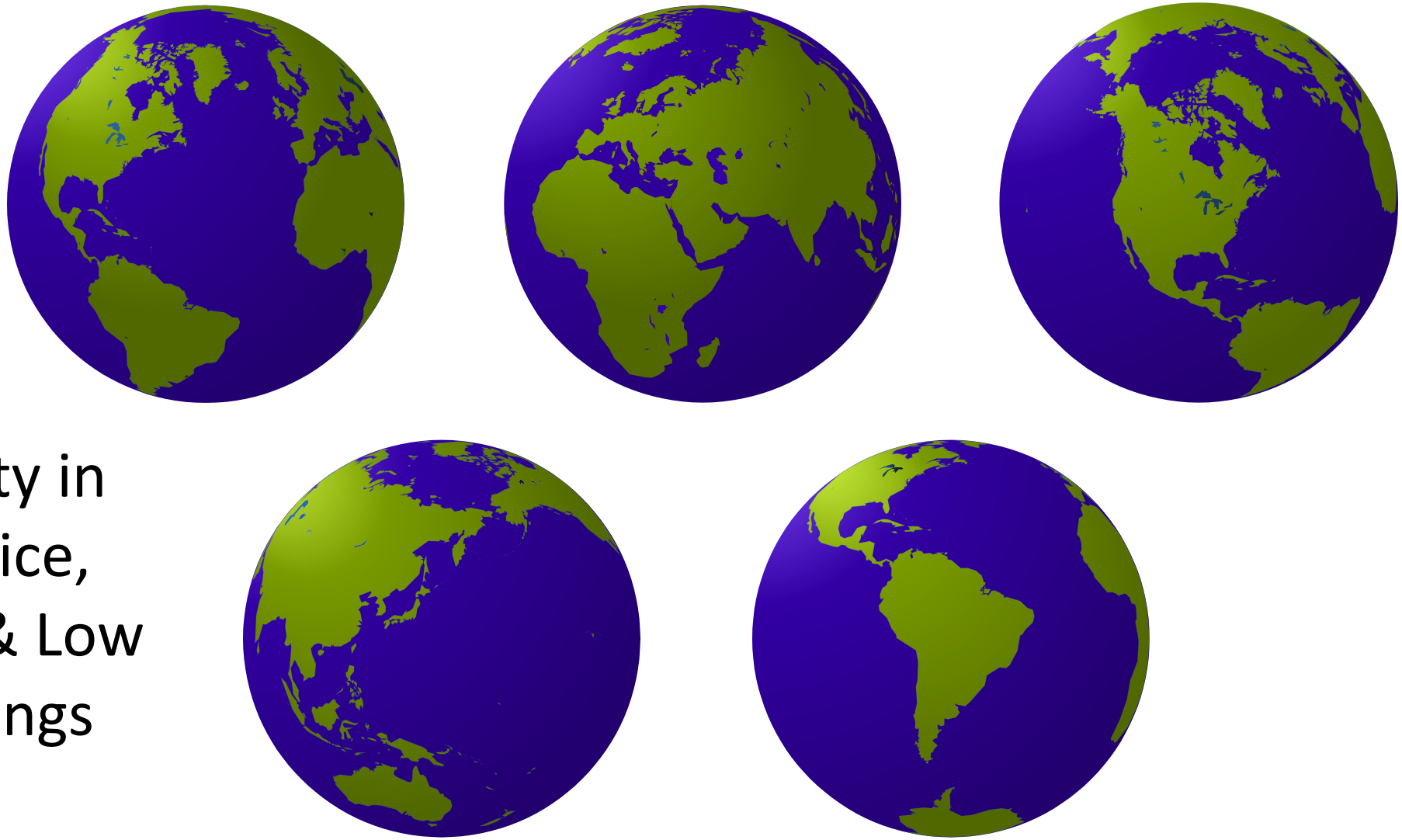


Access & Equity in Research: Justice, Vulnerability & Low Resource Settings

Professor Ames Dhai, University of the Witwatersrand

Declaration

South African Medical Association is a member of the WMA Working Group on the Revison of the DOH.

