European Society for Medical Oncology (ESMO) response to public consultation on WHO guidance for best practices for clinical trials, September 2023

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 Please also provide any comments about the strengths of the draft guidance.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**.

ESMO is the leading professional organisation for medical oncology. With more than 30,000 members representing oncology professionals from 168 countries worldwide, ESMO is the society of reference for oncology education and information. **ESMO Clinical Practice Guidelines** (https://www.esmo.org/guidelines), used by oncologists around the world to treat and care for cancer patients, are based on scientific evidence from clinical trials. ESMO addresses issues related to clinical trials through the expertise of **ESMO Public Policy Committee**, the ESMO Cancer Medicines Committee (https://www.esmo.org/about-esmo/organisational-structure/cancer-medicines-committee), and **ESMO Faculty** (https://www.esmo.org/about-esmo/organisational-structure/esmo-faculty). Moreover, ESMO is a major contributor to dissemination of scientific output generated from cancer clinical trials as well as to trialist networking via its scientific congresses and meetings. Therefore, ESMO welcomes the opportunity to be able to participate in the WHO consultation related to WHO guidance for global practices for clinical trials.

The draft ***WHO guidance for global practices for clinical trials*** addresses a wide range of critical factors that influence the successful conduct and implementation of clinical trials in a very comprehensive manner. The recommendations cover a broad range of topics comprehensively and are very clear. However, to enhance the utility of the roadmap, it might be beneficial to consider providing guidance on practical implementation of key aspects related to successful development of clinical research, with a patient-centred approach. Such aspects are, among others: promotion of diversity and inclusiveness; complexities of clinical trial design, especially in rare molecular subsets of tumours; selection of endpoints; geographic barriers to access; low patient recruitment; and ethical and regulatory hurdles.

More practical guidance should also focus on strategies for effective global data sharing, optimal resource allocation in resource-limited settings, development of streamlined global regulatory frameworks, measurement of the impact of patient engagement, and ensuring long-term sustainability of the strengthened clinical trial ecosystem.

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

Section A: Key scientific and ethical considerations for good clinical trials is well developed and covers many relevant aspects.

We would recommend strengthening the text with:

- further detailing how to better utilize digitization in clinical trials
- development of a framework and expertise on pragmatic clinical trials
- development of a framework of drug development based on clinical trials driven by complex biomarker selection, which will gradually replace the current organ- or histology-based model.

Such a model will better serve registration of precision therapeutics in rare, molecularly-defined tumour subsets.

- highlighting cancer patients with regards to appropriate trial population and consent
- noting the importance of collaboration between academic research groups and their interaction with the industry

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

Section B: Guidance on strengthening the clinical trial ecosystem is well developed and covers many relevant aspects.

We would recommend strengthening the text with:

- highlighting the importance of funding independent academic research
- highlighting the importance of establishing incentives and tools for clinical trials in orphan malignant diseases
- highlighting the importance of international collaboration in clinical research by providing funding tools and streamlining regulatory procedures
- providing a prominent example of a clinical research network

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

Section C: Addressing under-represented subpopulations is well developed and covers many relevant aspects.

We would recommend strengthening the text with:

- stressing the point that trial populations should be representative of the real world
- encouraging pragmatic clinical trials
- noting specifically the need for trials in rare and very rare diseases specifically

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

ANNEX 1: Provisions for rapid funding and approval of good randomized evidence generation in emergencies is well developed and covers many relevant aspects.

We would recommend strengthening the text with:

- adding a reference to the need to develop an international governance framework to ensure rapid connection and integration of national/regional clinical trial networks
- calling for guidance to be developed for optimizing the use of resources and providing simplified procedures that do not affect a trial's quality or ethical principles during health emergencies and population lockdowns
- initiatives to establish systems, frameworks and guidance for the uninterrupted, continued enrolment of patients with cancer in clinical trials during emergencies

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

ANNEX 2: Recommendations for Member States, research funders and researchers is well developed and covers many relevant aspects. We would recommend strengthening the text with: • adding reference to people with rare malignant diseases • proposing to ensure representation of the physician/trialists in the ICH body developing and revising GCP guidance documents • promoting financial and organizational support of not-for-profit investigator-initiated clinical trials • promoting the development of frameworks and funding schemes for clinical trials of precision therapeutics in molecularly defined 'niche' populations of patients with tumours

Suggested amendments (maximum 30 amendments):

Please indicate the line number the suggested amendment starts	**355**
Amendments	**A multistakeholder approach should be implemented for in principle inclusion of elderly, immunocompromised patients in cancer clinical trials or for providing a robust scientific rationale for their exclusion. Stakeholders should be investigators, trial authorization bodies, ethics committees, patient associations.**
Please provide the rationale for the suggested amendments	Multi-disciplinary expertise is necessary so as to build a robust case for inclusion, or if needed exclusion, of elderly, socially deprived or immunocompromised patients in clinical trials.

