Clinical research in resource-limited settings

A consensus by a CIOMS Working Group

Council for International Organizations of Medical Sciences (CIOMS)

Geneva 2021

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Geneva, Switzerland, June 2021

Dr Lembit Rägo, MD, PhD
Secretary-General, CIOMS

[1] See reference *34*

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ABBREVIATIONS AND ACRONYMS

AVAREF	African Vaccine Regulatory Forum
CIOMS	Council for International Organizations of Medical Sciences
COVID	Coronavirus disease
CRO	Contract research organization
CTD	Common Technical Document (ICH)
DALY	Disability-adjusted life year
DNDi	Drugs for Neglected Diseases initiative
DOI	Digital Object Identifier
EHRs	Electronic health records
EMA	European Medicines Agency
EML	Essential Medicines List (WHO)
EMLc	Essential Medicines List for Children (WHO)
ESTRI	Electronic Standards for the Transfer of Regulatory Information (ICH)
EU	European Union
FDA	Food and Drug Administration (United States)
GBT	Global Benchmarking Tool (WHO)
GCP	Good clinical practice
GDPR	General Data Protection Regulation (EU)
GMP	Good manufacturing practice
HIC	High-income country
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICT	Information and communication technologies
ICTRP	International Clinical Trials Registry Platform (WHO)
IPD	Individual participant data
IT	Information technology
LMICs	Low-and middle-income countries
MedDRA	Medical Dictionary for Regulatory Activities (ICH)
NGS	Next-generation sequencing
NIH	National Institutes of Health (United States)

OHRP	Office of Human Research Protections (United States)
PAHO	Pan American Health Organization
PANDRH	Pan American Network on Drug Regulatory Harmonization
PD	Pharmacodynamics
PEP	Post-exposure prophylaxis
PEPFAR	President's Emergency Plan For AIDS Relief (United States)
PK	Pharmacokinetics
PLWH	People living with HIV
PMC	PubMed Central®
PmRN	Paediatric medicines Regulators' Network (WHO)
PrEP	Pre-exposure prophylaxis
qPCR	Quantitative polymerase chain reaction
R & D	Research and development
REC	Research ethics committee
RIBEF	Iberoamerican Network of Pharmacogenetics
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDG	Sustainable Development Goal (United Nations)
SDI	Socio-demographic index
TDR	Special Programme for Research and Training in Tropical Diseases
U.S.	United States
UK	United Kingdom
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNCTAD	United Nations Conference on Trade and Development
UNDP	United Nations Development Programme
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNICEF	United Nations Children's Fund
WHO	World Health Organization

FOREWORD

Responsible clinical research drives the advancement of health care. There has been tremendous progress in improving the research and development environment for new medical products globally since the concept of randomized clinical trials was first introduced in the 1950s. There has also been an increased attention towards developing medical products to address the health needs of people in resource-limited settings, and new regulatory pathways have been created to enable access to such products. In a rapidly evolving global research environment, however, low- and middle-income countries (LMICs) continue to face social, ethical and regulatory challenges. As a result, most clinical research is still being conducted in high-income countries (HICs) to develop new medicines and products for these settings, even though most of the preventable morbidity and mortality occurs in LMICs.

Clinical research in resource-limited settings has a complex historical background. Despite significant progress achieved in the past decades, and even with best intentions, some projects have worked out adversely for the study participants or communities involved. Perspectives in different parts of the world are diverse, and sometimes even contrary. And instances of exploitative research initiated by entities from high-income settings in resource-limited settings—so-called "ethics dumping"—continue to occur.

The spirit of this report is to acknowledge this complex history, to highlight that important improvements still need to be made, but also to provide balanced arguments to promote good quality clinical research in resource-limited settings. **While the report builds on the 2016 CIOMS *International Ethical Guidelines for Health-Related Research Involving Humans*,[1] it is not intended to supersede those guidelines**.