The views presented are my personal ones

OUTLINE

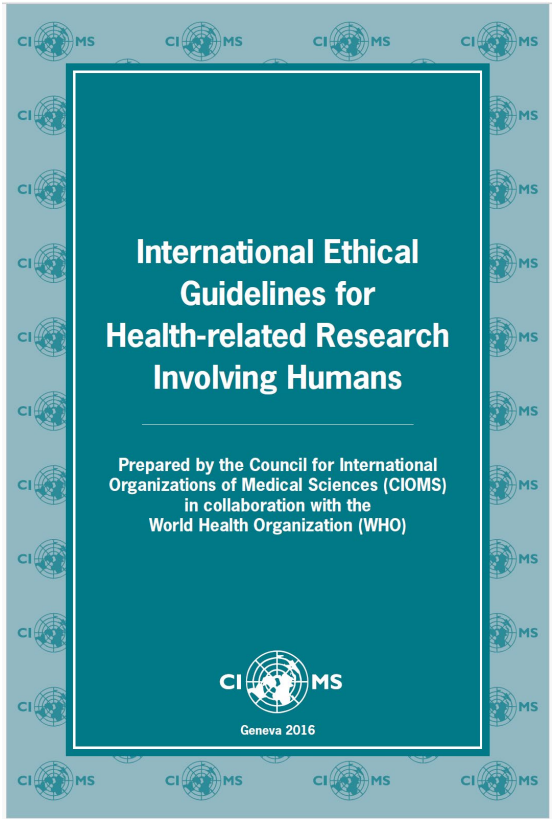
Equity in research

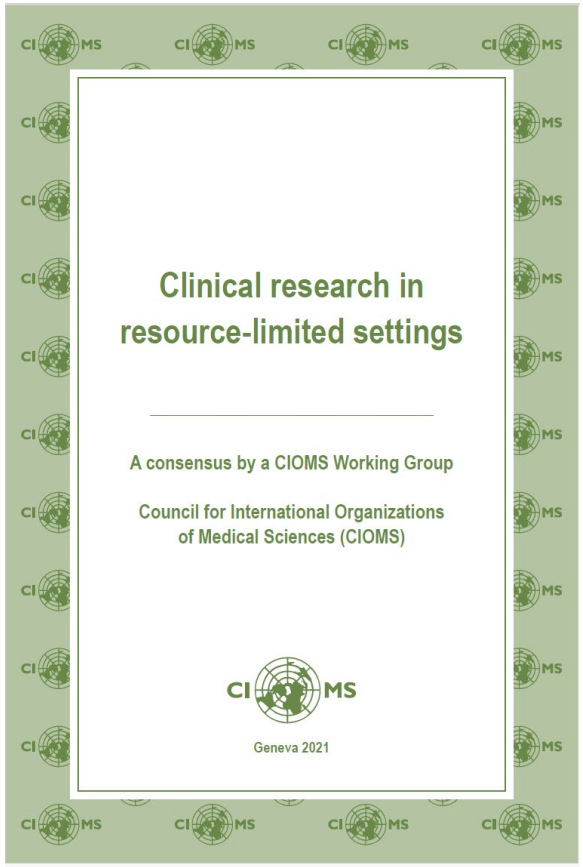
Social value

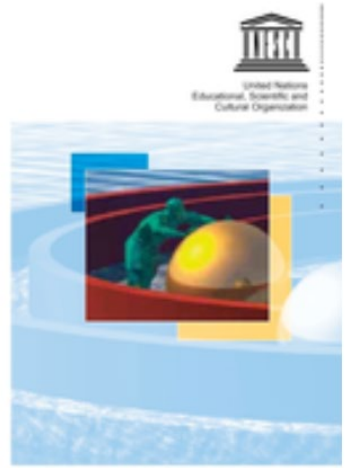
Vulnerability & Exploitation

Case Study

PRIORITY RESOURCES







Universal Declaration on Bioethics and Human Rights

Equity in Health & Research

Health equity: all to have equal opportunities & equal resources to access health.

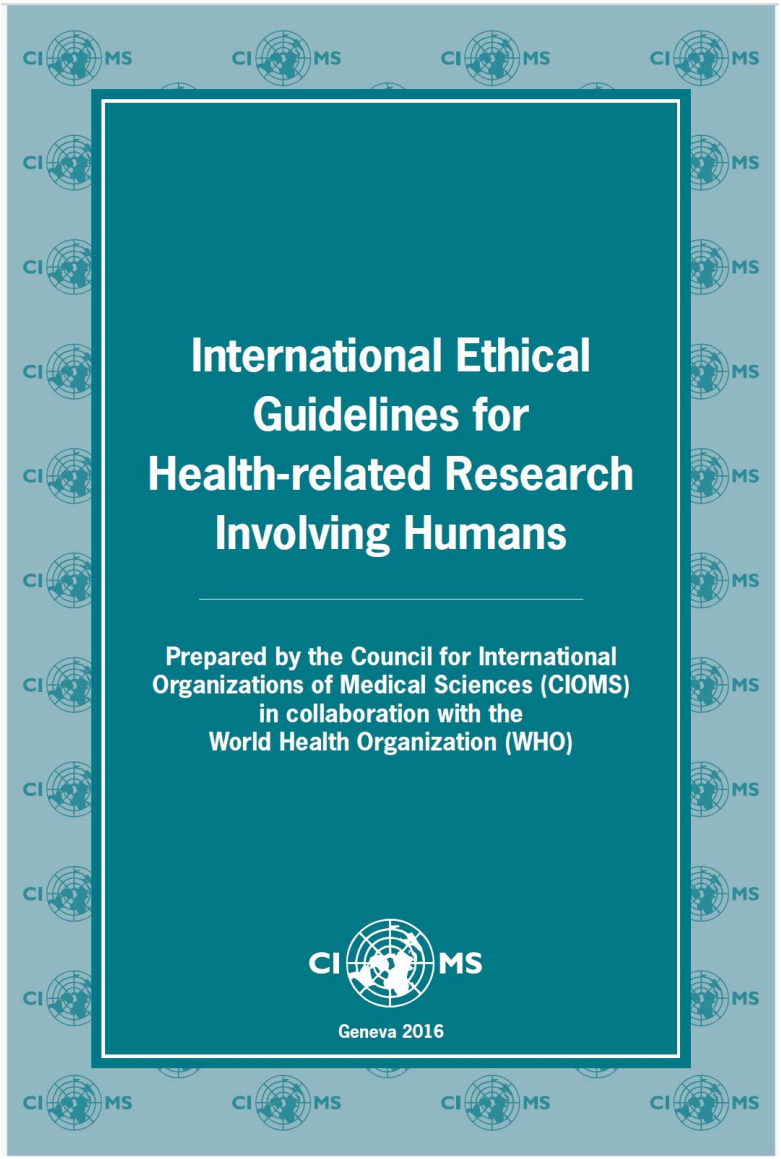
WHO - equity: "the absence of avoidable or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically" (WHO, 2018).

Based on concept of social justice: differences in access to health → ethically immoral and unjustifiable.

Research equity: all those affected by research / who can benefit from its outcomes to have equal opportunities to contribute to it & to benefit from it.

Research equity – includes those absent / silent in research - important means of addressing health equity

https://engageplus.org/en/objectifs-mission.asp



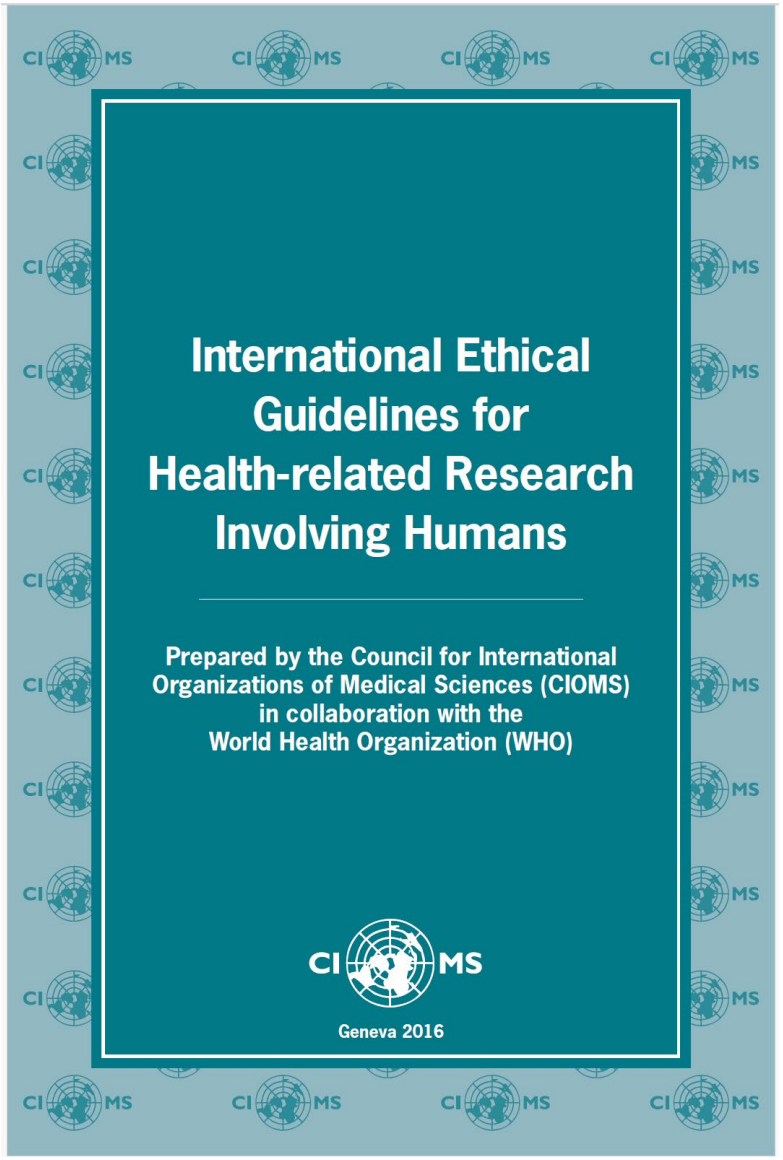
GUIDELINE 3:

EQUITABLE DISTRIBUTION OF BENEFITS AND BURDENS IN THE SELECTION OF INDIVIDUALS AND GROUPS OF PARTICIPANTS IN RESEARCH

Sponsors, researchers, governmental authorities, research ethics committees and other stakeholders must ensure that the benefits and burdens of research are equitably distributed. Groups, communities and individuals invited to participate in research must be selected for scientific reasons and not because they are easy to recruit because of their compromised social or economic position or their ease of manipulation. Because categorical exclusion from research can result in or exacerbate health disparities, the exclusion of groups in need of special protection must be justified. Groups that are unlikely to benefit from any knowledge gained from the research should not bear a disproportionate share of the risks and burdens of research participation. Groups that are under-represented in medical research should be provided appropriate access to participate.

Synthesis Guideline 3

- No group / class of persons to bear more than fair share of risks/burdens from research participation.
- Equitable distribution →participants drawn from qualifying population in geographic area of study where results can be applied
- No unfair discrimination re inclusion/exclusion criteria.
- Under-representation →perpetuate health disparities
- Research benefits → to address diverse health needs across different classes/groups
- Unjust to selectively include disadvantaged individuals/groups:
  - risks and burdens concentrated in those already socially/economically disadvantaged.
  - overuse in research
  - most likely to be excluded from/have difficulty accessing research benefits
  - broader inclusion of different social groups – helps ensure research conducted in socially & ethically acceptable manner.



GUIDELINE 1:

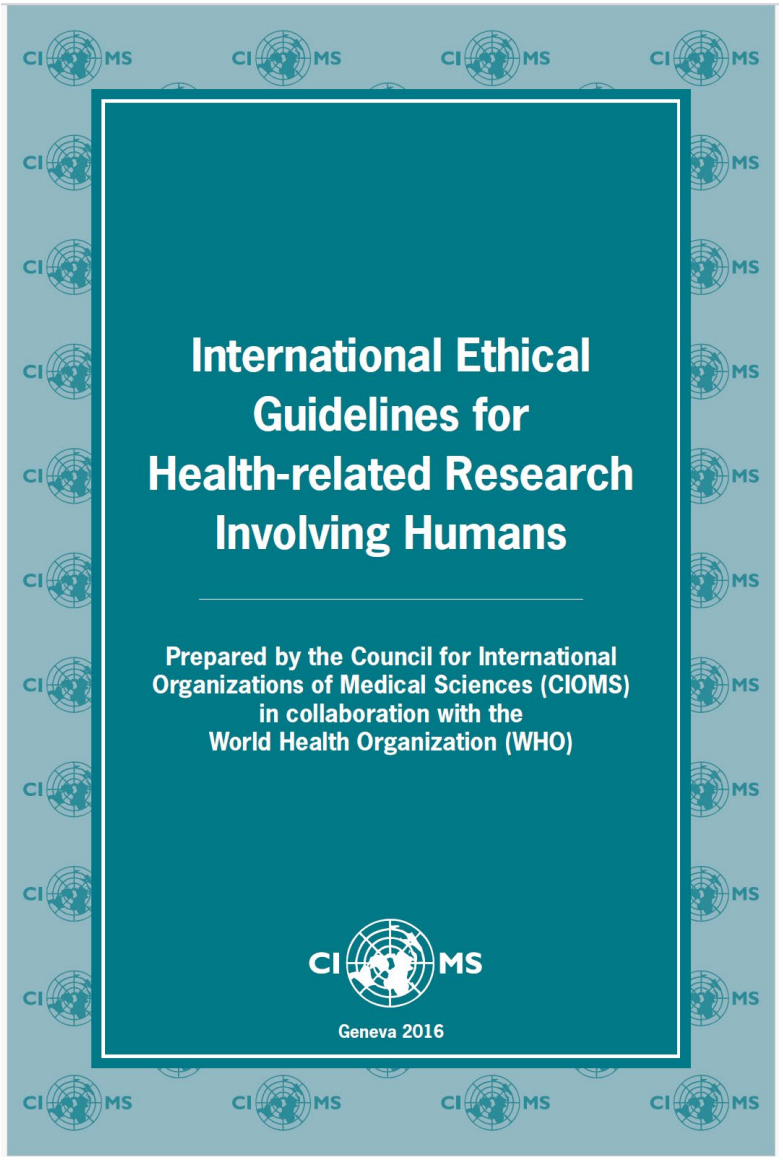
SCIENTIFIC AND SOCIAL VALUE AND RESPECT FOR RIGHTS

The ethical justification for undertaking health-related research involving humans is its scientific and social value: the prospect of generating the knowledge and the means necessary to protect and promote people's health. Patients, health professionals, researchers, policy-makers, public health officials, pharmaceutical companies and others rely on the results of research for activities and decisions that impact individual and public health, welfare, and the use of limited resources. Therefore, researchers, sponsors, research ethics committees, and health authorities, must ensure that proposed studies are scientifically sound, build on an adequate prior knowledge base, and are likely to generate valuable information.

Although scientific and social value are the fundamental justification for undertaking research, researchers, sponsors, research ethics committees and health authorities have a moral obligation to ensure that all research is carried out in ways that uphold human rights, and respect, protect, and are fair to study participants and the communities in which the research is conducted. Scientific and social value cannot legitimate subjecting study participants or host communities to mistreatment, or injustice.

Social Value

- Importance of information that study is likely to produce
- Likely to promote individual or public health
- Endpoints need to be related to clinical decision-making → clinicians , policymakers likely to alter practices based on study findings.
- Study to have sufficient social value to justify associated risks, costs, burdens.



