WMA
Declaration of Helsinki
Vatican City, January 2024

Session 3: Experiences of conducting research in low-resource settings (LRS) under the DoH

Melissa McRae
Senior Researcher Medical Ethics
Médecins Sans Frontières, Geneva

Raffaella Ravinetto
Chair of the MSF Ethics Review Board
Chair of the Institutional Review Board,
Institute of Tropical Medicine, Belgium

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Outline

- Brief overview of MSF, their role in research as a medical humanitarian organisation and current research agendas.
- Case study: Ebola Viral Disease post-trial access, challenges
- MSF inputs and suggestions concerning the revision of DOH

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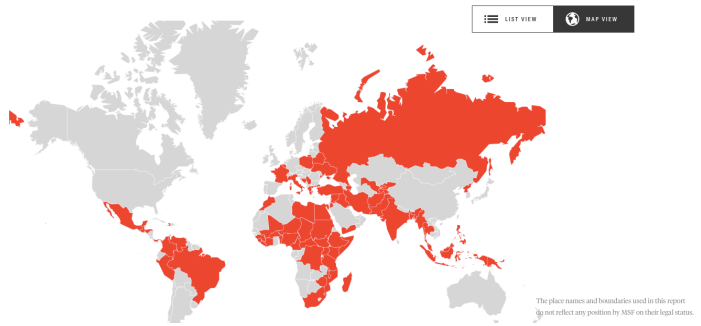
Map of MSF activities around the world



MEDECINS SANS FRONTIERES

Source: https://www.msf.org/where-we-work

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MSF Charter

- We carry out our work with respect for **medical ethics**, in particular the duty to provide care without causing harm to individuals, groups and communities
- We respect **patients' autonomy, patient confidentiality and their right to informed consent**
- We treat patients with dignity, and respect for their cultural and religious beliefs

MSF in Research

- Confronted with lack of effective, safe, feasible and/or context-tailored interventions
- Attempting to make research investment more equitable (i.e cancer, new antibiotics)
- Medical research meant to serve the needs of the beneficiaries
- Independent MSF Ethics Research Committee

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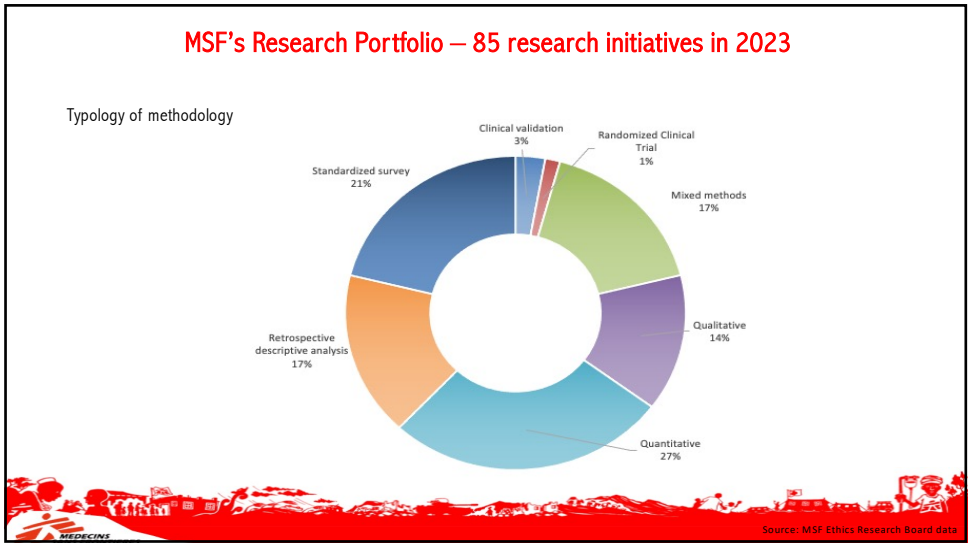
MSF's Research Portfolio – 85 research initiatives in 2023
Typology of methodology
Clinical validation 3%
Randomized Clinical Trial 1%
Mixed methods 17%
Qualitative 14%
Quantitative 27%
Retrospective descriptive analysis 17%
Standardized survey 21%
Source: MSF Ethics Research Board data

