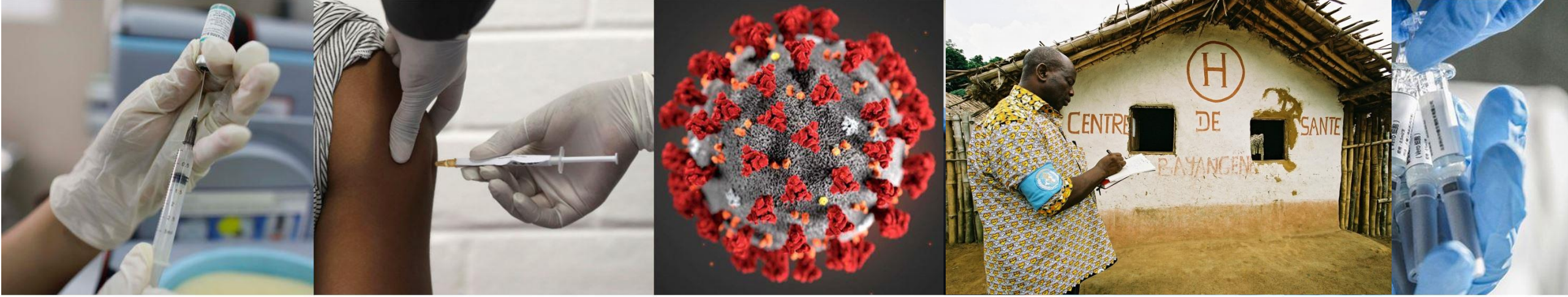
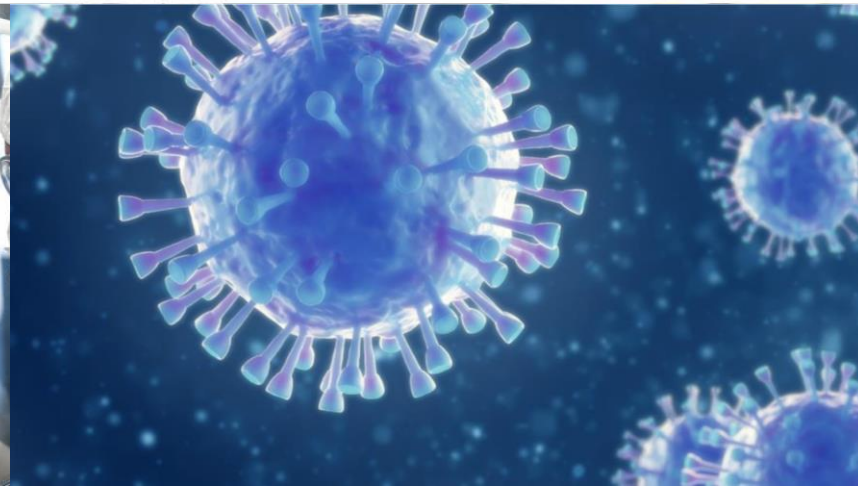


Strengthening research ethics oversight: the work of WHO

Dr Andreas Reis, PD, MD, MSc
Co-Unit Head, Health Ethics & Governance,
Department of Research for Health, WHO Geneva

World Health Organization

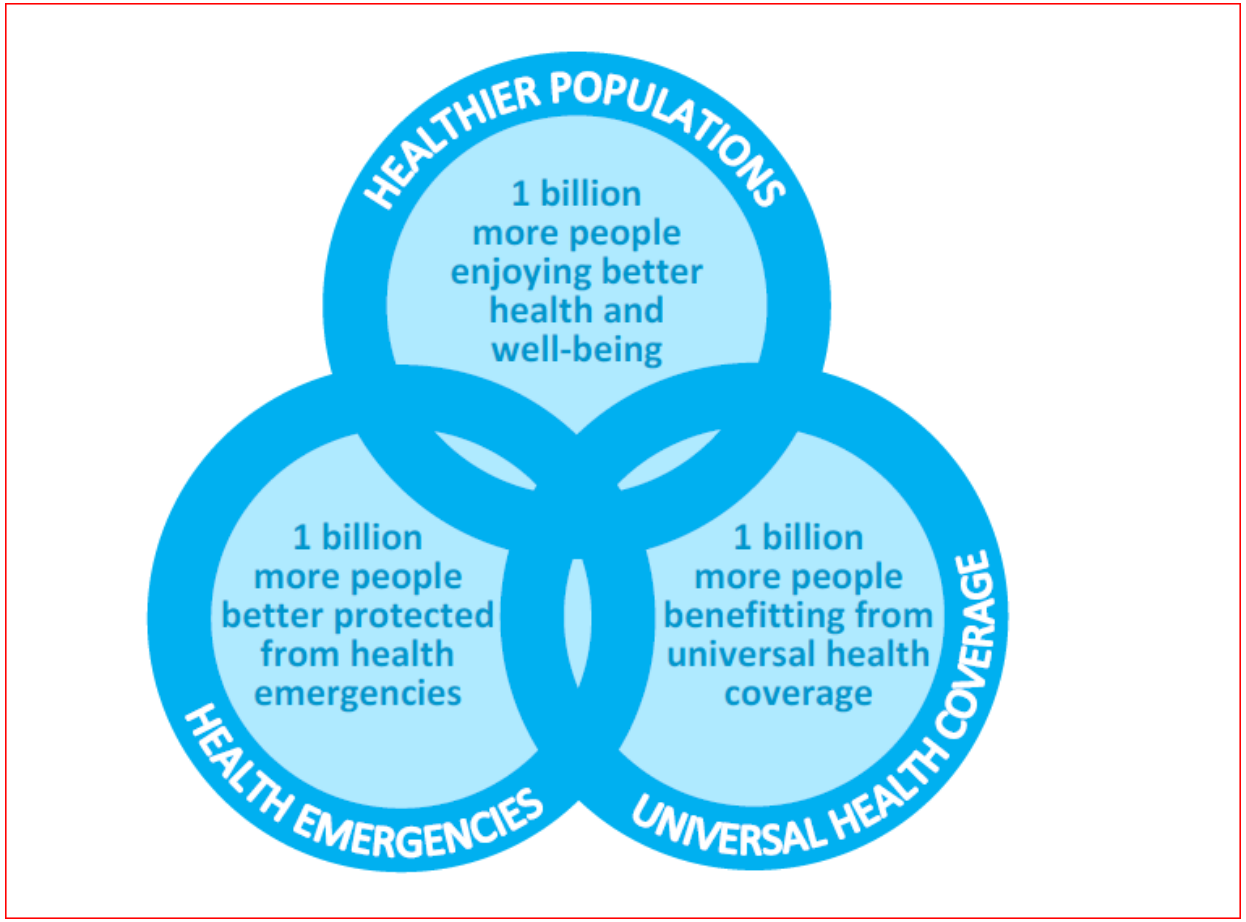


Outline

- Background
- Research ethics during emergencies: Key WHO documents & actions
- WHO's work on capacity building in research ethics:
  Tool for Benchmarking Ethics Oversight of Health-Related Research
- Conclusion