GUIDELINE 2:

RESEARCH CONDUCTED IN LOW-RESOURCE SETTINGS

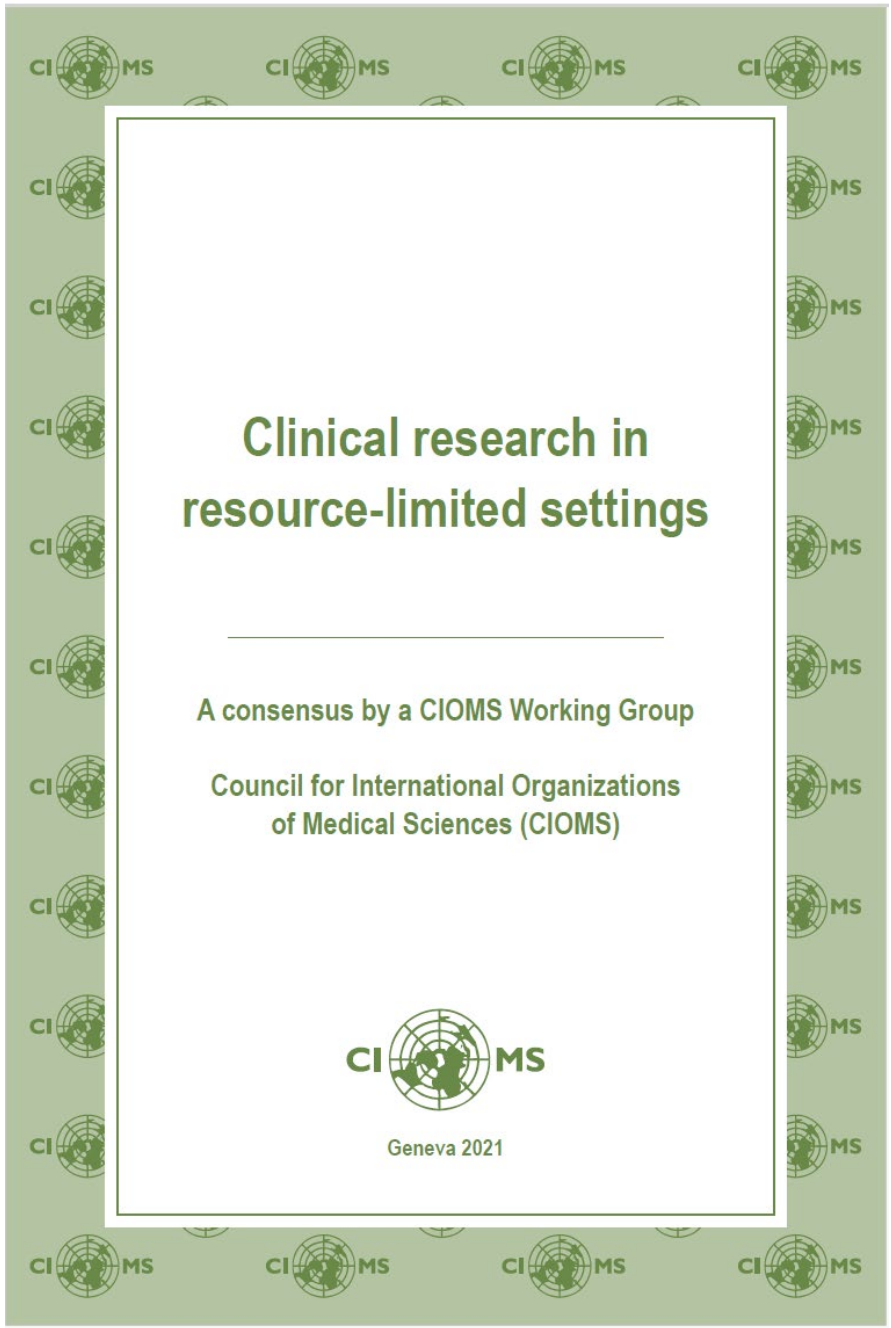
Before instituting a plan to undertake research in a population or community in low-resource settings, the sponsor, researchers, and relevant public health authority must ensure that the research is responsive to the health needs or priorities of the communities or populations where the research will be conducted.

As part of their obligation, sponsors, and researchers must also:

- make every effort, in cooperation with government and other relevant stakeholders, to make available as soon as possible any intervention or product developed, and knowledge generated, for the population or community in which the research is carried out, and to assist in building local research capacity. In some cases, in order to ensure an overall fair distribution of the benefits and burdens of the research, additional benefits such as investments in the local health infrastructure should be provided to the population or community; and
- consult with and engage communities in making plans for any intervention or product developed available, including the responsibilities of all relevant stakeholders.

Synthesis Guideline 2

- ↓Resources → vulnerability to exploitation
- Local social value to be created → equitable benefit
- Responsiveness of research to health needs & priorities → provides social value to community / population
- Shared responsibility
- Post trial availability
- Community engagement
- Counter “ethics dumping”



- Global health divide: LMICs – highest burden of preventable disease globally
- Most R&D focussed on diseases in HICs – considerable + costly infrastructure available
- SDGs - ensuring healthy lives & promoting well-being for all with universal access to needed meds & vaccines
- Require good quality research to identify & address unmet needs
- Clinical research drive advancement of healthcare – entire populations miss out if not done in LRS
- Regulatory & administrative impediments
- Resource limitations – may also exist in HICs