The CIOMS Working Group on Clinical Research in Resource-Limited Settings was established in November 2017 to develop guidance to facilitate clinical research in resource-limited settings effectively in the interest of public health, building on earlier work done by CIOMS in the area of product development. The Working Group was composed of senior scientists from drug regulatory authorities, the pharmaceutical industry, public-private partnerships for product development and academia. A list of members and Working Group meetings is shown in Appendix 6.

The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949. Its mission is to advance public health through guidance on health research and policy including ethics, medical product development and safety. This document reflects the consensus opinion of the CIOMS Working Group on Clinical Research in Resource-Limited Settings. The group members are solely responsible, in their capacity as experts, for the views expressed in this publication. These views do not necessarily represent the decisions, policies or views of any specific organization or agency.

It is anticipated that this report will prove useful for governments and regulatory authorities, the research community and sponsors, as well as international organizations involved in funding or conducting clinical research in resource-limited settings.

EXECUTIVE SUMMARY

Chapter 1: Introduction and problem statement

Low-and middle-income countries (LMICs) bear the highest burden of preventable disease globally. Resource limitations are common in low- and middle-income countries and may also exist in high-income countries.[1, *Guideline 2*] They severely affect migrants, displaced persons and other disadvantaged individuals and groups, and they may affect entire societies in global emergencies.

One of the goals of the sustainable development agenda is ensuring healthy lives for all, with universal access to needed medicines and vaccines. Good quality research to identify and address the unmet health needs of people living in resource-limited settings, including women and children (see Appendix 1), is essential. In recent decades, cross-sectoral and global partnerships have emerged to address issues such as antimicrobial resistance or the development of new vaccines.

However, most research is still conducted in high-income countries, where a conducive environment, infrastructure and capacity have been built up in past decades to address the health priorities of these countries. Communities in other parts of the world are missing out on new interventions to address their specific health needs, and they often view research with distrust. Therefore, there is a need to promote and advance good quality clinical research in resource-limited settings.

Chapter 2: The research environment

Clinical research in resource-limited settings is challenging for many reasons. Corruption, legal uncertainties, regulatory weaknesses, excessive bureaucracy and limited public funding, as well as a lack of infrastructure such as safe road transportation and consistent power, significantly hinder research. Research funders' agendas do not always address the most pressing problems in LMICs. Access to health care is a major problem in LMICs but is an issue in all parts of the world, and there have been calls for alternative and more sustainable models, including de-linking costs for R&D from product prices.[2]

Research infrastructure and capacity in resource-limited settings must be created and —even more importantly—sustained. This requires investments in training and career structures for researchers and reviewers, data and safety monitoring, laboratory infrastructure, quality assurance and capacity. Introduction of new technologies and an adapted digital regulatory and research framework is essential (see Appendix 2). Optimizing clinical research also means learning from each other's experiences. Researchers and sponsors should collaborate to create and maintain standing clinical research networks, with basic functions that could serve both academic and industry-led clinical trials.

Chapter 3: Guiding principles for clinical research

Modern ethical and regulatory principles for clinical research have evolved in high-income countries (HICs) after the Second World War in response to rapid technological advances and increasing globalization. Current, internationally accepted requirements for pre-registration studies are reflected in the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)'s good clinical practice (GCP) guidelines. It is recognized that current ICH GCP guidelines may be excessive for many post-registration clinical investigations and trials. A revision of ICH GCP is under way to make the guidance proportionate and flexible enough to address the increasing diversity of clinical trial designs and data sources.[3] The principles of GCP also hold true in emergencies (see Appendix 3 for some topical issues related to research in outbreaks).