Background

13th Global Programme of Work, WHO



- 2019-2024
- ambitious programme, structured around three interconnected strategic priorities to ensure healthy lives and well-being for all at all ages
- Ethics a key component

Ethics at the heart of GPW

"…WHO must continue to ensure that policy-makers and health implementers – both at the international and at the national level − **keep ethics at the heart of their decision-making**. By focusing on individual values such as human dignity, and respect; by bringing in the language of obligations and responsibilities; and by advocating at a national and global level for solidarity, reciprocity, and mutual understanding amongst other values, WHO can foster trust, improve transparency, and enhance accountability. **WHO will work to ensure that all policies, public health interventions and research are grounded in ethics……."**

WHO & Global Health Ethics

Thirteenth Global Programme of Work (2019-2024)

"WHO's normative guidance will be informed by developments at the frontier of new scientific disciplines such as genomics, epigenetics, gene editing, artificial intelligence, and big data, all of which pose transformational opportunities but also risks to global health."

WHO Clinical Trials Resolution (2022)

World Health Organization

SEVENTY-FIFTH WORLD HEALTH ASSEMBLY
Agenda item 16.2

WHA75.8
27 May 2022

Strengthening clinical trials[1] to provide high-quality evidence on health interventions and to improve research quality and coordination

The Seventy-fifth World Health Assembly,

Recalling resolutions WHA58.34 (2005) acknowledging th
the generation and application of knowledge are critical i
health-related development goals, WHA63.21 (2010) outlining
health research, WHA66.22 (2013) and WHA69.23 (2016) on
Consultative Expert Working Group on Research and Develop
WHA67.20 (2014) on regulatory system strengthening for medi
health intervention and technology assessment in support of univers
on strengthening local production of medicines and other health
WHA74.7 (2021) on strengthening WHO preparedness for and re
notes the importance of basic and clinical research and recogni
collaboration in research and development, including in multicoun
as rapid diagnostics test and assay development, while acknowl
scientific evidence;

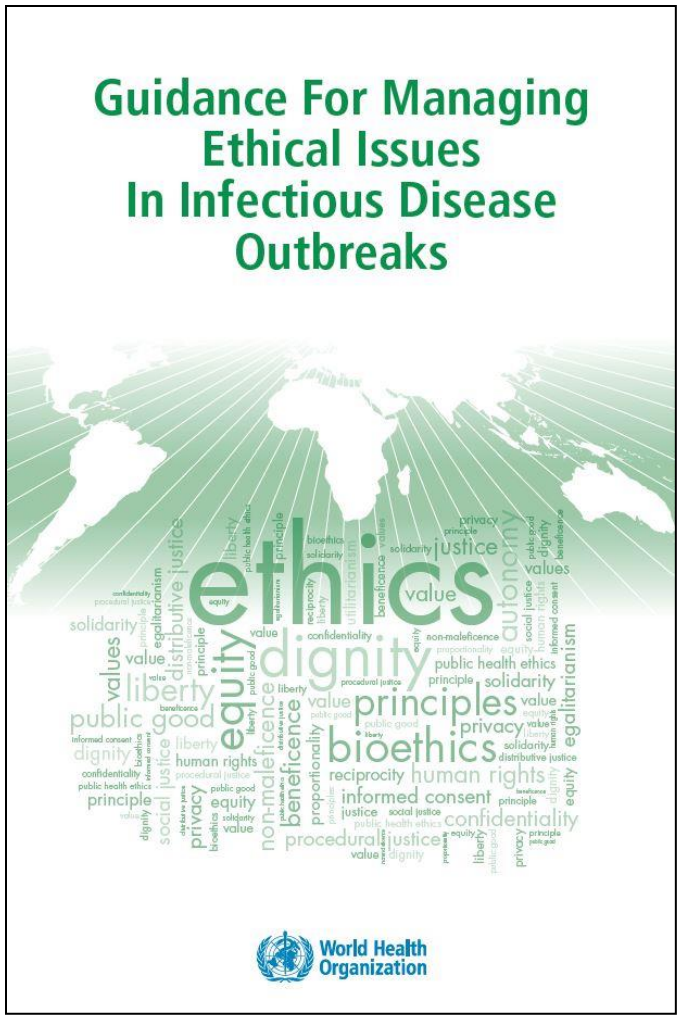
Noting the recommendations made by the Independent Pa
Response in their review "COVID-19: make it the last pandem
development, including clinical trials;

… Underscoring that **clinical trials should be** health-needs driven, evidence based, well designed and well implemented and be **guided by established ethical guidance**, including principles of fairness, equity, justice, beneficence and autonomy; and that clinical trials should be considered a shared responsibility;

…**to support ethics committees and regulatory authorities** to enable efficient governance processes to focus on the fundamental scientific and **ethical principles that underpin randomized controlled trials**…