Clinical research in resource-limited settings

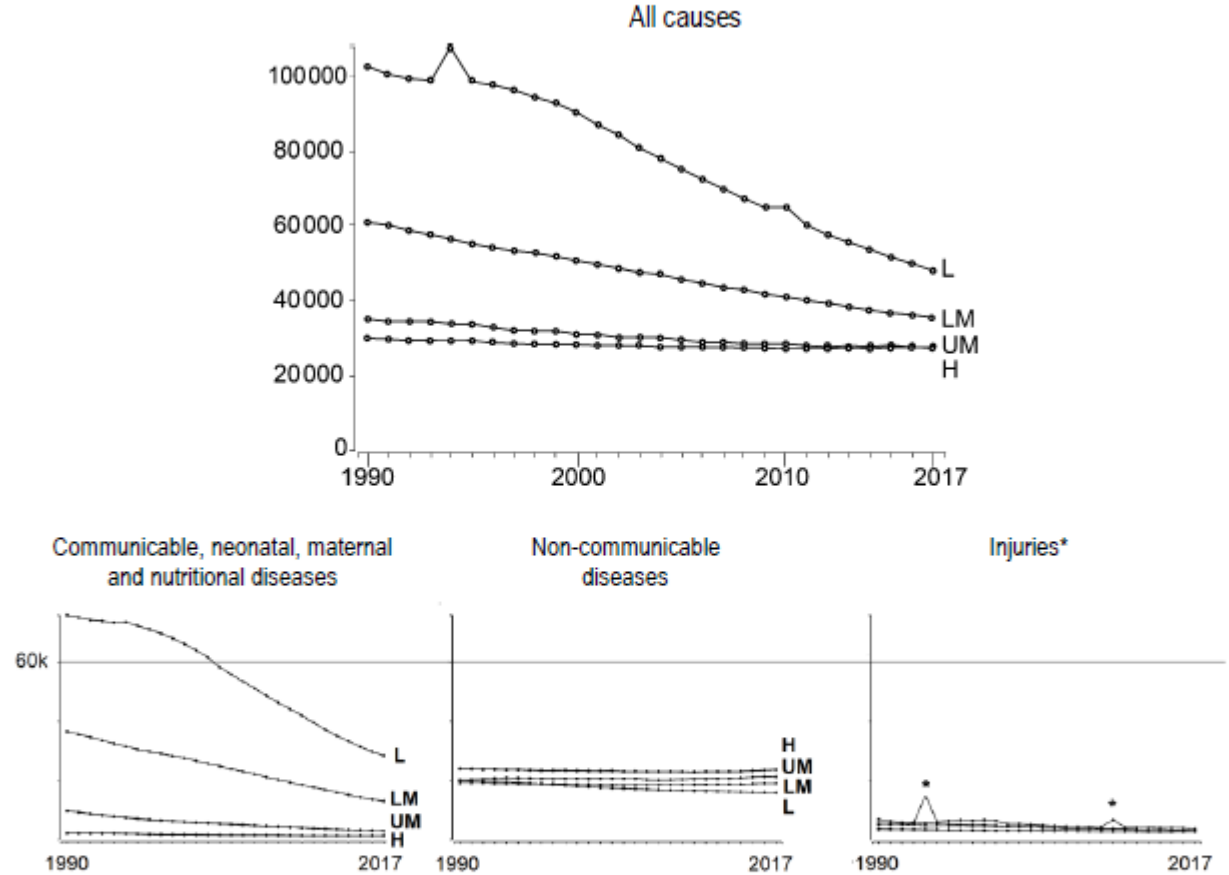
A consensus by a CIOMS Working Group

Council for International Organizations of Medical Sciences (CIOMS)

CIOMS

Geneva 2021

Figure 1. Global burden of disease, 1990-2017, by World Bank income levels
(DALY per 100,000 population) [9]



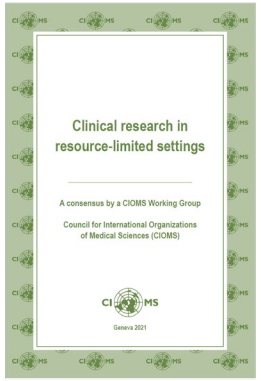
Legend:

DALY: Disability-adjusted life year. The sum of years lost due to premature death and years lived with disability. DALYs are also defined as years of healthy life lost.

H=High income; **UM**=Upper middle income; **LM**=Lower middle income; **L**=Low income

*1994: Rwandan genocide; 2010: Haiti earthquake

Source: Institute for Health Metrics Evaluation. Used with permission. All rights reserved. [9]