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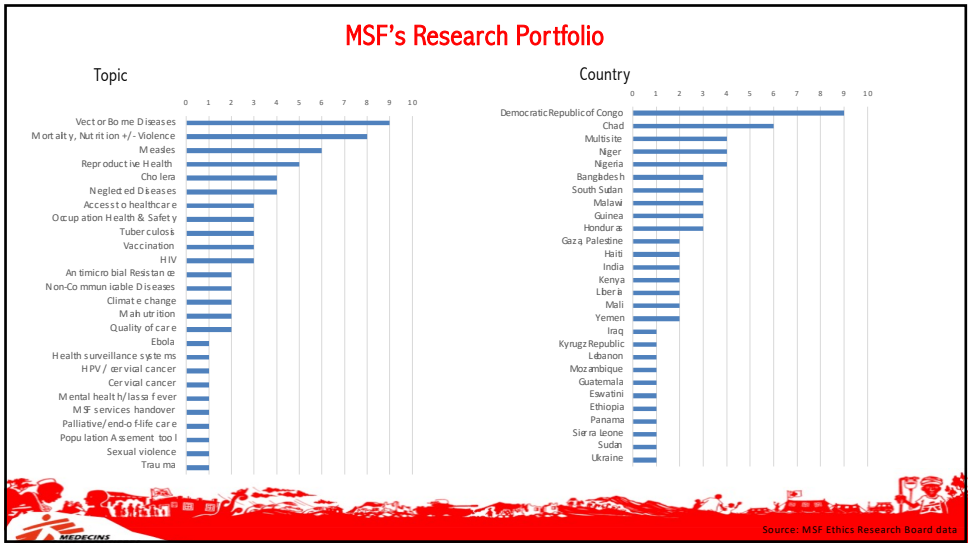
MSF's Research Portfolio
Topic
Vector Borne Diseases
Mortalty, Nutrition +/- Violence
Measles
Reproductive Health
Cholera
Neglected Diseases
Access to healthcare
Occupation Health & Safety
Tuberculosis
Vaccination
HIV
Antimicrobial Resistance
Non-Communicable Diseases
Climate change
Mah utrition
Quality of care
Ebola
Health surveillance systems
HPV / cervial cancer
Cervial cancer
Mental health/lassa fever
MSF services handover
Palliative/end-of-life care
Population Assement tool
Sexual violence
Trauma
Country
Democratic Republic of Congo
Chad
Multisite
Niger
Nigeria
Bangladesh
South Sudan
Malawi
Guinea
Honduras
Gaza Palestine
Haiti
India
Kenya
Liberia
Mali
Yemen
Iraq
Kyrugz Republic
Lebanon
Mozambique
Guatemala
Eswatini
Ethiopia
Panama
Sierra leone
Sudan
Ukraine
Source: MSF Ethics Research Board data

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Part II: MSF case study: Ebola Viral Disease post-trial access challenges

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Case Study: research for Ebola Viral Disease

- 2014-2016: West African outbreak, 30 000 cases → Ebola could become 'global'
  - unprecedented public research funding and collaborative effort under WHO leadership
  - a wide range of stakeholders …. including MSF, Ebola patients and their communities

- A number of ethics challenges:
  - Shortened R&D plan based on risk-assessment
  - Resources allocation: routine care vs research (in LRS with shortage of medical doctors)
  - Informed consent modalities
  - Equipoise and placebo
  - Community engagement
  - Ownership of research data and samples
  - Post-trial access

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Setting the scene: Ebola Virus R & D timeline

- 1976: Zaire Ebola virus disease (EVD) discovered
- 2014: after many outbreaks in rural areas in LRSs, no treatment existed yet
- West African outbreak: accelerated research agenda, triggered by global biosecurity concerns
- 2018-19: PALM trial in DRC → mAb114 and REGN-EB3 found effective
- 2022: WHO guideline treatment recommendations → post trial access for future patients
- 2023: no capacity to produce mAb-114 + REGN-EB3 stockpiled in US: "*Should a major outbreak happen tomorrow in Africa, there will be no readily available stocks* (Torreele et al, Lancet ID 2023)
- 2022-2022: over five outbreaks and only 34% of patients received either drug

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Analysis 1: costs, prices

- Overwhelming in-kind and financial contributions by public sector for the R&D of mab114 & REGN-EB3. (i.e. US*, DRC governments) and NGOs (i.e. MSF)
- Limited private sector (i.e., developers) contributions by Ridgeback & Regeneron, who hold exclusive licensing rights
- In the current innovation & intellectual property ecosystem, there is no 'space' for alternative suppliers.