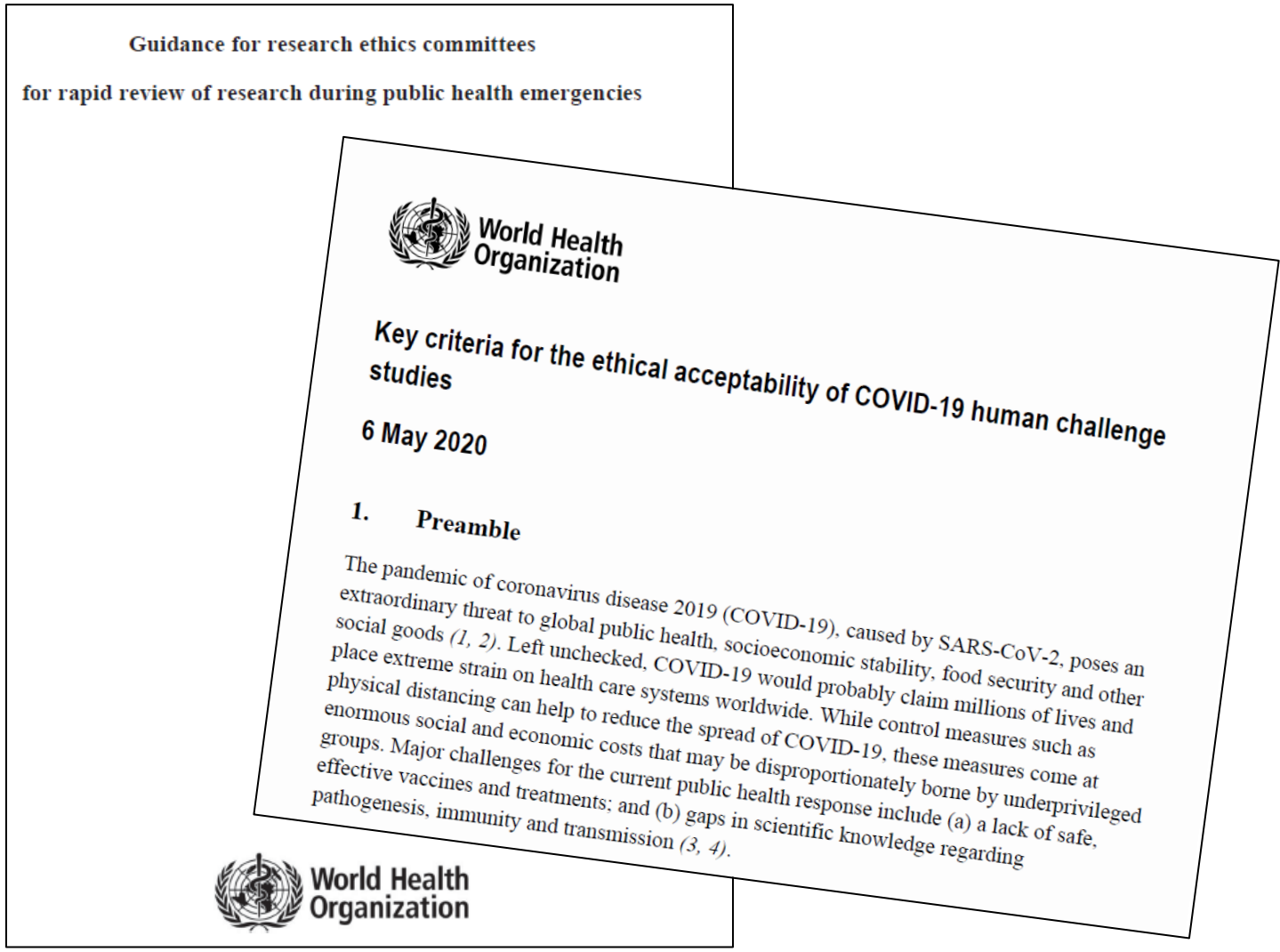
Research ethics during emergencie
Key WHO documents & actions

Outbreaks: WHO guidance on ethical issues



Ethics of COVID-19 Research - WHO Ethics Guidance

- Ethical Standards for Research During Public Health Emergencies: Distilling Existing Guidance to Support COVID-19 R&D
- Emergency Use Designation of COVID-19 candidate vaccines: Ethical considerations for current and future COVID-19 placebo-controlled vaccine trials and trial unblinding
- Key Criteria for the Ethical Acceptability of COVID-19 of Human Challenge Studies
- Guidance for Research Ethics Committees for Rapid Review of Research During Public Health Emergencies



WHO guidance for research ethics committees

World Health Organization

Rapid review of research during public health emergencies (SOPs)

WHO emergency SOPs

Guidance for research ethics committees for rapid review of research during public health emergencies

- Guidance to be implemented on declaration of emergency
- Aim: accelerate study commencement
- Virtual meetings and processes
- Language considerations – core documents in the official language of the reviewing country
- 20 recommendations to facilitate rapid review

- Checklist of items & additional documents to facilitate fast-tracking of outbreak related research - study structure, oversight, data-sharing plan and MTAs, dissemination plan, insurance
- Agreed process for rapid review - clearly communicated to stakeholders

Source: WHO (2020) https://www.who.int/publications/i/item/9789240006218

COVID-19 – Emergency use of unproven clinical interventions

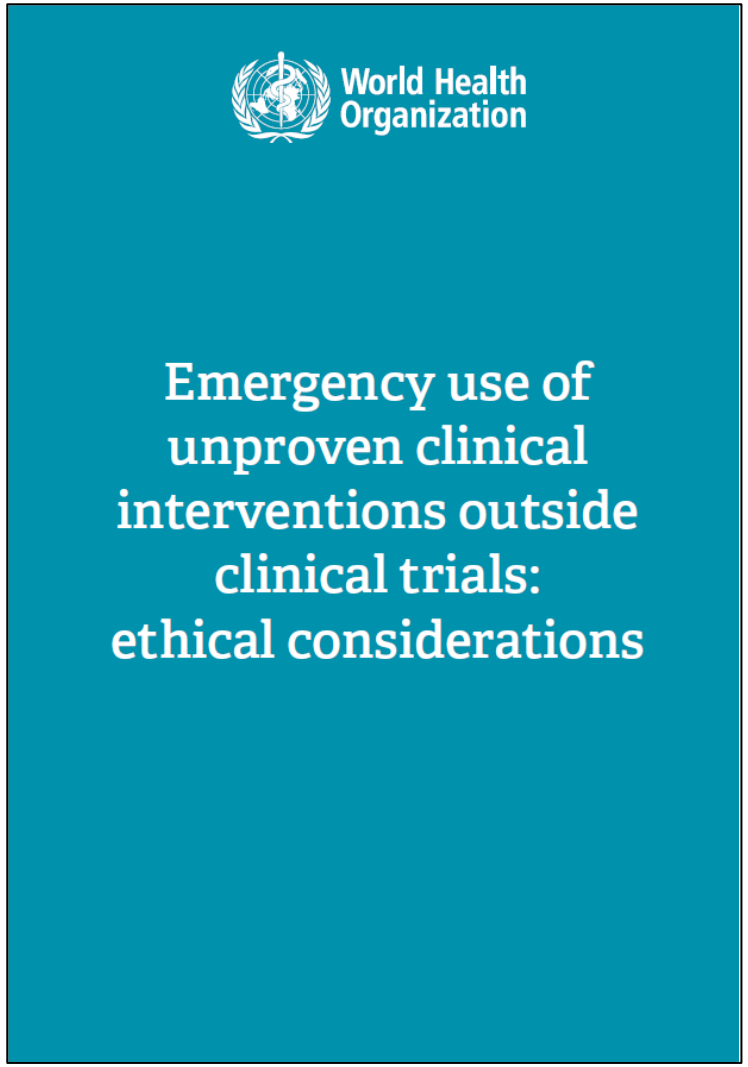
- Emergency use of unproven clinical interventions outside clinical trials – including “off-label” interventions – surged during the COVID-19 pandemic
- unjustified, unconstrained use of unproven interventions
- serious ethical concerns

Ebola 2014 - MEURI

- In the face of the outbreak of Ebola virus disease (EBV) in West Africa in 2014, WHO issued a framework for the ethical permissibility of use of unproven interventions outside clinical trials during public health emergencies.

