MEDICAL RESEARCH TODAY: THE GEOGRAPHICS OF VULNERABLE POPULATIONS - AFRICA

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WMA Revision of the Declaration of Helsinki: Research in Resource-Poor Settings – Vatican City (January 2024)

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PRESENTATION OUTLINE

- Overview of factors complicating clinical research in resource poor settings
- Complexities specific to Africa
- African indigenous values & research
- Ethical developments since DoH 2013

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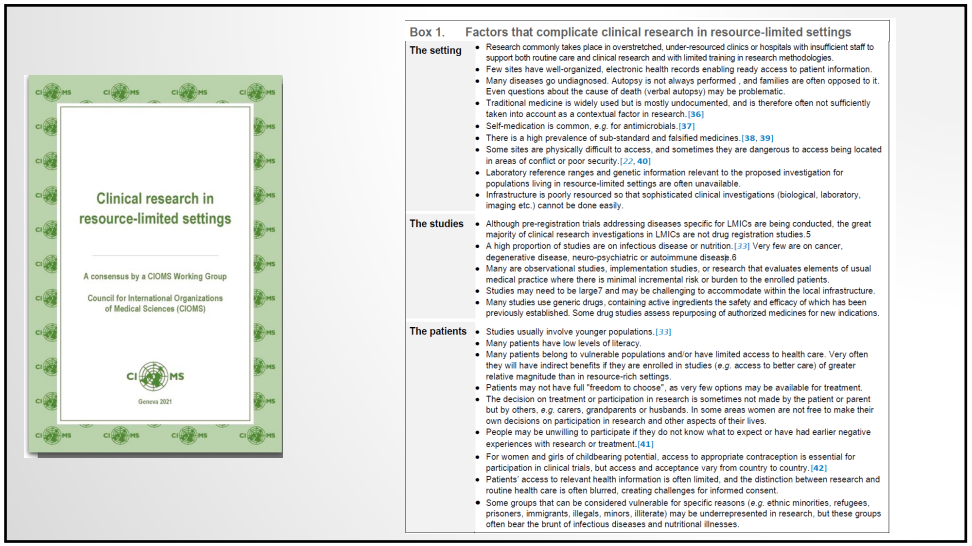
Clinical research in resource-limited settings
A consensus by a CIOMS Working Group
Council for International Organizations of Medical Sciences (CIOMS)
CIOMS
Geneva 2021
Box 1. Factors that complicate clinical research in resource-limited settings
The setting
Research commonly takes place in overstretched, under-resourced clinics or hospitals with insufficient staff to support both routine care and clinical research and with limited training in research methodologies.
Few sites have well-organized, electronic health records enabling ready access to patient information.
Many diseases go undiagnosed. Autopsy is not always performed , and families are often opposed to it. Even questions about the cause of death (verbal autopsy) may be problematic.
Traditional medicine is widely used but is mostly undocumented, and is therefore often not sufficiently taken into account as a contextual factor in research. [36]
Self-medication is common, e.g. for antimicrobials. [37]
There is a high prevalence of sub-standard and falsified medicines. [38, 39]
Some sites are physically difficult to access, and sometimes they are dangerous to access being located in areas of conflict or poor security. [22, 40]
Laboratory reference ranges and genetic information relevant to the proposed investigation for populations living in resource-limited settings are often unavailable.
Infrastructure is poorly resourced so that sophisticated clinical investigations (biological, laboratory, imaging etc.) cannot be done easily.
The studies
Although pre-registration trials addressing diseases specific for LMICs are being conducted, the great majority of clinical research investigations in LMICs are not drug registration studies.5
A high proportion of studies are on infectious disease or nutrition. [33] Very few are on cancer, degenerative disease, neuro-psychiatric or autoimmune disease.6
Many are observational studies, implementation studies, or research that evaluates elements of usual medical practice where there is minimal incremental risk or burden to the enrolled patients.
Studies may need to be large7 and may be challenging to accommodate within the local infrastructure.
Many studies use generic drugs, containing active ingredients the safety and efficacy of which has been previously established. Some drug studies assess repurposing of authorized medicines for new indications.
The patients
Studies usually involve younger populations. [33]
Many patients have low levels of literacy.
Many patients belong to vulnerable populations and/or have limited access to health care. Very often they will have indirect benefits if they are enrolled in studies (e.g. access to better care) of greater relative magnitude than in resource-rich settings.
Patients may not have full "freedom to choose", as very few options may be available for treatment.
The decision on treatment or participation in research is sometimes not made by the patient or parent but by others, e.g. carers, grandparents or husbands. In some areas women are not free to make their own decisions on participation in research and other aspects of their lives.
People may be unwilling to participate if they do not know what to expect or have had earlier negative experiences with research or treatment. [41]
For women and girls of childbearing potential, access to appropriate contraception is essential for participation in clinical trials, but access and acceptance vary from country to country. [42]
Patients' access to relevant health information is often limited, and the distinction between research and routine health care is often blurred, creating challenges for informed consent.
Some groups that can be considered vulnerable for specific reasons (e.g. ethnic minorities, refugees, prisoners, immigrants, illegals, minors, illiterate) may be underrepresented in research, but these groups often bear the brunt of infectious diseases and nutritional illnesses.