However, many regulatory authorities of LMICs have not reached a level of maturity whereby they have a stable, well-functioning, capable and integrated regulatory system. This means that they are unable to oversee adequately the meaningful implementation of GCP in their jurisdictions, or to process applications for marketing authorization of new medicines or for important research with the necessary expertise and within reasonable time. To speed up access to health products in resource-limited settings, additional pathways have been created such as WHO prequalification and the European Medicines Agency (EMA)'s Article 58 procedure. Progress has meanwhile been achieved in building regulatory capacity and promoting harmonization, but significant shortcomings remain. For sustainable regulation at the global level there is a need for more regulatory cooperation and reliance, where each authority concentrates on those functions for which it has capabilities.[4]

WHO recommends that the principles of GCP should be applied in all clinical trials,[5] including the post-approval and clinical practice studies that account for a large part of the research currently being done in resource-limited settings. Ethical and scientific considerations by researchers seeking to implement GCP principles meaningfully in these settings are described in Chapters 4 and 5 of this report.

Chapter 4: Ethical considera-tions

Rather than considering entire classes of individuals as vulnerable, it is useful to look at the specific characteristics that may render research participants vulnerable, and to identify additional protections to safeguard their rights and well-being.[*1, Guideline 15*] Issues that require special attention in resource-limited settings include scientific and medical validity of studies, informed consent, compensation for participation in research, indemnity in the event of research-related harm, and caring for participants' health needs during and after the study. The benefit-risk balance of research may differ between studies, and between sites participating in a multi-site clinical trial; therefore, researchers and sponsors should do a tailored analysis for each study and site.

In recent years, HIC organizations and companies have been increasingly conducting clinical trials at study sites in LMICs. Such partnerships can be highly advantageous for both parties, but they can also pose significant risks of exploitation as a result of

the continued inequity between economic settings. An example of a controversial debate in this regard is found in Appendix 4. Adherence to the *Global Code of Conduct for Research in Resource Poor Settings* [6] will support long-term equitable research relationships between partners in lower-income and high-income settings.

Research ethics committees (RECs) have a central role in ensuring that the general ethical principles for clinical research are followed, including in public health emergencies. In LMICs a number of constraints threaten the RECs' ability to facilitate good clinical research efficiently and to function to an acceptable global standard. An informed, unbiased, efficient and effective REC is critical to the research process. Capacity-building, including training for ethical review, should be supported by governments, funders and RECs themselves.

Potential study participants and communities should be involved in research through a meaningful participatory process.[*1, Guideline 7*] Community engagement is particularly important in resource-limited settings, where the realities of life are often vastly different from those that are familiar to the researchers. The community advisory board is an example of a useful approach. Community engagement can advance good quality clinical research in resource-limited settings by building trust, managing expectations, facilitating communication of research outcomes to participants, and enabling negotiations for investments in research projects and infrastructure. Formal communication plans that address how a researcher will encourage, moderate and sponsor community engagement are critical.

Chapter 5: Scientific considera-tions

Clinical trials in resource-limited setting should be designed to answer relevant research questions in the local context, taking into account local factors such as co-morbidities, nutritional specificities or relevant host genetics (see Appendix 5). Adaptive study designs, use of simulation to ensure large enough sample sizes, and pharmacokinetic/pharmacodynamic modelling can improve the efficiency of clinical trials. Clinical studies should be of sufficient size to yield valid data that lead to robust conclusions and potential translation into health benefits and/or can be used to inform future research. Standardized methodologies, data sharing and meta-analysis should be encouraged. Investments in local data management and laboratory infrastructure will facilitate this relevant research and thus benefit the population.

Information-sharing supports transparency and collaboration in research. While this is increasingly the norm in HICs, information-sharing activities remain challenging to implement in the complex research environments of LMICs. Information is shared through clinical trial registries, patient- or disease-based databases and scientific publications, and raw data are also increasingly shared although controlling this can require significant resources. Importantly, sponsors have a duty to inform clinical trial participants and their communities about the research being conducted. Doing this in an appropriate, yet realistic manner is particularly important in resource-limited settings in order to build trust and facilitate implementation of research findings.

RECOMMENDATIONS

The recommendations listed below are all aimed at enabling good quality, locally relevant clinical research in resource-limited settings, with fair sharing of responsibilities, burdens and benefits. They have been grouped by target audiences here. While the recommendations for the readers' own group will be of primary interest, those for the other groups can facilitate understanding of the other stakeholders' perspectives and thus promote successful cooperation.