- “**monitored emergency use of unregistered and experimental interventions” (MEURI),** known as “the MEURI ethical framework”, avoids the common yet misleading designation of “compassionate use”, which is associated with too narrow a scope of unproven interventions and is not based on harmonized ethical and regulatory criteria

WHO Guidance on ethics and emergency use of unproven clinical interventions



- Developed by WHO Expert Group
- published in April 2022
- Update of the 2014 & 2016 ethical frameworks
- Spells out key ethical aspects

WHO MEURI Working Group – 2021/2022

Lead writer: Ignacio Mastroleo, National Scientific and Technical Research Council and Facultad Latinoamericana de Ciencias Sociales, Argentina
Chair of the WHO Working Group: Ross Upshur, University of Toronto, Canada

Members: Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto, Canada); Aasim Ahmad (Aga Khan University, Karachi, Pakistan); Dereck Angus (University of Pittsburgh (PA), USA); Yaseen Arabi (King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia); Arthur Caplan (New York University School of Medicine, New York City (NY), USA); Stéphanie Dagron (University of Geneva, Switzerland); John Marshall (Maimonides Medical Center, New York City (NY), USA); Roli Mathur (Indian Council of Medical Research Bioethics Unit, Bangalore, India); Keymanthri Moodley (Stellenbosch University, South Africa); Srinivas Murthy (University of British Columbia, Canada); Tina Garani-Papadatos (National School of Public Health, Athens, Greece); Virginie Pirard (Université Libre de Bruxelles, Belgium); Lembit Rago (Council for International Organizations of Medical Sciences, Geneva, Switzerland); Maxwell Smith (Western University, London, Canada); Le Van Tan (Oxford University, United Kingdom of Great Britain and Northern Ireland); Voo Teck Chuan (National University of Singapore); Béatriz Thomé (University of São Paolo, Brazil)

WHO's updated ethical framework for emergency use of unproven clinical interventions outside clinical trials

I. Justification	II. Ethical and regulatory oversight
1. Public health emergency	6. Review and approval by authority and ethics committee
2. Absence of proven intervention	7. Minimization of risks
3. Impossibility of initiating research immediately	8. Responsible transition
4. Scientific support based on a favourable risk–benefit ratio	9. Fair access to scarce unproven interventions
5. Effective use of resources	
III. Consent process	**IV. Contribution to evidence**
10. Individual informed consent	12. Monitoring, collecting and sharing relevant data
11. Community engagement	

Way forward

Lessons Learned

build an evidence base and strengthen relationship between global/local and technical

Defining Solidarity, Equity and Access: Ethics to Policy Programme of Work

work building on Pandemic Summit to more effectively operationalize ethics

Trust and Trustworthiness: Ethics, social listening and infodemic management

sub-group established to develop WHO guidance (publication early 2024)

Ethical Governance follow-up work

Public-private partnerships

New models of global governance architecture – regional hubs?

Research Ethics Oversight/Governance

Input into Clinical trial resolution

Addressing gaps in guidance - adaptive trial designs, evidence & ethics

Focusing on underrepresented & marginalized populations

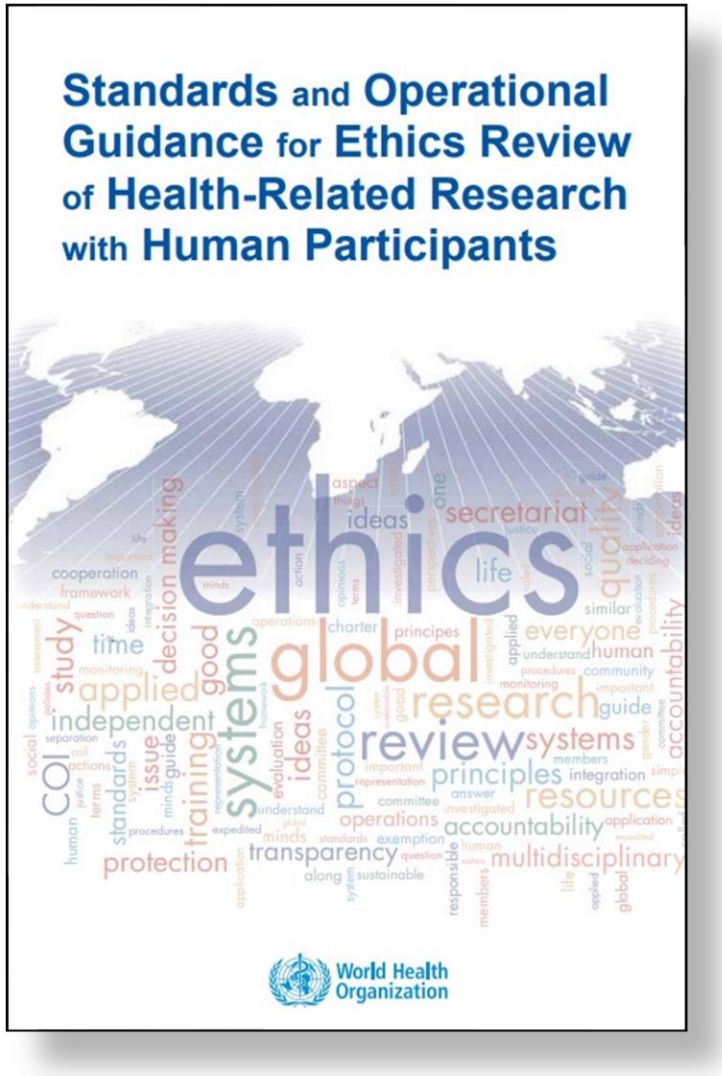
Reforming ethics oversight – i.e. follow-up to Lisbon meeting and survey

Strengthening capacity – WHO benchmarking tool

Strengthening Research Ethics Oversight: the WHO Benchmarking Tool

Background

- Most countries have established some sort of system for ethical oversight of research.
- WHO Standards for the functioning of research ethics have existed since 2011.
- Yet, little is known about how well these systems are working.



https://iris.who.int/bitstream/handle/10665/44783/9789241502948_eng.pdf?sequence=1