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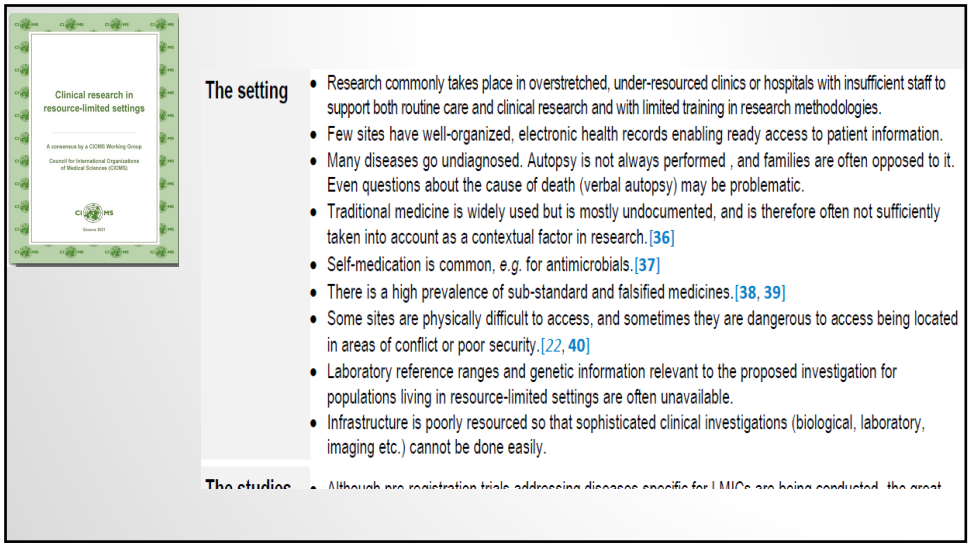
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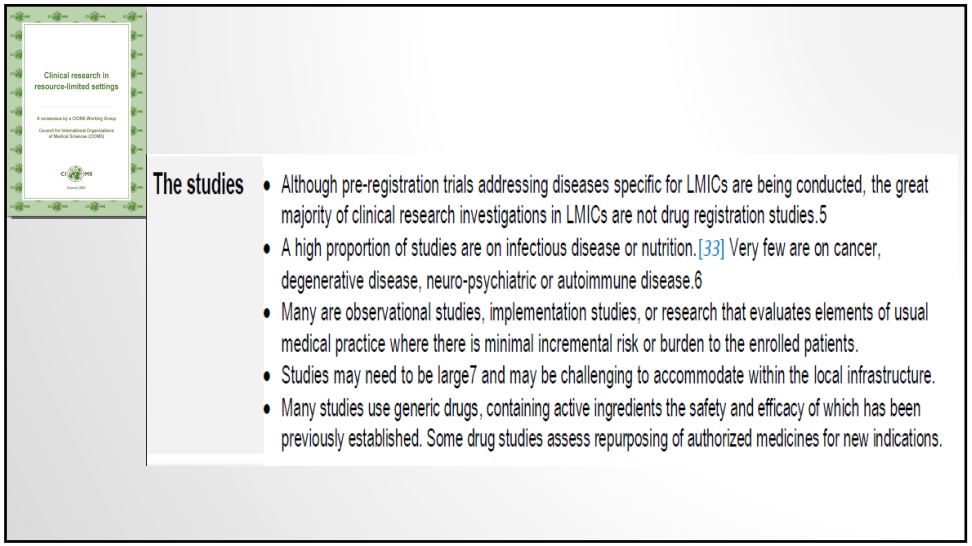
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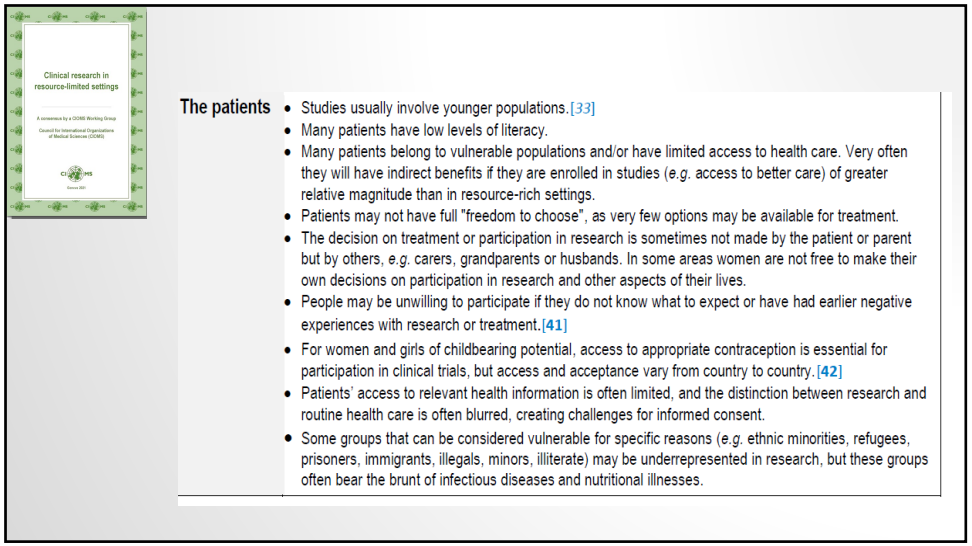
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AFRICAN CONTEXT