REGN-EB3
- Price (paid by USG): $6900/Treatment Course (TC)
- Estimated COGS: $750-$1875/TC

Mab114
- Price: unknown
- Estimated COGS: $250-$625/TC

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Analysis 2: stockpiling & access to monoclonal treatments

- **Stockpiles** in high income-countries, but not in endemic countries
  - Monoclonal Ab stock under WHO supervision (1,000 TC), under review in 2024
- Unclear/no agreed mechanisms for rapid supply in case of outbreak overseas
- The current situation is **inequitable and inadequate** for outbreak response
  - Ad-hoc donations with no clear governance/rules
  - Access heavily dependent on goodwill of developers/ governments with stock
  - For instance: small mab114 donation program in DRC, equated to very few TCs

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Analysis 3: post-trial access to the communities/countries

- **R&D contributions** of Ebola survivors, communities, NGOs, public funders, researchers and governments in endemic countries is unrewarded
- **High price of REGN-EB3**
  - Unaffordable for endemic countries, who are made dependent on donations
  - A supply-demand loop issue: future manufacturing not ensured
- **Slow regulatory pathways c**omplicate access
- Lack of clear rules and ”will” to respect **equitable and fair partnerships**
- **? outbreak preparedness: access for future needs is highly compromised**

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Case study reflections on post trial provisions (art. 22, 34)

22. The design and performance [….] In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions

Comment: post-trial provisions should include the community and the country, in addition to individual participants.

This can be achieved by protocols that address local health system capacity strengthening and include adequate measures for translating research findings into local policies and practices (consider commercial and intellectual property provisions, fair pricing etc).

Even if it goes beyond researchers' power, they can advocate for this to happen.

Recommendation: add at the end "for study participants when applicable, and for the study community and country"

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34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Comment: post-trial provisions should encompass all those in need, either now or in the future, particularly in countries where innovative, high-priced health interventions are not available/ affordable at an individual and/or collective level. Even if it goes beyond the researcher's power, individual researchers can advocate for this to happen.

Recommendation: complete art. 34 as "…. all participants who still need an intervention identified as beneficial in the trial, as well as all those who are/will be in need in the future in the general population".

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Part III: MSF inputs and suggestions concerning the revision of DOH specific articles

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Suggestions for the DoH from this case study (and other) MSF research experience in LRS and vulnerable groups

- Be explicit that DoH applies to all health researchers (**other health professionals)** (art. 2)
- **Benefit sharing and community engagement**, including support to local health systems, should be built in research from the start, and **post-trial access** include community and country level (art. 22, 34)
- In **global health research**, you need to reconciliate ethical approaches (e.g. ethics principle, ethics review) in both the study country and sponsor country (art. 10, 23)
- Extend the concept of '**risk**' to both individuals **and communities**, and be explicit about medical and non-medical risks (art. 9, 15, 17, 24)
- **Vulnerability** can be caused by inequalities, either pre-existing or introduced by research conditions→ be cognizant of the duty to detect and protect those who are (made) socially or economically vulnerable. This can create higher risks for coercion and therapeutic misconception (art. 14, 19, 20, 27)

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Comment on the Preamble

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

Comment: This is particularly important in LRS with dearth of health care staff, where tasks are often shifted to nurses, clinical officers etc.

Recommendation: we warmly support the underlined, and propose that the WMA becomes binding for, at least, other health professions , or for 'health researchers' as a whole

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LRS Focus: Being inclusive of communities and local ethical norms (art. 10, 23)

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

Comment: In global (North-South) research, researchers and research institutions may work elsewhere than in 'their country'.