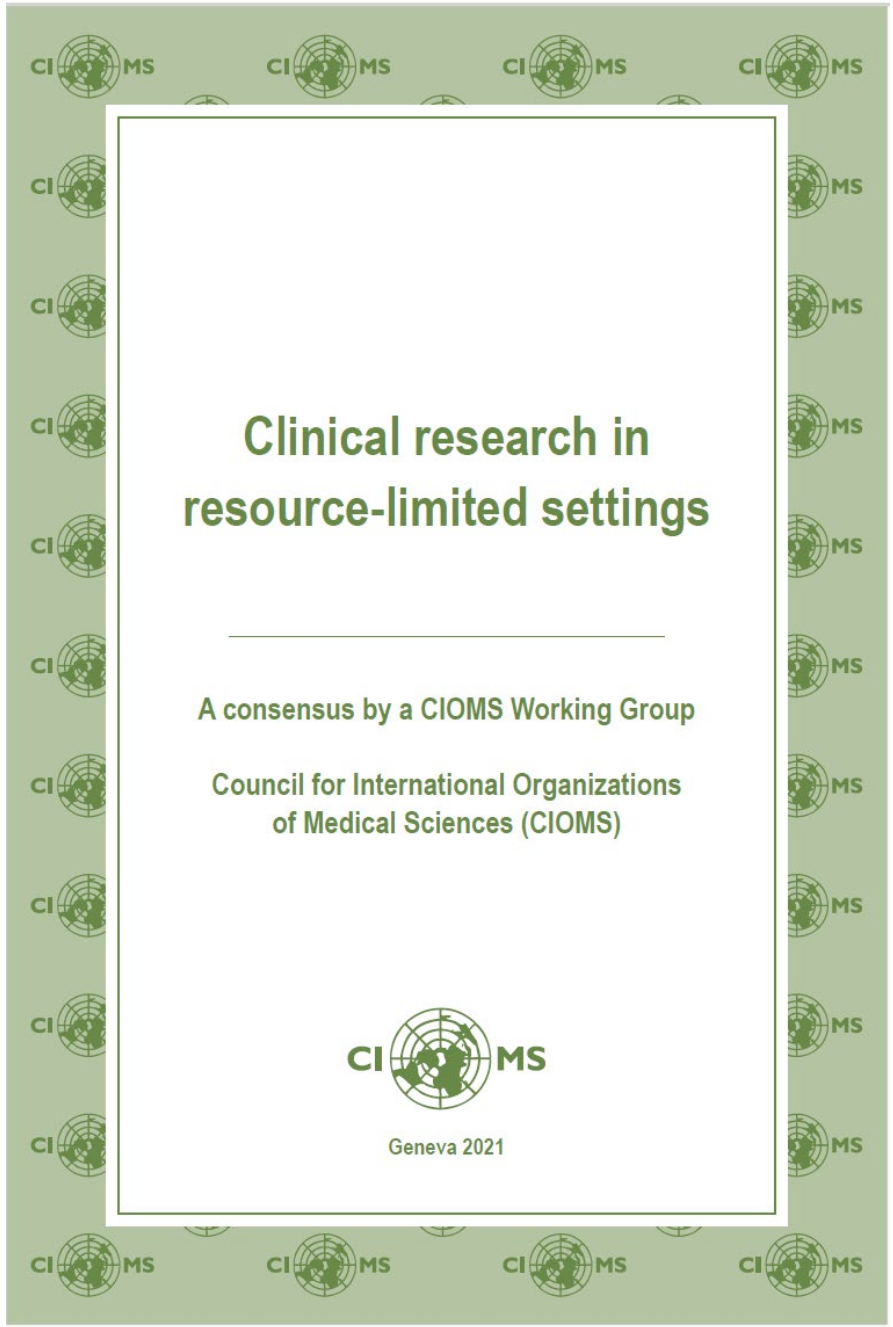


1.3

Improving public health

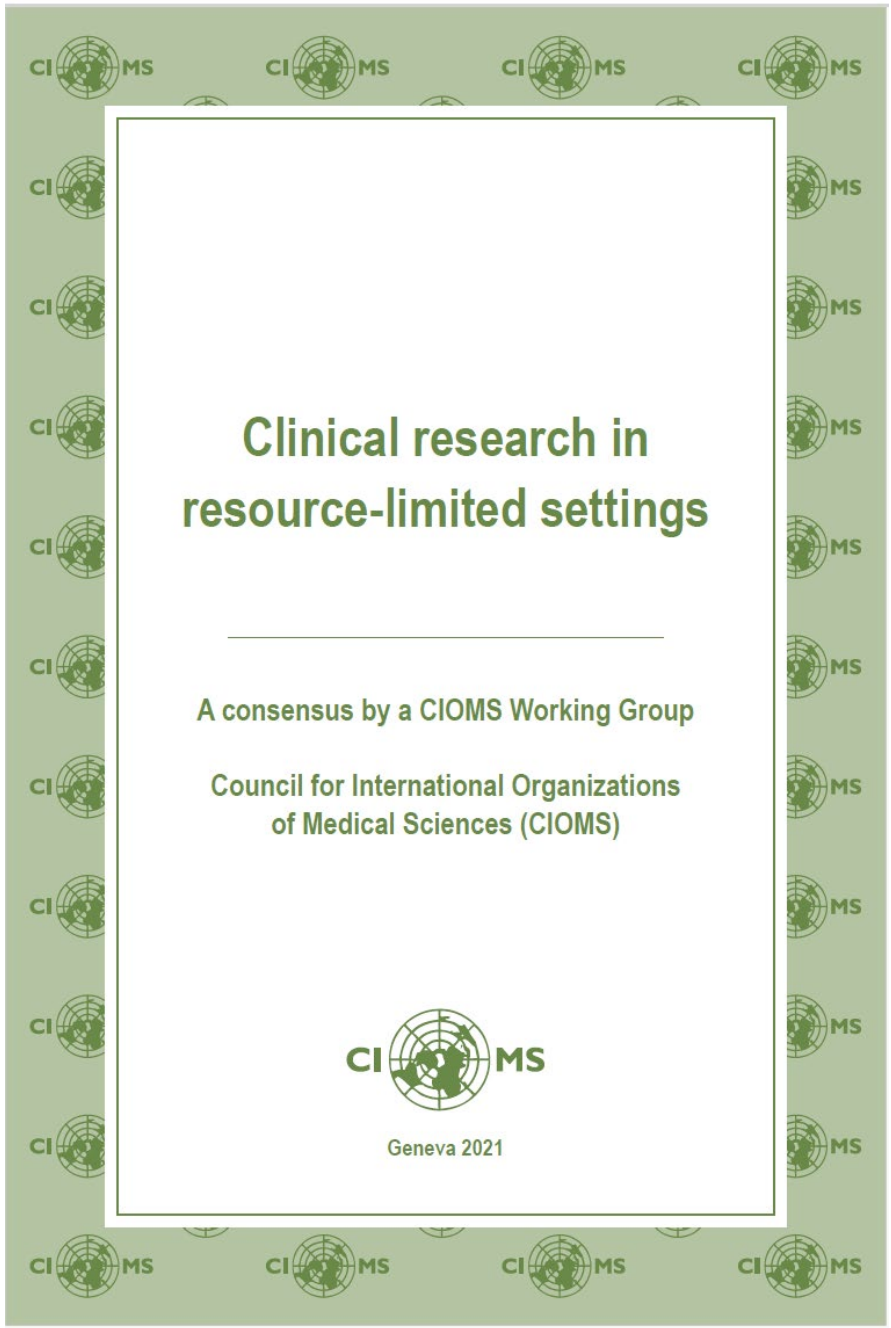
Health research as a social responsibility

A well-developed healthcare system offering substantial benefits for all its citizens is a quintessential part of social responsibility. Implementation of a healthcare system should not be limited to providing available therapies in line with best practice, but should include strategies and practical tools for improving healthcare to cover unmet health needs, and thus to deliver effective and safe, evidence-based care. Such strategies include the conduct of clinical studies[3] with the aim of increasing the knowledge of health problems affecting the population, developing and evaluating medicines and health products that target these health problems, studying medicines in the local context, and optimizing their accessibility and use. In addition, pragmatic disease management trials [13] bring evidence on how to improve health care by comparing, for example, different approaches to disease management or different mechanisms to improve patient adherence to therapy to improve outcomes.



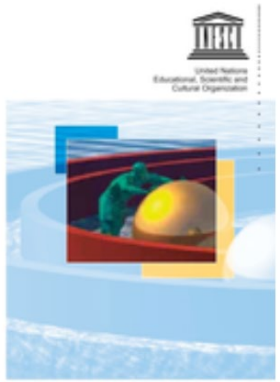
Trust-building

While ethical guidelines and clinical trial regulations have greatly advanced in past decades, and clinical research in resource-limited settings is critically important,[33] the aim and nature of such research are often not well understood by the local population, and some continue to see research as exploitative, with researchers from high-income countries taking advantage of the low-cost, under-regulated environments of low- and middle income countries (LMICs). There is therefore a need for a consensus report showing that good quality, ethical research is possible in



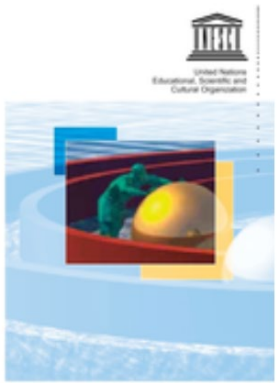
Inclusion of special and vulnerable populations

Secondly, in the past general guidance on clinical research did not usually consider physiologically special populations such as children, pregnant women and women of child-bearing age (see also Appendix 1). Recent years have seen a move from exclusion to inclusion of these populations in high level recommendations and guidance, for example to safeguard the interests of children [19] or pregnant women and their offspring in vaccine R&D.[20] Beyond these physiological differences, there are many circumstances that can render research participants vulnerable in different and overlapping ways.[21] While unnecessary research with vulnerable persons— or indeed any persons—should be avoided,[16] it is a matter of basic justice that, like any other societal group, vulnerable persons should be included in research that is necessary to show that they can be treated with a medicine safely and effectively. The updated ICH GCP principles state that when designing a clinical trial the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations.[18] Researchers and research ethics committees must find ways to safeguard the rights and welfare of these vulnerable research participants.