- Africa: region of vast differences in health, education, income between populations:
  - Poverty with limited economic development
  - Poor / no access to healthcare / limited options
  - Low levels of formal education & literacy
  - Inadequate community or cultural experience with understanding scientific research
  - Inadequate protection of human rights
  - Discrimination on basis of health status
  - Gender-based violence
  - Corruption
  - Civil war
  - Digital divide
  - Still recovering from colonialism, apartheid and more recently, pandemic

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AFRICA: CHALLENGES WITH RESEARCH ETHICS

- Suspicious of researchers from HICs → reluctant to participate in multinational clinical trials
  - ethics dumping from HICS continues in Africa despite international and local norms, standards and guidelines
  - moral imperialism and colonialist thinking in some multinational clinical trials persists and perhaps researchers from HICs see no need for ethical guidelines to apply in regions like Africa where research that will not be allowed in their countries can be outsourced to the continent
- Building trust amongst these communities is essential. It is critical that local communities are consulted and engaged with early on during the planning of research.

Dhai A Chapter 2. Equitable Access To Covid-19 Vaccines, Vaccine Research And Vaccine Apartheid On The African Continent: Challenges And Recommendations. In:Ethical Innovation for Global Health. Pandemic, Democracy and Ethics in Research. Eds: Kurihara C, Greco D, Dhai A

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AFRICA: CHALLENGES WITH RESEARCH ETHICS

- capacity of research Ethics Committees (RECs) to review and approve the research in a timely manner.
  - African governments and institutions have not adequately invested in setting up RECs.
  - Poor infrastructure leading to delays and inefficiencies in the administrative processes is commonplace.
  - Lack of / insufficient expertise for ethics review
  - Lack of regular participation from members
  - Lack of understanding of importance of REC functions - conflated with other administrative functions
  - Pressures from institutional heads, governments, sponsors, researchers – interference with independence
  - Unequal treatment of applicants – conflicts
  - REC over-reach

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AFRICA: CONTEXT AFRICAN UNION, AFRICA CDC. PARTNERSHIPS FOR AFRICAN VACCINE MANUFACTURING (PAVM) FRAMEWORK FOR ACTION. FILE:///C:/USERS/A0004256/DOWNLOADS/PAVM-FRAMEWORK-FOR-ACTION%20(1).PDF

- Weak regulatory capacity for research, development and production;
- Foreign donations: perpetuate dependence and add to the impediments to development of interventions against diseases in Africa;
- Insufficient funds to medical scientists, research and development
- While expertise exists in Africa - spread across the continent, with limited connections.
- Lack of open and well paid posts, graduates of training programs frequently leave their countries for opportunities in higher-income regions

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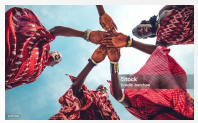
AFRICAN INDIGENOUS VALUES