Recommendation: reformulate as "in their own countries and (if different) in the country/ies where the research takes place, as well as applicable international norms and standards. In case of conflict, the highest ethical standard for participants' protection should prevail".

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23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins….[etc]

Comment: MSF research is submitted both to its own ERB and to the country ethics committee, so as to ensure respect of local rules and regulations, and to prevent ethics dumping. This 'double ethical review' often results in a rich complementarity of views.

Recommendation: specify that the 'concerned' ethics committees include both the (main) one in the study country, plus the one in the country of the sponsor.

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LRS Focus: Respect for Research participants - Risks, Burdens & Benefits (art. 9, 15, 17, 24)

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

Comment: It is equally important to protect the research participants and the research communities, which may be vulnerable as such to exploitation, confidentiality breaches, stigmatization etc.

Recommendation: add "and communities"

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15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Comment: the classical approach of ad hoc (no-fault) research insurances may be difficult to achieve in LRSs (e.g. lack of insurers, poor familiarity with the concept in).

Additionally, research participants in many LRSs pay out-of-pocket for essential and life-saving treatments (*not the case for MSF).*

Recommendation 1: add "…. must be ensured, by using measures that are tailored to and effective in each specific context"

Recommendation 2: include provisions for "ancillary care" when research participants lack access to care for medical events unrelated to research participation

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17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

Comment: in our experience, we often witness a bias of researchers toward physical medical risks. However, non-medical risks (e.g. psychological, social, reputational, and legal) can also be important, and even be more prevalent in LRSs and vulnerable communities, both at individual and community level. The risk assessment must be context and health system-specific.

Recommendation: add "…Measures to minimise all risks, medical and non-medical, should be assessed and implemented for the specific context and research population.

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24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

C*omment:* privacy and confidentiality concerns need close attention in LRSs and vulnerable communities. They should be protected not only at individual but also at group level (e.g. in case of disease with a high potential for stigma, a full village, or a full ethnic group may be blamed and stigmatised in case of data breach)

Recommendation: "the privacy of research subjects and the relevant community, and the confidentiality of their personal and community information".

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LRS Focus: Recognising and addressing vulnerability (art. 19, 20)

19. 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.

Comment: While some individuals may be intrinsically prone to exploitation (e.g. minors), more often people and communities are **made vulnerable by the circumstances**: external conditions that create or perpetuate poverty, exclusion, marginalisation, injustice.

Protection measures are the responsibility of researchers, to be carefully tailored to the kind of vulnerabilities. This should be explicitly reminded.

Recommendation: reformulate as "are particularly vulnerable or are made vulnerable under certain medical or socio-economical circumstances" and may have….

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20. 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.

Comment: This is critical for LRSs, and measures for benefit-sharing should be built in the research protocol/plan, in concertation with the representatives of the local communities and health systems. Even if it goes beyond researchers' power, they can push for this to happen.

Recommendation: add at the end "Measures for benefit sharing should include consultation with local communities and health actors, and be prospectively built in the research plan, not post hoc".

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LRS Focus: Higher risk of coercision and misconception (art. 14, 27)

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

Comment: in so-called "humanitarian misconception", prospective participants may tend to perceive research participation as a part/ a condition of aid. Like therapeutic misconception, it cannot be fully prevented, and researchers should be aware of it.

Recommendation: add "Researchers who combine medical research with medical care or medical (humanitarian) aid"

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27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

Comment: there are other reasons that can cause unwanted coercion, such as "humanitarian misconception", and lack of access to healthcare elsewhere.

Recommendation: add "if the potential subject is in a dependent relationship with the researcher, may consent under duress or if a risk of other potential reasons of coercion"

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In summary

- Prospective research participants & communities in LRS, as well as other vulnerable individuals and groups in other settings, are at higher risk of exploitation
  - This requires respectful engagement, for adequate protection,
  - Co-ownership rather than paternalism
- By upholding and enhancing ethics awareness among health researchers, the DoH can prevent and correct structural injustices in (global) health research
- The DoH should be explicit that ethics principles equally apply in conditions of emergency and non—emergency research.

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Thank you

Questions and comments please

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