WHO TOOL: BENCHMARKING ETHICS OVERSIGHT OF HEALTH-RELATED RESEARCH WITH HUMAN PARTICIPANTS

World Health Organization

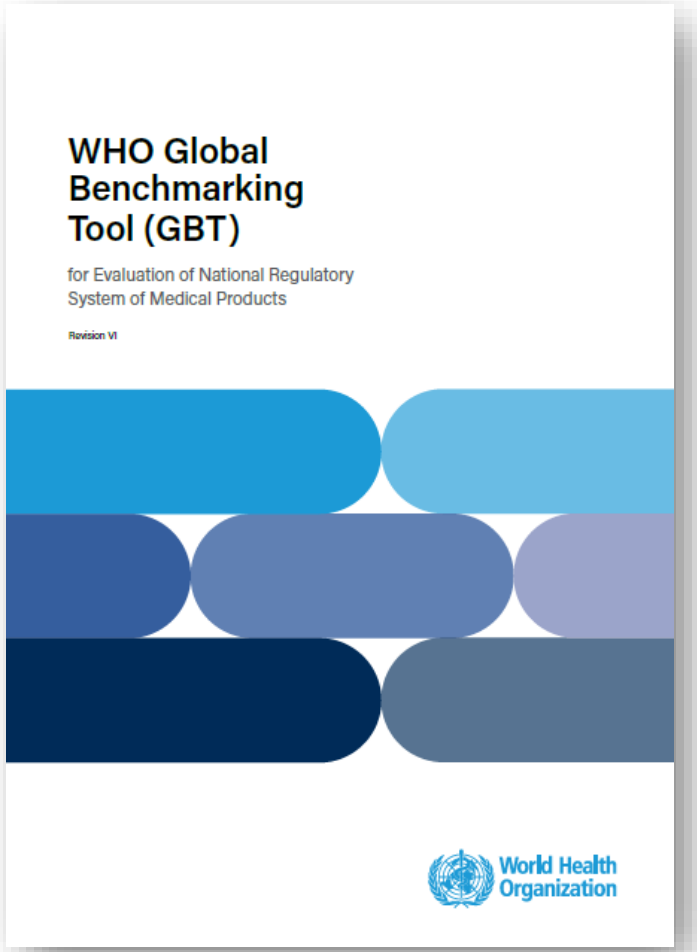
Objectives:

- To assist in evaluating the existing capacity to provide appropriate ethical oversight
- To guide the development of recommendations to address the identified gaps
- To assist in capacity-building efforts
- To promote policy convergence and best practices in research ethics oversight and to enhance public trust in health research.

Scope:

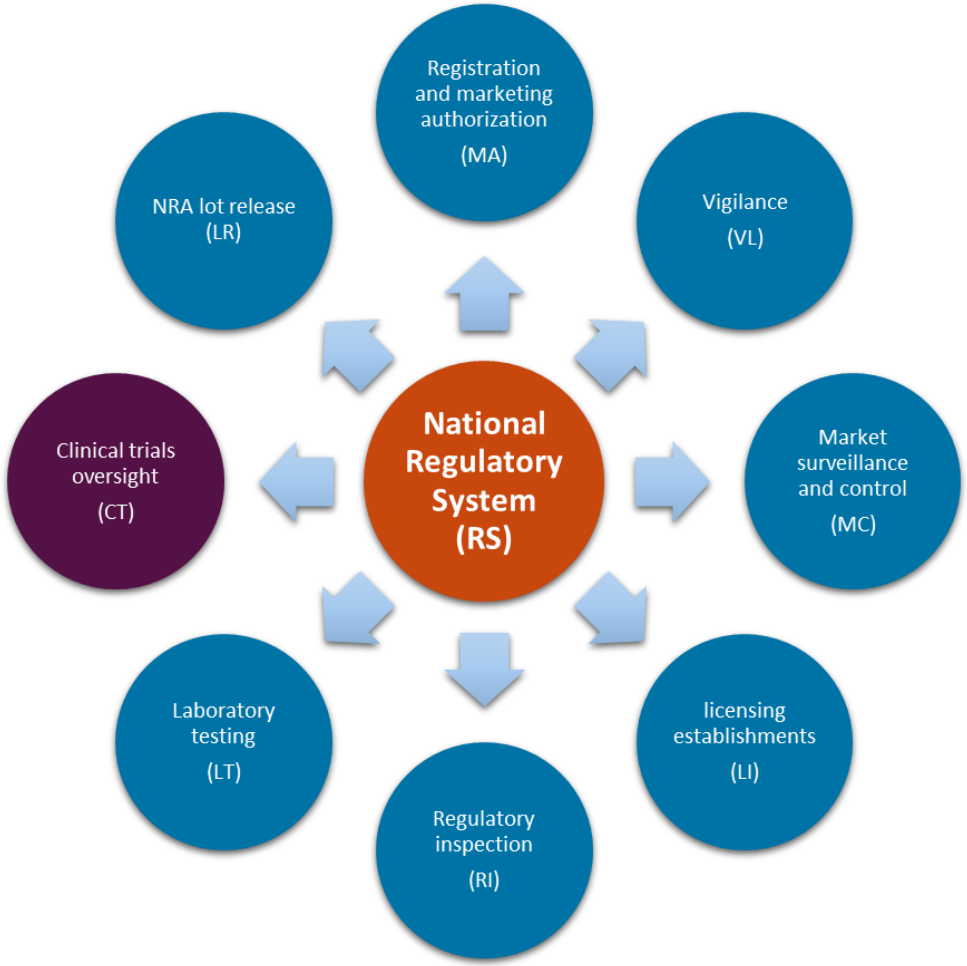
Designed for all entities involved in the ethical oversight of health-related research involving humans, including research ethics committees (RECs) at the national, sub national, or institutional levels, and institutions whose employees or agents conduct health-related research involving humans.

WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems of medical products: Revision VI