Please note that this report builds on the 2016 CIOMS *International Ethical Guidelines for Health-Related Research Involving Humans*,[1] but is not intended to supersede those guidelines.

To governments and regulatory authorities

This would include relevant ministries e.g. of health or science; authorities in charge of regulating health products, and bodies in charge of scientific and ethical review of research protocols.

Governments and regulatory authorities of countries that host clinical research should take measures to create a conducive research environment. This includes the following:

Chapter 2

1) Invest in a sustainable research environment in terms of general infrastructure, security, health systems infrastructure, equipment and human resources; support the establishment and maintenance of standing centres and networks to conduct clinical research.

2) When planning to introduce electronic health records, consider lessons learned in other countries and aspire to bring clinical research and information technology experts together to build efficient and transparent systems that can be used for high quality clinical research (see Appendix 2).

3) Combat inefficiency and corruption in governmental institutions and ethics committees as a priority.

4) Create incentives and opportunities for engaging and training new researchers and for setting up and maintaining research sites; inform local researchers of options where funding for clinical research can be obtained.

Chapter 3

5) Clarify regulatory requirements and harmonize them with those of other countries; identify unnecessary obstacles and reduce bureaucracy; shorten ethics and regulatory review timelines and rely on the decisions of other authorities wherever possible.

(continued)

Recommendations to governments and regulatory authorities — continued

Chapter 4

6) Establish and enforce effective regulations for ethical review; ensure appropriate protection—which does not mean exclusion—of vulnerable persons and groups in research.

7) Support the establishment of platforms for researchers to engage with patient representatives and communities, *e.g.* community advisory boards; request and consider formal communication plans as part of applications for clinical studies.

Chapter 5

8) Invest in constructive dialogue with stakeholders, including patients and communities, on research priorities and methods to generate relevant evidence, including in specific populations such as children; ensure that the research findings are implemented in national health systems to advance evidence-based health care delivery.

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.

(continued)

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.

To international organizations and funders

Examples include organizations such as the Bill & Melinda Gates Foundation or the Wellcome Trust; public-private partnerships such as the Drugs for Neglected Diseases initiative (DNDi), Medicines for Malaria Venture (MMV) and other new actors mentioned in section 1.4 of this report.

Organizations that initiate and/or fund research in resource-limited settings have a significant influence in shaping policies and practices. They should also monitor the financial resources disbursed and ensure effective budget management, and where necessary build capacity to do so. These groups are urged to synergize their resources and to support building and maintaining clinical research capacity through the following strategies:

Chapter 2

16) Support policies and multi-functional coalitions that facilitate a conducive environment for investing and participating in good quality local clinical research.

Chapter 3

17) Support the establishment and maintenance of functional, efficient and effective multi-country systems and coalitions for ethical and regulatory oversight of clinical research.

Chapter 4

18) Prioritize research that answers important questions definitively and is relevant for the specific setting and the health care systems of the communities involved.

19) Educate, empower and support patient organizations and communities to foster an understanding of the value of clinical research.

Chapter 5

20) Make agreements mandating open collaboration and data-sharing through information technology and electronic health records, avoiding fragmentation of research efforts and capacity; support dissemination of study information and results.

CHAPTER 1.

BACKGROUND AND PROBLEM STATEMENT

This chapter sets the scene and explains why more should be done to promote, support and facilitate clinical research in resource-limited settings.