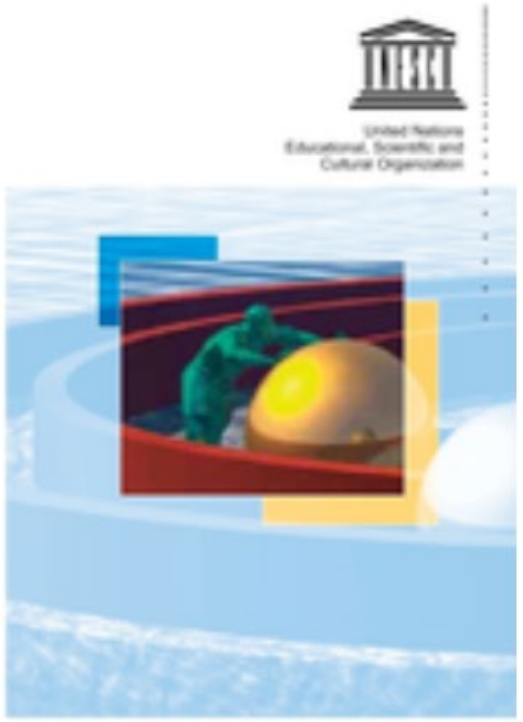
Article 8 Respect for human vulnerability and personal integrity

In applying and advancing scientific knowledge, medical practice and associated technologies, human vulnerability should be taken into account. Individuals and groups of special vulnerability should be protected and the personal integrity of such individuals respected.



Article 13 Solidarity and cooperation

Solidarity among human beings and international cooperation towards that end are to be encouraged.



Article 15 — Sharing of benefits

1. Benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries. In giving effect to this principle, benefits may take any of the following forms:

(a) special and sustainable assistance to, and acknowledgement of, the persons and groups that have taken part in the research;

(b) access to quality health care;

(c) provision of new diagnostic and therapeutic modalities or products stemming from research;

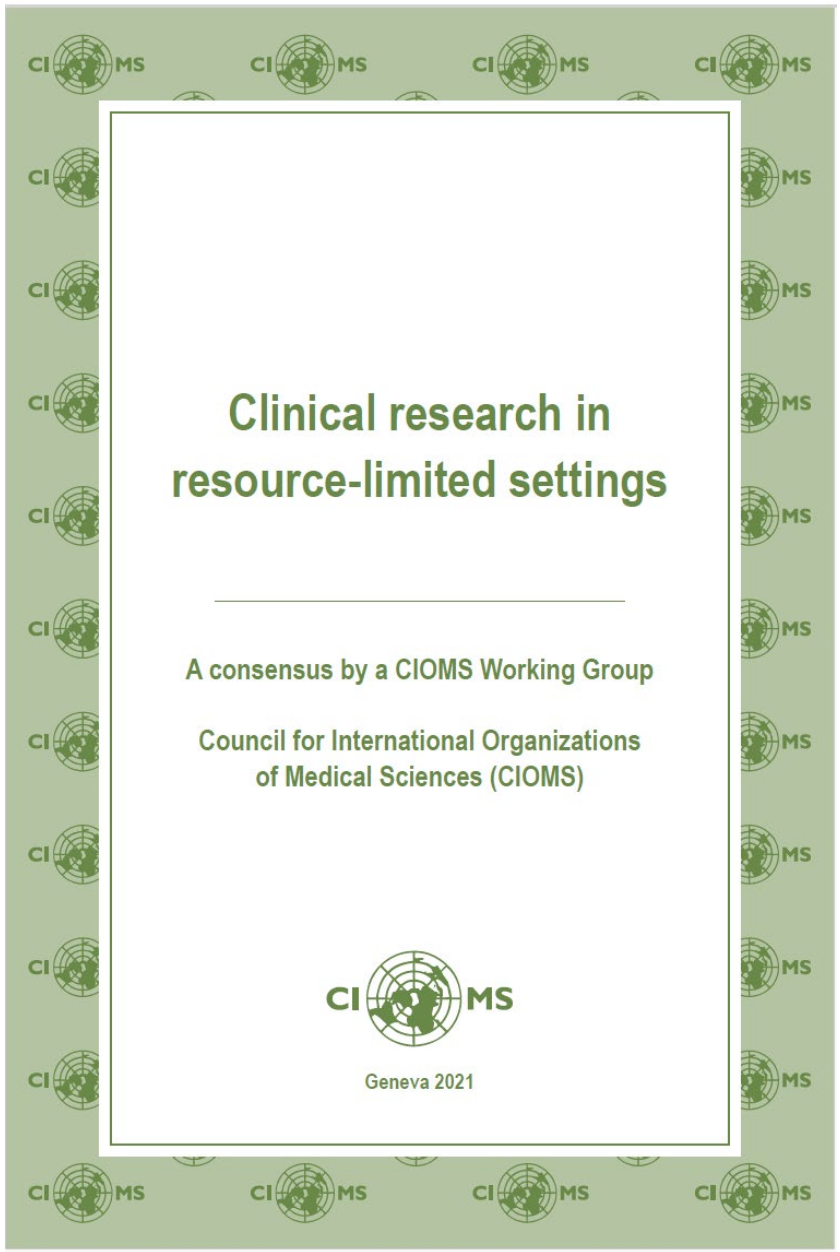
(d) support for health services;

(e) access to scientific and technological knowledge;

(f) capacity-building facilities for research purposes;