- Underscores interconnectedness, interrelatedness and interdependence.
- African autonomy, personhood and communalism demonstrated appropriately by Mbiti "I am because we are, we are therefore I am."*
  - indicates the importance of the community in African indigenous value systems and what it means to be a human person – common humanity.
- In line with the Nguni and Sotho/Tswana sayings, *umuntu ngumuntu ngabantu* and *motho ke motho ka batho*, a human being is a human being because of other human beings. Hence, a person cannot function in isolation and participate independently in a community of other people - being human necessitates the affirmation of the humanity of others
- In health research, translates to the need for participating in studies towards the greater good for all. It would also require that those participating be protected from exploitation and other forms of harm and wrong.

* Mbiti J. Introduction to African Religion and Philosophy. Oxford Portsmouth: Heineman Educational Books 1991

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AFRICAN INDIGENOUS VALUES

- *Ubuntu* standard:
  - reflects living in solidarity with other people and humanness that is grounded in social life. Engaging and getting engrossed in the life world of the Other, without taking a stance of superiority, is a prerequisite for ethical conduct in this context. This has particular bearing, *inter alia,* in the researcher-participant relationship, international collaborative research, ethics dumping, community engagement.
- *Lekgotla:*
  - discussion and dialogue in the community as seen with respect to the indigenous African tradition of *lekgotla* where all gather under a tree to discuss and exhaust all the options, opportunities and risks involving a particular topic could be likened to meaningful community engagement in health research. There has to be a mutually respectful conversation in which members of the community are given a chance to voice their opinions towards reaching a consensus. Hence, the knowledge generated from the research would not only be scientifically constructed, but also socially and communally negotiated.
  - through this type of *lekgotla,* the issue of the type of informed consent for the study in question can be explored and consensus arrived at.

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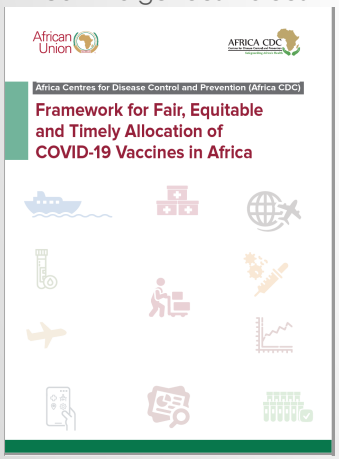
Example of application of African Indigenous Values



2021

4.1. COVID-19 vaccine allocation framework guided by African indigenous values

The goals of the vaccine programme are to decrease morbidity and mortality, minimise further disruptions to society and economies, and enable the rebuilding of the society and economies. A framework guided by African indigenous values is outlined as follows:

a. **Affirming the humanity of others**: Allocation decisions must be for societal benefit and promote common good while respecting human dignity. Every person has equal dignity, worth, and value, hence allocation decisions must be non-discriminatory. Characteristics such as ethnicity, nationality, gender, sexual orientation, race and religion are not to play a role in allocation decisions. People are to be treated fairly and equally. Allocation decisions should be impartial and in accordance with fair criteria.

b. **Survival of the community**: Allocation decisions should be based on the best available evidence. Essential service workers and those who contribute to the prevention and treatment of diseases could be considered as essential for the survival of the community. Those at greatest risk of severe illness and death could be included in the priority groups. In this way, benefits will be maximised, the risks of severe morbidity and mortality from SARS-CoV-2 reduced, and the community will survive.

c. **Social solidarity**: Allocation decisions should consider the bonds unifying communities, their interdependence, attachment to or interest in others and the significant social, economic and personal disruptions and hardships experienced. The possibility that the pandemic may widen existing inequities and create new inequalities should be considered.

d. **Meaningful community engagement:** Allocation decisions must be trusted. Active community engagement allows for authenticity and promotes accountabilty and ownership of the decisions made about allocation thereby engendering trust. Active community engagement is needed to address vaccine hesitancy, maintain public trust and simultaneously control the pandemic. For these reasons, integrity, which reflects the need to act with honesty, reliability and fairness, and a willingness to be held accountable to explain one's actions, is crucial.

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2016

RESPECT

We require respect, not only for individuals but also for the community.

We require respect for our culture, which also includes our history. We have certain sensitivities that are not known by others. Respect is shown when we can input into all research endeavours at all stages so that we can explain these sensitivities.

Respect for our culture includes respect for our relationship with the environment.