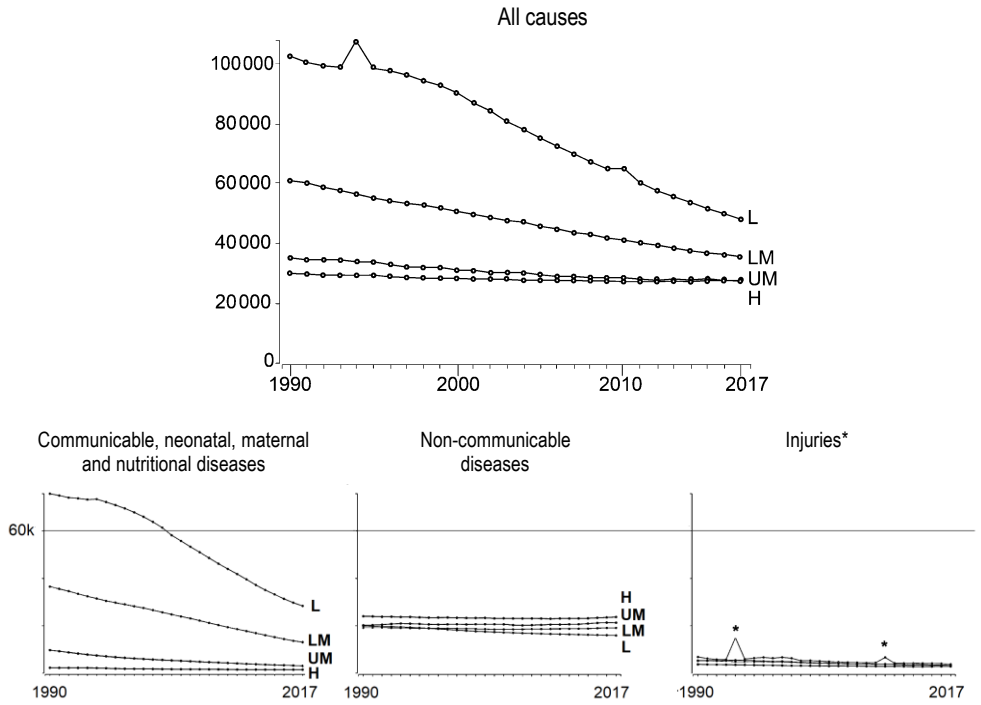
- **Low-and middle-income countries (LMICs) bear the highest burden of disease globally. Children represent a high proportion of the population in these settings, and the majority of preventable deaths there occur in children (section 1.1).**
- **Resource-limited settings and related health issues exist both in low- and high-income countries (section 1.2).**
- **Clinical research is necessary to identify and address a population's unmet health needs (section 1.3).**
- **There is a trend towards more research to address the diseases and morbidity and mortality risks affecting people in resource-limited settings, and towards inclusion of special and vulnerable groups (section 1.4).**
- **Nevertheless, more research should be conducted in resource-limited settings in line with the principles of good clinical practice (GCP) (section 1.5).**
- **Regulatory and administrative requirements should be designed efficiently to promote and facilitate good quality, ethical research in low-resource settings, thereby getting robust answers to relevant clinical questions and increasing the social acceptance of the research (section 1.6).**

1.1 The global health divide

As a direct consequence of scarce resources in health care, low- and middle-income countries (LMICs) [7] bear the highest burden of disease globally (**Figure 1**). They continue to face a high level of communicable diseases such as neonatal sepsis, malaria, tuberculosis, chronic hepatitis B and C, HIV, diarrhoeal diseases and

neglected tropical diseases,[2] and in some areas are being seriously impacted by epidemic outbreaks of diseases. In 2019 children up to 14 years of age accounted for 30% of the population of LMICs (range: 16-47%).[8] Neonatal, maternal and nutritional diseases are prevalent, and neonatal, under-five and maternal mortality is high. In addition, LMICs have similar rates of non-communicable diseases as upper-middle and high income countries. While the burden of disease in LMICs has decreased since 1990, more efforts are needed to maintain these gains and close the significant remaining gap.

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]

[2] A list of neglected tropical diseases is provided on the WHO website at https://www.who.int/neglected_diseases/diseases/summary/en/

1.2 What are resource-limited settings?

Socio-demographic index

World Bank income levels (as shown in Figure 1 above) are commonly used to classify countries in terms of resources. Another classification proposed in the Global Burden of Disease study [9] is the socio-demographic index (SDI), which is based on rankings of per capita incomes, average educational attainment, and fertility rates of the areas included in the study.