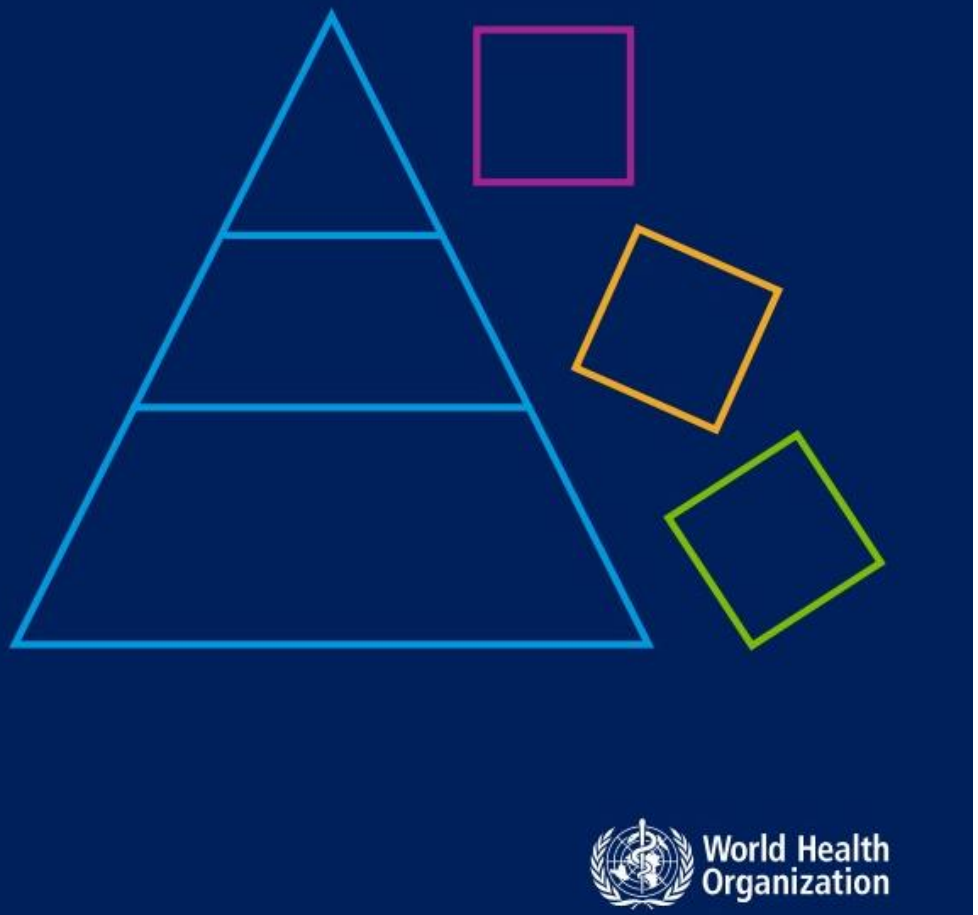


Link: https://apps.who.int/iris/handle/10665/341243

Link: https://www.who.int/tools/global-benchmarking-tools



Development of the Benchmarking Tool



World Health Organization

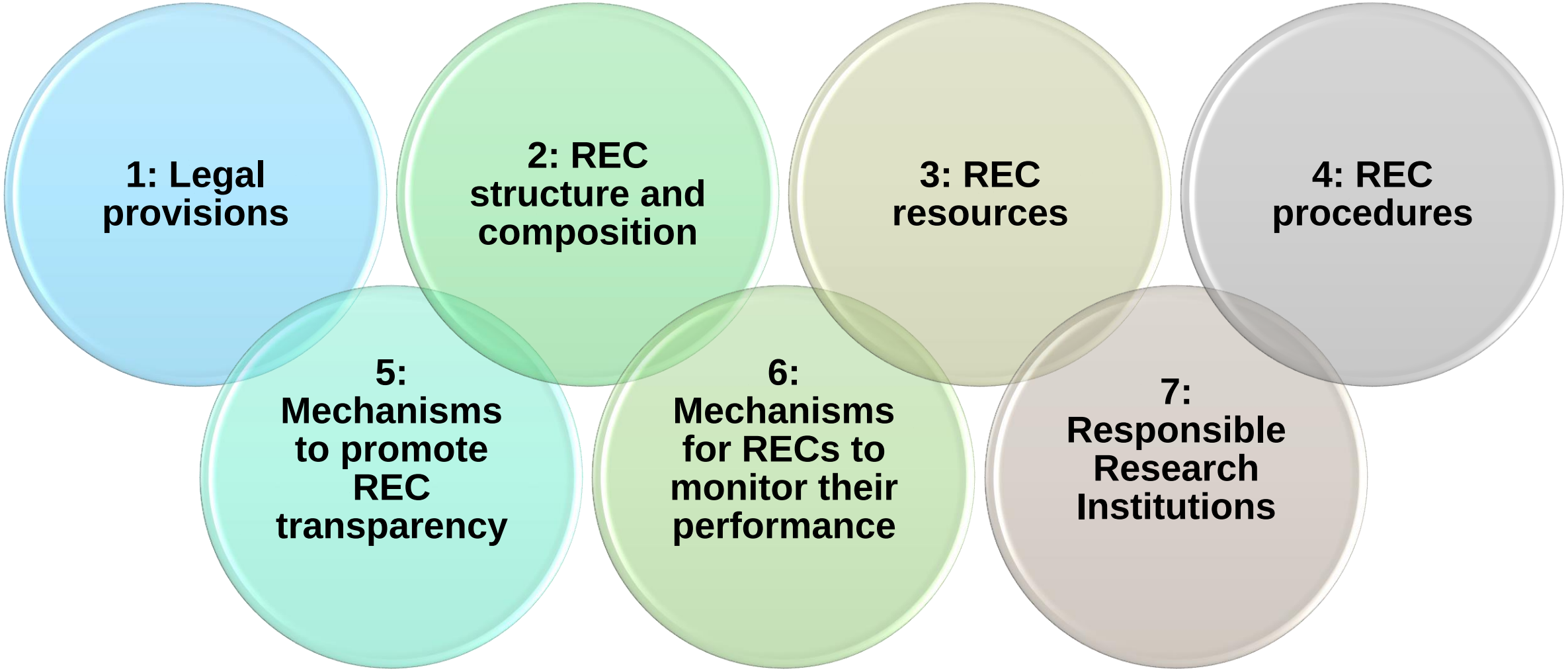
- Developed with support of WHO Expert Group
- 100+ Research Ethics Committees involved
- WHO Secretariat:
  - Alireza Khadem, Regulatory System Strengthening
  - Andreas Reis, Health Ethics & Governance Unit

Link:

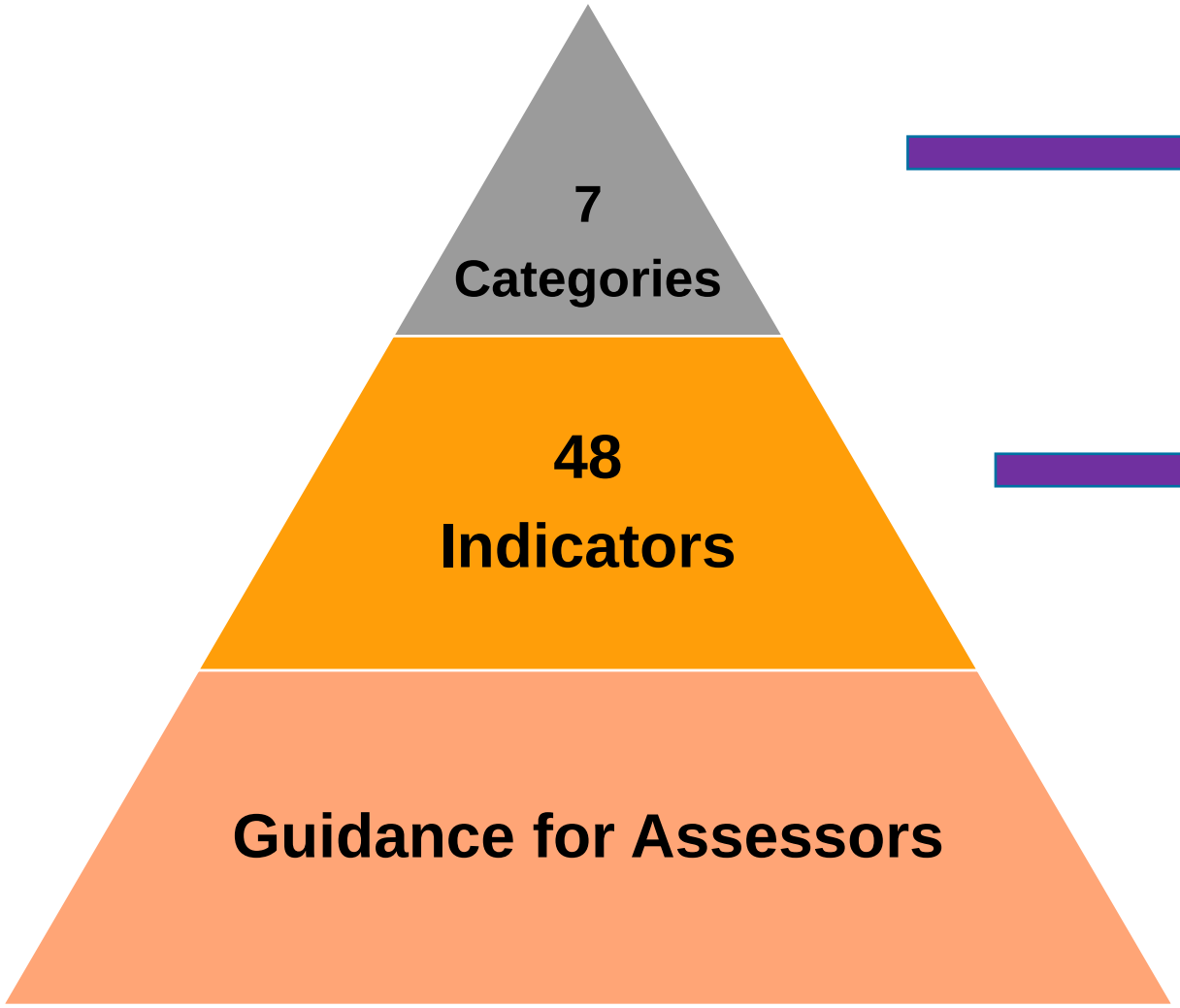
https://iris.who.int/bitstream/handle/10665/372984/9789240076426-eng.pdf

Ethics Oversight Benchmarking Tool: Overview

World Health Organization



Structure of the Tool



Category 1 = Legal provisions (National context)

Category 2 = Structure and composition (RECs)
Category 3 = Resources (RECs)
Category 4 = Procedures (RECs)
Category 5 = Transparency (RECs)
Category 6 = Performance (RECs)

Category 7 = Responsible research institutions

Example: Category 1 = Legal provisions

Indicator 1.1: Legal provisions requiring health-related research with humans to be reviewed and approved by RECs.
Indicator 1.2: Legal provision ensuring that RECs have the authority to function independently.
Indicator 1.3: Legal provision requiring RECs to review proposed research to determine that it satisfies the ethical standards…

….

- **Objective**
- **Description**
- **Evidence to review**
- **Rating scale**

Category 1:

Indicators for Assessment of the Legal and Regulatory Context

Indicators for assessment of the legal and regulatory context (category 1)

Category:	01: LEGAL PROVISIONS[2] AND REGULATORY FRAMEWORK
Objective:	To determine whether the legal and regulatory framework is adequate to support ethical oversight of health-related research involving humans.
Indicator:	**01.01: Legal provisions that require health-related research involving humans to be reviewed and approved by RECs.**
Description:	Consistent with the ethical principles in WHO guidance,[3] countries should have legal provisions that explicitly require ethical review and approval of health-related research involving humans before recruitment of participants begins (or, in studies of previously collected biological specimens or data, before the research commences). Countries may choose to exempt specified categories of low-risk studies from this requirement.
Evidence to be reviewed:	Relevant evidence may include: ▪ legal provisions that require RECs to review and approve health-related research involving humans in accordance with ethical principles in WHO guidance, as well as any national laws or policies consistent with those principles; and ▪ any relevant guidance documents that provide interpretation of those provisions.
Rating scale:	➔ **Fully implemented:** Legal provisions (1) explicitly require ethical review and approval of health-related research involving humans before recruitment of participants begins (or, in studies of previously collected biological specimens or data, before the research commences); and (2) these provisions apply to all health-related research involving humans, regardless of funding source (with the possible exception of specified categories of minimal-risk studies). ➔ **Partially implemented:** Legal provisions require ethical review and approval of health-related research involving humans but do not explicitly require review to be conducted before recruitment of participants begins (or, in studies of previously collected biological specimens or data, before the research commences), and/or the provisions do not cover all health-related research involving humans presenting more than minimal risk. ➔ **Not implemented:** There are no legal provisions that explicitly require ethical review and approval of health-related research involving humans.

Categories 2-6:

Indicators for assessment of individual Research Ethics Committees

Category 2 = Structure and composition (RECs)

Category 3 = Resources (RECs)

Category 4 = Procedures (RECs)

Category 5 = Transparency (RECs)

Category 6 = Performance monitoring (RECs)

Indicators for assessment of RECs (categories 2–6)

Category:	02: REC STRUCTURE AND COMPOSITION
Objective:	To determine whether RECs have appropriate mechanisms for appointing and retaining diverse, qualified members and for supplementing members' contributions with outside expertise when necessary.
Indicator:	**02.01: The REC membership satisfies the requirements of ethical principles in WHO guidance and of any national laws or policies consistent with those principles.**
Description:	According to ethical principles in WHO guidance, RECs must have a multidisciplinary, multisectoral membership that is gender balanced, reflects the social and cultural diversity of the communities from which research participants are most likely to be drawn, and includes individuals with backgrounds relevant to the areas of research that the committee is most likely to review. The following factors should be considered when appointing members: 1. RECs should consist of a reasonable number of members who collectively have the education, training, skills and experience to review and evaluate the type of research proposals the committee is most likely to receive. 2. Members should include individuals with relevant scientific expertise (depending on the type of research the REC reviews, this may include experts in behavioural and social sciences, health-care providers and pharmacologists); members who have expertise in legal matters, public health and ethics; and lay people whose primary role is to share their knowledge about the communities from which participants are likely to be drawn. 3. Lay people and other members whose primary background is not in health research involving human participants should be appointed in sufficient numbers to ensure that they feel comfortable in voicing their views. 4. To support independence, committee membership should include individuals who are not affiliated with organizations that sponsor, fund or conduct research reviewed by the REC. 5. All REC members should declare any conflicts of interest, and the REC should ensure that members do not participate in reviewing studies in which they have a conflict of interest. 6. Committees should be large enough to ensure many perspectives in the discussion. Quorum requirements should provide that at least half of the members, including at least one lay member and one non-affiliated member, are present to make decisions about proposed research.
Evidence to be reviewed:	Relevant evidence may include: ▪ legal provisions and guidance documents related to the qualifications of REC members;

