the context of a study programme that will collectively provide sufficient confidence to move forward in a manner that increases knowledge and reduces risk. This may include gradually opening up indications and populations based on accrued knowledge rather than any degree of certainty overall. Any certainty may be limited to the exposed population and should only be extrapolated with a sound rationale and assessment of the benefits and risks.    There should be a recognition that outcomes may not be definitive and may be based on surrogate measures for reasons of time or medical need and that these may be validated to different degrees. Including patient-relevant measures is essential to the likelihood of any intervention being implemented.    Sample size, power and prospective definitions for any study are all vital.    Protecting individuals is similarly important to ensure voluntary informed consent without coercion. The points on governance, oversight and transparency are all important and are reflected in GxP studies and the rules surrounding them. These important protections should be present in any interventional or observational study.    In section 2.1.1 on patient population, a key point regarding diversity, etc., is that the eligibility criteria should make every attempt to reflect the demographics of the population with the disease under investigation. Performance status is a good example here- often, trials are limited to good performance status patients, whereas the general population with the disease may have lower performance status.    In 2.1.8 on data collection, etc., it is important to discuss the time aspects of data collection to allow adequate opportunities for source data verification and query resolution. Our members have seen examples of trials in the past where the database was not set up until 6m into the trial, so it would be very hard to ensure the quality of the data from the first patients entered.    Another point that should be made relevant to data quality relates to the quality of bio-assays used for biomarker assessments, as third-party vendors often provide these. If these assays have insufficient validation (e.g., for use on long-term stored samples), it can invalidate the results and make an endpoint uninterpretable. It might help to link this guidance to some guidance on GLP (Good Laboratory Practice) lab assays.    Another point related to data quality is that it is good practice to design the case report forms in parallel with the protocol’s design to ensure that all the correct information is being collected to address all the study objectives, including exploratory objectives. There are several examples of trials where a question is asked by a regulatory authority or health technology assessor at the end of the trial, but the data has not been collected. |

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

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| FPM agrees with this section. This enshrines the important quality standards that are required as well as their applicability to protecting and validating the results that derive the outcomes of the study.    For subpopulations and diverse groups, the concept of prospective stratification can be useful to protect and not dilute any wider effects or differences.    Agree (see comments above) on priorities and relevance, as well as prospectively understand the likelihood and magnitude of any benefit. It is possible that a low-tech intervention is more impactful than a high-tech one due to the ability to adapt it to the environment to have the desired effect. Ensuring proportionate complexity, with proportional safeguards, perhaps by limiting the use to which data are put, initially reflects the ongoing assessment needed and the incremental nature of clinical trial data.  Coordination, pooling across common protocols (umbrella or bucket protocols) that can be implemented locally with sufficient power but pooled to amplify any effect and applicability. A ‘stick’ rather than ‘carrot’ may be helpful here to ensure no poorly designed studies that compete for patients are approved. This can prevent poor studies and permit cooperative approaches and simpler designs.    The availability of experienced clinical trial sites coupled with mature regulatory and ethical review is critical to the generation of high-quality clinical data. Post-pandemic, we have noticed a reduction in the number of suitable clinical sites due to the loss of experienced people resources. Efforts to build and maintain experienced clinical trial infrastructure will be important moving forward, as will be ensuring geographic diversity (i.e., it is important that systems are in place in diverse countries/regions and that poorer regions are supported to achieve this), which will include underrepresented populations in studies. |

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

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| Supportive of the concepts here as noted in comments above. Fair and proportional representation based on biological differences, as well as extrinsic environmental differences, are vital. There must be a likelihood for practical implementation, so modelling between (sub) populations and surrogate markers to provide additional confidence is important.    Inclusion of underrepresented groups is important, as is their protection. Protection from harm in any study using pilot data, data monitoring committees and safety boards is vital. Additionally, protection from exploitation based on their underlying higher levels of need should be explicitly stated as a protection with active measures in place. Protocol frameworks that are strongly recommended or enforceable may help in some circumstances, and expansion to different populations should be managed safely and proportionally that does not provide undue risk to a more vulnerable (biologically or economically) population. |

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

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| Build infrastructure early, not in an emergency, ensuring that standards, procedures, and training are all in place. Based on sound studies and analyses, this feeds the understanding of requirements, harmonisation, transparency, and reporting in good time to good quality. |

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

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| These should be principles-based and high levels to apply to all settings. They should have minimum standards but must not be one highest standard for all. Delivering the dynamic tension between small scale and high control vs larger scale and less control is essential.  As risk (or benefit risk vs doing nothing) decreases, studies can expand and become less well-controlled. An algorithmic approach can allow safe but managed expansion once the initial risk is offset and some degree of proportional but expanding exposure is planned.  Until governments and NGOs take a prospective approach to invest early and sustainably, this will be difficult and will only be a priority once there is another global health emergency. Once the emergency fades, people forget, and it is ignored again. Prioritising infrastructure investment as much as interventions based on their expected utility and benefits will be vital. Implementing small but population-based interventions that have a major public health benefit is preferred to high-tech small patient population approaches (replicating HICs) in LMICs to level the global health playing field before looking at studies into higher priced interventions that will have a benefit for fewer (perhaps more affluent) people in LMICs.  Lines 1541 –1544 – FPM strongly supports these. |

**Suggested amendments (maximum 30 amendments):**

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| Please indicate the line number the suggested amendment starts |  |
| Amendments |  |
| Please provide the rationale for the suggested amendments |  |

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

**Thank you for your participation in the public consultation.**