Causes and consequences of health inequities

The WHO Commission on Social Determinants of Health (CSDH) has attributed the health inequities within and between countries to the unequal distribution of power, income, goods, and services, globally and nationally, with consequent unfairness in the immediate, visible circumstances of people's lives.[10] These inequities affect people's health and limit their access to high quality, geographically accessible, affordable and acceptable health services.[11] A consensus statement [12] suggests that firstly the term "resource-poor" or "resource-constrained" setting defines a locale where the capability to provide care for life-threatening illness is limited to basic critical care resources, stratified by categories (no resources, limited resources, and limited resources with possible referral to higher care capability), and that secondly "critical care in a resource-poor or constrained setting" be defined by the provision of care for life-threatening illness without regard to the location.

Economic settings

It is important to note that low-resource settings should not be interpreted narrowly as low-resource countries but may also exist in middle- and high- income countries, *e.g.* in remote and/or deprived communities. Moreover, a setting can change over time and no longer be considered low-resource, or newly become low-resource.[*1, Guideline 2*]

1.3 Health research as a social responsibility

Improving public health

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

[3] **Clinical study:** A research study involving human volunteers (also called participants) that is intended to add to medical knowledge. There are two broad types of clinical studies: interventional studies (also called **clinical trials**) and observational studies. (https://clinicaltrials.gov/ct2/about-studies/glossary)

comparing, for example, different approaches to disease management or different mechanisms to improve patient adherence to therapy to improve outcomes.

Sustainable development goals

Understanding the medical needs and ensuring the highest attainable standards of health for the population relies in part on being able to access proper, scientifically researched information concerning the efficacy, safety and quality of medicines and other health interventions. To initiate and finance health research is therefore part of a society's moral obligation to improve the health of the population. These goals are fully aligned with the UN Sustainable Development Goals (SDG), in particular with SDG 3, "Ensure healthy lives and promote well-being for all at all ages", where support for the research and development (R & D) of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries is highlighted.[14] But also for diseases that exist globally there is a need to conduct research in distinct geographic areas to address local determinants that may influence disease manifestations, ethno-geographical variability of drug responses, co-morbidities and concomitant medications, socio-economic factors as well as factors relating to the health system infrastructure (point-of-care context, laboratory infrastructure, access to healthcare).

Ethical obligations

Clinical research in resource-limited settings should not only be responsive to health needs, but must also be conducted in a way that respects the rights and well-being of the study population. Thus, researchers have a responsibility to follow the principles of fairness, respect, care and honesty [6] (section 4.3) and to engage with local communities in meaningful ways (section 4.5).

1.4 Evolving landscape

New perspectives

Health as a social and economic priority

While the R & D environment has progressed tremendously since the modern concepts of clinical research have been introduced, important changes have also taken place in the social, ethical and regulatory environment globally, including in resource-limited settings. There is now a broader recognition of the very large health, social, and economic returns of investments in research.[15] This recognition, coupled with the founding of public-private partnerships for product development, revisions of the Declaration of Helsinki,[16] the CIOMS International ethical guidelines [1] ,ICH E6 good clinical practice guidelines,[17, 18] as well as the creation of new regulatory pathways for approval of products specifically developed for diseases in LMIC and recent public health emergencies, have significantly changed the environment for clinical research.

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.