Category 7:

Indicators for assessment of Research institutions

Indicators for assessment of research institutions (category 7)

Category	07: RESPONSIBLE RESEARCH INSTITUTIONS
Objective:	To assess whether research institutions fulfil their responsibility to ensure that any health-related research under their purview adheres to ethical principles in WHO guidance, as well as any national laws and policies consistent with those principles. These indicators are not designed to provide a comprehensive assessment of research institutions; rather, they focus on clear markers of institutions' commitment to the protection of research participants.
Indicator:	**07.01: The institution verifies that all proposals for health-related research involving humans are submitted to a registered REC if any part of the research is to be conducted by a researcher affiliated with the institution.[9]**
Description:	Research institutions should expressly commit to complying with international and national ethical standards in health-related research involving humans. As part of this commitment, they should verify that all proposals for health-related research involving humans are submitted to a registered REC if any part of the research is to be conducted by a researcher affiliated with the institution.
Evidence to be reviewed:	Relevant evidence may include: ▪ institutional policies that require that all health-related research involving humans be submitted to an REC if any part of the research is to be conducted by a researcher affiliated with the institution; ▪ institutional policies specifying the REC(s) on which the institution relies for reviewing research conducted by researchers affiliated with it; ▪ evidence that the institution ensures that researchers affiliated with it comply with these policies; ▪ information about any actions taken against researchers who failed to comply with these policies; ▪ information about all health-related research involving humans conducted by researchers affiliated with the institution in the current and previous years, with evidence that the studies were submitted to RECs; and ▪ evidence of the institution's express commitment to comply with international and national ethical standards in health-related research involving humans.
Rating scale:	→ **Fully implemented:** The institution has a policy that requires that all health-related research involving humans be submitted to a registered REC if any part of the research is to be conducted by a researcher affiliated with the institution, and there is evidence that researchers affiliated with the institution comply with those policies. In addition, there is evidence of the institution's express commitment to comply with international and national ethical standards in health-related research involving humans. → **Partially implemented:** The institution has a policy that requires that all health-related research involving humans be submitted to a registered REC if any part of the research is to be conducted by a researcher affiliated with the institution; however, all researchers

Implementation & impact in countries

Piloting the tool

The draft tool was piloted in workshops in the following countries:

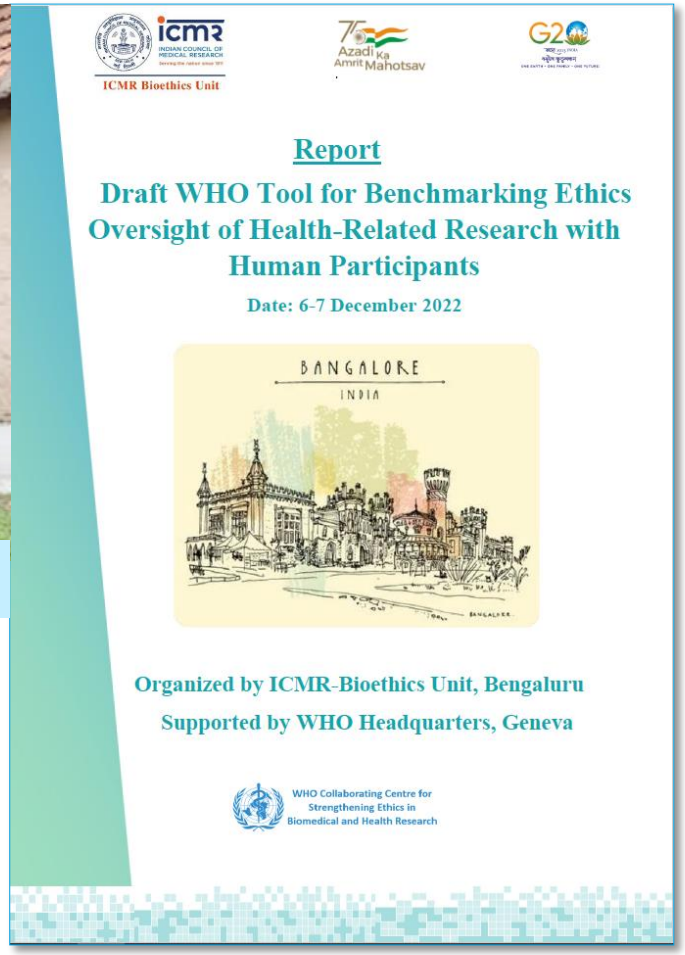
- Nairobi, Kenya, 10-14 October 2022
- Lagos, Nigeria, 17-21 October 2022
- Kathmandu, Nepal, 14-16 November 2022
- Bengaluru, India, 6-7 December 2022
- Cairo, Egypt, 22 January 2023
- Karachi, Pakistan, March 3-4, 2023

Country Workshops

ICMR Bioethics Unit

Benchmarking Tool Workshop 6-7 December, 2022, Bengaluru, India

Benchmarking Tool Workshop 14-16 November, Kathmandu, Nepal



Implementation in countries

Contents

Various options:

- Self-assessments
- Collaborative assessments / peer review
- Nationally coordinated assessment
- External assessments

After assessment:

- Report with areas for further improvement
- Follow-up plan

Link: https://iris.who.int/bitstream/handle/10665/373001/9789240080713-eng.pdf

Implementation in countries

- Launch 25th September 2023
- Dissemination and translation
- Self-assessments/ peer review
- Implementation workshops (in country or online)
- Collaboration with regional and national networks, e.g. AVAREF, FERCAP, FERCI, EURECNET etc.
- Future revisions

Conclusion

- (Research) Ethics - a key component of WHO's Programme of Work 2019-2024
- Adequate capacity for research ethics oversight is crucial for implementing international research ethics standards
- Robust capacity needs to be built in «normal» times, so it can also function during emergencies
- WHO and partners are supporting Member States by providing specific guidance and tools for research ethics oversight

Thank you very much!