Please indicate the line number the suggested amendment starts	**473**
Amendments	**Measures should be streamlined and implemented for the development/promotion of:** **• Digital infrastructure** **• Digital literacy** **•Electronic consent (eConsent) guidelines together with patient representatives, and the use of remote eConsent** **• Research into the use of remote monitoring and data in clinical trials (e.g., quality of life scales; wearable devices; phone apps; online reports)** **• Telemedicine and decentralising the point of care through the development and use of validated electronic patient reported outcomes and tools** **• Common data dictionaries** **• Adherence to ICH practices for clinical research** **• Interoperable, modular IT and EHR systems**

	• **Consistent regulatory frameworks for digital health and digitized clinical trials, including data security** • **Available funding mechanisms and incentives for digital infrastructures and for digitized clinical trials**
Please provide the rationale for the suggested amendments	The clinical trial ecosystem needs to be enriched with expertise, skillsets, knowledge and frameworks/policies for the integration of digital health technologies and AI.

Please indicate the line number the suggested amendment starts	**609**
Amendments	"…organization or individuals conducting the trial." **Cancer patients must have access to the most useful precision medicine tests and the best information to maximize their timely access to clinical trials of targeted therapeutics.**
Please provide the rationale for the suggested amendments	Access to tumour molecular characterization by means of in vitro diagnostic tests is a pivotal requirement both for clinical practice as well as for screening for clinical trial participation.

Please indicate the line number the suggested amendment starts	**712**
Amendments	"… and the communities from which they come." **Build upon existing guidelines to address collaboration between research groups and their appropriate interaction with the industry to clarify the roles and responsibilities of all partners involved in the clinical trials from the onset.**
Please provide the rationale for the suggested amendments	Industry-sponsored and academic, non-commercial clinical trials should complement each other in the research landscape. Moreover, collaboration between industry and independent investigator groups should be promoted in joint or complementary clinical trials, based on clear governance frameworks.

Please indicate the line number the suggested amendment starts	**997**
Amendments	"Health research funders should **increase independent funding mechanisms for independent academic clinical research, especially for international collaboration, and** also ensure that funding is efficiently aligned with…"
Please provide the rationale for the suggested amendments	Several valid clinical questions will never be studied by industry, especially in orphan malignancies or related to sequencing/de-escalating therapeutic strategies. These questions need answers which are important for patients,

	consequently, independent clinical research should be supported, funded and collaboration enabled.

Please indicate the line number the suggested amendment starts	**1086**
Amendments	**As an example, rare cancers urgently need collaboration and networking of national research groups.**
Please provide the rationale for the suggested amendments	Several valid clinical questions will never be studied by industry, especially in orphan malignancies, rare molecular subtypes of frequent histotypes of cancers or related to sequencing/de-escalating therapeutic strategies. These questions need answers which are important for patients, consequently, independent clinical research should be supported, funded and collaboration enabled.

Please indicate the line number the suggested amendment starts	**1181**
Amendments	**Incentive schemes are needed to promote real world representativeness of trial populations and to implement the linkage of trial populations to restrictive authorisations/reimbursement of new therapies only in the populations under study.**
Please provide the rationale for the suggested amendments	Clinical trial eligibility criteria are often very strict, resulting in data generated in silo/non representative populations, not applicable in the real-world general population. Using more pragmatic real world eligibility criteria should be encouraged and linking the approval/reimbursement of a new therapy to the trial population studied may function as an incentive mechanism.

Please indicate the line number the suggested amendment starts	**1307**
Amendments	**Guidance should also be provided for health emergencies and population lockdowns in order to optimize the use of resources and provide simplified procedures that do not affect a trial's quality or ethical principles.**
Please provide the rationale for the suggested amendments	During emergencies, it is imperative to develop protocols and resource use guidance that will allow cancer patient access to clinical trials. The latter often provide an irreplaceable lifeline of novel investigational therapies for patients with severe diseases not controlled by standard therapies.

Please indicate the line number the suggested amendment starts	**1363**

Amendments	**Rapid connection and integration of national/regional clinical trial networks requires the development of international governance framework.**
Please provide the rationale for the suggested amendments	International collaboration in clinical research is impossible without a functioning, streamlined governance framework, acceptable by patients, investigators and authorities.

Please indicate the line number the suggested amendment starts	**1439**
Amendments	"…pregnant and lactating women and older people, **and people with rare disease**."
Please provide the rationale for the suggested amendments	People with rare diseases are often deprived of clinical trial opportunities due to difficulty in trial accrual, paucity of trials and lack of financial sponsor interests.

Please indicate the line number the suggested amendment starts	**1449**
Amendments	**Ensure representation of the physician/trialists in the ICH body developing and revising GCP guidance documents.**
Please provide the rationale for the suggested amendments	Physicians actually running clinical trials and managing patients in the context of the latter should contribute to the ICH guidance documents by bringing on board their expertise, on the ground experience and expert opinion.

Please indicate the line number the suggested amendment starts	**1451**
Amendments	**Promote financial and organizational support of not-for-profit investigator-initiated clinical trials by the public and private sector.**
Please provide the rationale for the suggested amendments	Several valid clinical questions will never be studied by industry, especially in orphan malignancies or related to sequencing/de-escalating therapeutic strategies. These questions need answers which are important for patients, consequently, independent clinical research should be supported, funded with public fund support, for academic research groups reinforcing/facilitating collaborations.