Respect for individuals requires the protection of our privacy at all times.

Respect requires that our contribution to research is acknowledged at all times.

Respect requires that promises made by researchers need to be met.

Respectful researchers engage with us in advance of carrying out research. There should be no assumption that San will automatically approve of any research projects that are brought to us.

We have encountered lack of respect in many instances in the past. In Genomics research, our leaders were avoided, and respect was not shown to them. Researchers took photographs of individuals in their homes, of breastfeeding mothers, or of underage children, whilst ignoring our social customs and norms. Bribes or other advantages were offered.

Failure by researchers to meet their promises to provide feedback is an example of disrespect which is encountered frequently.

HONESTY

We require honesty from all those who come to us with research proposals.

We require an open and clear exchange between the researchers and our leaders. The language must be clear, not academic. Complex issues must be carefully and correctly described, not simply assuming the San cannot understand. There must be a totally honest sharing of information.

Open exchange should not patronise the San. Open exchanges implies that an assessment was made of possible harms or problems for the San resulting from the research and that these possible harms are honestly communicated.

Prior informed consent can only be based on honesty in the communications, which needs to be carefully documented. Honesty also means absolute transparency in all aspects of the engagement, including the funding situation, the purpose of the research, and any changes that might occur during the process.

Honesty requires an open and continuous mode of communication between the San and researchers.

We have encountered lack of honesty in many instances in the past. Researchers have deviated from the stated purpose of research, failed to honour a promise to show the San the research prior to publication, and published a biased paper based upon leading questions given to young San trainees. This lack of honesty caused much damage among the public, and harmed the trust between the collaborating organisation and the San.

Another common lack of honesty is exaggerated claims of the researcher's lack of resources, and thus the researchers' inability to provide any benefits at all.

JUSTICE AND FAIRNESS

We require justice and fairness in research.

It is important that the San be meaningfully involved in the proposed studies, which includes learning about the benefits that the participants and the community might expect. These might be largely non-monetary but include co-research opportunities, sharing of skills and research capacity, and roles for translators and research assistants, to give some examples.

Any possible benefits should be discussed with the San, in order to ensure that these benefits do actually return to the community.

As part of justice and fairness the San will try to enforce compliance with any breach of the Code, including through the use of dispute resolution mechanisms.

In extreme cases the listing and publication of unethical researchers in a "black book" might be considered. An institution whose researchers fail to comply with the Code can be refused collaboration in future research. Hence, there will be "consequences" for researchers who fail to comply with the Code.

We have encountered lack of justice and fairness in many instances in the past. These include theft of San traditional knowledge by researchers. At the same time, many companies in South Africa and globally are benefitting from our traditional knowledge in sales of indigenous plant varieties without benefit sharing agreements, proving the need for further compliance measures to ensure fairness.

CARE

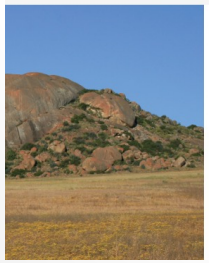
Research should be aligned to local needs and improve the lives of San. This means that the research process must be carried out with care for all involved, especially the San community.

The caring part of research must extend to the families of those involved, as well as to the social and physical environment.

Excellence in research is also required, in order for it to be positive and caring for the San. Research that is not up to a high standard might result in bad interactions, which will be lacking in care for the community.

Caring research needs to accept the San people as they are, and take note of the cultural and social requirements of this Code of Ethics.

We have encountered lack of care in many instances in the past. For instance, we were spoken down to, or confused with complicated scientific language, or treated as ignorant. Failing to ensure that something is left behind that improves the lives of the San also represents lack of care.



PROCESS

Researchers need to follow the processes that are set out in our research protocols carefully, in order for this Code of Ethics to work.

The San research protocol that the San Council will manage is an important process that we have decided on, which will set out specific requirements through every step of the research process.

This process starts with a research idea that is collectively designed, through to approval of the project, and subsequent publications.

The San commit to engaging fairly with researchers and manage effectively all stages of the research process, as their resources allow. They also commit to respecting the various local San structures (e.g. Communal Property Association, CPA leaders) in their communications between San leaders and San communities.

Andries Steenkamp, the respected San leader who contributed to this Code of Ethics until he passed away in 2016, asked researchers to come through the door, not the window.

The door stands for the San processes. When researchers respect the door, the San can have research that is positive for us.