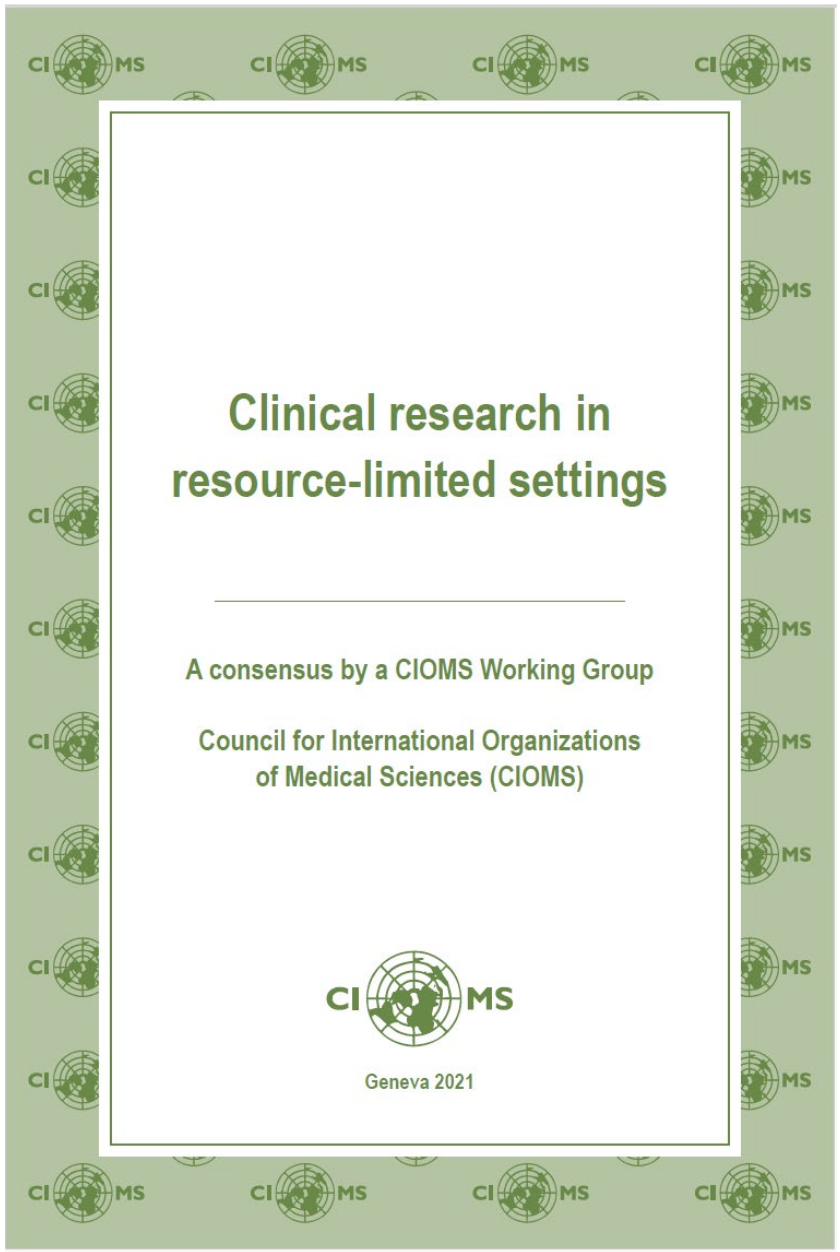
(g) other forms of benefit consistent with the principles set out in this Declaration.

2. Benefits should not constitute improper inducements to participate in research.



4.3 Avoiding exploitative research

The positive value of research partnerships between high-income countries (HICs) and low- and middle-income countries (LMICs) is well established. International collaborative clinical research promotes exchange of scientific information, supports training on novel methods and improves outcomes. However, in such partnerships exploitative and unethical research practices can also occur. For example, a study being conducted in a low-resource country to reduce costs may fail to take into consideration if there is a need for such research, if there are plans to make products and services available locally, or if there are conflicts of interest or other issues that may affect participant safety or the validity of the research findings. This section describes the possible consequences of power imbalances in research and calls for good practices for research based on the values of fairness, respect, care and honesty.



A contro-versial example

A controversial example is the debate about the standard of care provided to the control groups in three clinical trials on cervical cancer screening conducted in India with funding from the U.S. and France.[137-139] The international standard for screening is the Pap smear (cytology), however not all LMICs have been able to offer it to all women as part of public health care. The studies aimed to identify an alternative screening method for implementation under the Indian government programme. This research was criticized on the premise that cervical cancer screening has been proven effective to avert deaths from cancer and should not be withheld from any women, including those enrolled in clinical studies.[140,141] The controversial viewpoints are illustrated in Appendix 4, showing the complexity of the issues involved.

Question	Researchers' perspective [301]	Complainant's perspective [140,302]
Was there a need for a more locally feasible screening method in India (and hence for the research)?	*Yes* "The fact that population-based cytology screening is not feasible in India is not our invention; it has been determined by the Indian Council of Medical Research (ICMR) in 1992 (6) and again in 2006 by a joint WHO–government of India guideline Committee (7)."	*No* "Papanicolaou screening is feasible anywhere that cervical screening is appropriate."
Did the no-screening control group expose participants to increased risks?	*No, the participants received even more care than they would have outside the study* "...control group… received routine care plus education on prevention of cervical cancer and early detection by screening as well as advice on how and where to seek screening, early diagnosis and treatment services"	*Yes, in a moral sense, since all women should be given access to Papanicolaou screening* "..I do acknowledge that I have harboured—for more years than I care to count—an evolving sense of anger in the face of what I have perceived as meaningless, avoidable harm and death visited on desperately vulnerable women …"

		…"
Was withholding or delaying the screening methodologically necessary for the study?	*Yes, no methodological issues were raised in the protocol review* "The study proposal was reviewed and approved by [*the local RECs*] and the International Agency for Research on Cancer (IARC) of the WHO, Lyon, for both studies."	*No. IARC should not have approved the study protocols* "It is profoundly alarming for the health of the world's women that the World Health Organisation's International Agency for Research on Cancer harbours such immutable yet irrational opposition to cytology screening for precisely those communities in the world that are at highest risk for death from cervical cancer. Unintended negative consequences may result when research professionals are given leadership roles in development efforts."

Question	Researchers' perspective [301]	Complainant's perspective [140,302]
(continued) Were the women informed of the benefits and risks of participating in the study?	*Yes, with some initial problems; corrective action was taken* "Our studies were explained in the local language to all eligible women and written informed consent was obtained from each participant. As experienced Indian scientists and clinicians, we find it misleading when someone implies that Indian women do not have the common sense and intelligence to understand and comprehend the study procedures, interventions, harms, and benefits in order to make an informed decision to consent to participation." "..the corrective actions taken by the Tata Memorial Hospital Institutional Review Board (TMH IRB) adequately address the earlier determination of non-compliance. These letters of determination, which Dr Suba has avoided mentioning, are available in the public domain on the OHRP web site (11,12)."	*No* "To suggest, as do [the researchers], that Indian women would knowingly consent to be randomly assigned to more death – instead of to more life – is to suggest that Indian women are unimaginably stupid. To enrol and sustain the unscreened control groups in these US-funded studies required withholding critical information from all 363,553 study participants regarding the predictable health benefits of one to four rounds of cervical screening, compared to no screening whatsoever."