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2016
International Ethical Guidelines for Health-related Research Involving Humans
Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)
CIOMS
Geneva 2016
GUIDELINE 2:
RESEARCH CONDUCTED IN LOW-RESOURCE SETTINGS
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.

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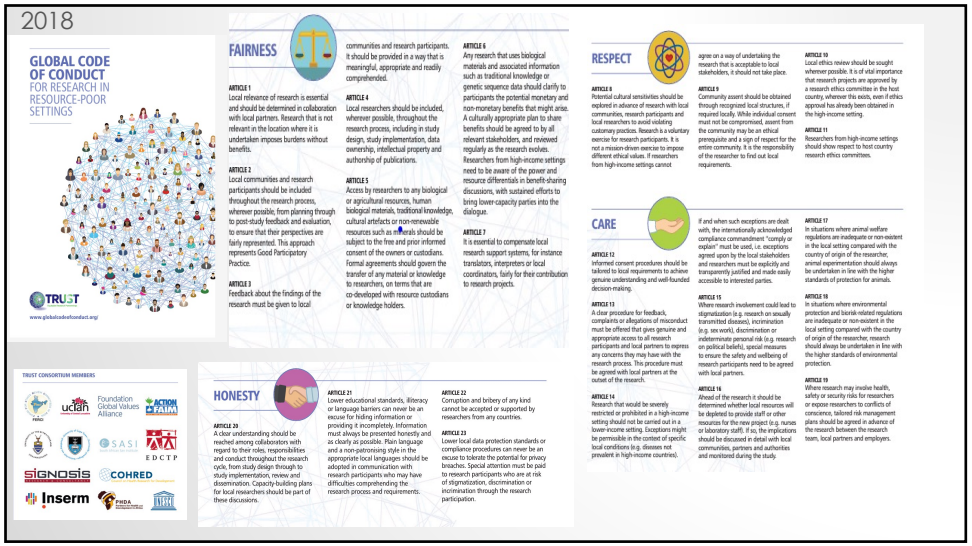
2018
GLOBAL CODE OF CONDUCT FOR RESEARCH IN RESOURCE-POOR SETTINGS
TRUST
www.globalcodeofconduct.org/
FAIRNESS
RESPECT
CARE
HONESTY
TRUST CONSORTIUM MEMBERS
uclan
Foundation Global Values Alliance
ACTION AIDS
SASI
EDCTP
SIGNOSIS
COHRED
Inserm

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2021

Recommendations to:

- Governments and Regulatory authorities
- Researchers
- International Organisations & Funders

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To researchers

This would include researchers from academic institutions, the health care industry, contract research organizations, and non-commercial entities conducting research in low-resource settings.

Domestic and international researchers have the responsibility to act accountably and transparently, and to build public trust in the value of clinical research for the populations in which it is conducted. Therefore they should:

Chapter 2 — **9)** Understand and respect the local context, *e.g.* social and cultural aspects, health systems, laboratory equipment and facilities, assay technologies, scientific and administrative capacities, as well as local epidemiology and genetics of diseases of the population; aim to build sustainable research capacity in resource-limited settings.

Chapter 3 — **10)** Apply the principles of good clinical practice.

Chapter 4 — **11)** Engage local study participants and communities throughout the research, from an early stage of study design, to ensure that the research adheres to high ethical standards. This will help to generate relevant findings and facilitate their translation into health benefits, thereby justifying the burdens of the study for the local population. Do not divert resources from already overstretched local health care systems.

12) Plan in advance how to communicate and engage, throughout all phases of the clinical research, with community stakeholders such as participants, participants' partners and families, community, traditional and religious leaders, community engagement or advisory boards; be transparent about the aims and interests of all parties involved.

Recommendations to researchers — continued

Chapter 5 — **13)** Ensure that any clinical research project in resource-limited settings has scientifically justified research questions, with study designs and data collection methods that are robust enough to generate quality evidence and, where relevant, contribute to systematic reviews that underpin policies and guidelines.

14) Consider the use of innovative, adaptive study designs and novel digital technologies, *e.g.* trial-at-home, electronic health records and artificial intelligence.

15) Invest in scientific data integrity, transparency and confidentiality of personal data at all phases of the planning, conduct and implementation of the study, including dissemination of study results and reporting.

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WMA DECLARATION OF HELSINKI 2013

- "Although it may be appropriate to consult family members or community leaders …"(art25)
- Vulnerable Groups & Individuals:
  - "Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.(art19)
  - Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research."(art20)
- General Principles & articles relevant to resource poor settings but not sufficient

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