New actors

Non-industry funded research and public-private partnerships

The research landscape continues to evolve. Increasingly, non-industry parties and public private partnerships are funding clinical research such as comparative effectiveness studies, sometimes with support from external partners in translational research. Examples of this are the work of Médecins sans Frontières in epidemic situations, and the support of funding organizations such as Wellcome Trust, Bill & Melinda Gates Foundation, the European and Developing Countries Clinical Trials Partnership (EDCTP), the U.S. National Institutes of Health (NIH), the Biomedical Advanced Research and Development Authority (BARDA) for international health programmes, the Japan-based Global Health Innovative Technology (GHIT) Fund and Unitaid. Past decades have seen the establishment of various product development partnerships for clinical research targeting diseases in resource-limited settings, such as the Drugs for Neglected Diseases initiative (DNDi),[22] the Foundation for Innovative New Diagnostics (FIND), Medicines for Malaria Venture (MMV), TB Alliance and the Sabin and International Vaccine Institute; and there are many others whom space does not permit to mention here. The experience and lessons learned from these partnerships and clinical trial networks should be used to inform the next-generation studies. National medical research councils can also play a catalytic role in aligning the research agenda to local health priorities.

Advocacy groups and collaboration networks

Patient organizations have come to the fore globally in recent years, including in resource-limited settings, raising awareness of the issues affecting patients as well as the role of scientific research in improving their quality of life. In addition, specific health needs are being addressed by advocacy groups and collaboration networks such as the AIDS Vaccine Advocacy Coalition (AVAC), the Treatment Action Group

(TAG), the International Treatment Preparedness Coalition (ITPC), the International Partnership for Microbicides, the HIV Prevention Trials Network, the HIV Vaccines Trials network, the International Federation of Associations of People Affected by Chagas disease (FINDECHAGAS) and others.

New study sites

Research in resource-limited settings

Past decades have seen an increase in the number of clinical trials conducted in LMICs.[4] Evidence of safety and efficacy, as well effectiveness in a particular setting, is very important for drugs against diseases prevalent in resource-limited settings, such as malaria, tuberculosis and helminthic infections. It is also crucial for vaccines, and late-stage clinical trials of relevant vaccines are increasingly being conducted in LMICs.[23] While the conduct of vaccine trials in resource-limited settings is an opportunity to address public health threats, oversight of these trials poses significant challenges for national regulatory systems (see section 3.4).

Early-stage research

While most phase 1 studies for interventions responding to health needs in LMICs are conducted in HIC where adequate testing facilities exist, some Asian countries are beginning to conduct early-stage clinical trials.[24] For investigational Ebola vaccines phase 1 studies were done in high-income countries (HIC) [25-27] as a demonstration of solidarity with burdened populations, but also in low-resource communities not experiencing an outbreak.[28] Developing facilities to conduct phase 1 studies in LMICs is an important component of research capacity strengthening.

1.5 Need for research in resource-limited settings

The research gap

Over the last decades clinical research has resulted in the development of many health interventions that have had a major positive impact on health globally (see Figure 1 above). However, much of the medical product R & D has focused on diseases prevalent in high-resource settings, and has been carried out in settings where the considerable and often costly infrastructure needed for clinical research has been built up over the years and is readily available. On the other hand, there is still a lack of substantial R & D activity to address the diseases and ethnic-related morbidity and mortality risks affecting people in resource-limited settings,[29-31] where there is limited research capacity and/or commercial viability.

Clinical research in low-resource settings: "WHY?"

Clinical research drives the advancement of health care. If research is not done in low-resource settings, entire populations will miss out on the vaccines, diagnostics and treatments that are needed as part of sustainable development globally.

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[4] Top three countries in terms of numbers of clinical trials; Sub-Saharan Africa: South Africa (2,928 trials), Uganda (620 trials), Kenya (536 trials); Latin America: Brazil (8,075 trials), Argentina (3,068 trials), Chile (1,758 trials). Source: clinicaltrials.gov map search, accessed 12 April 2021.

In addition, research can have indirect benefits that are unconnected to the knowledge gained by it. Some research initiatives, including the partnerships mentioned in section 1.4 above, have a component of capacity-building, from infrastructure to education and training of the next generation of researchers. Infrastructure and skilled staff can support continuity in research and follow-on projects, or improve regular medical care when the initial studies are completed. Also, it is often through participation in well-designed, responsible clinical research that local medical doctors and other health care professionals are introduced to the principles of evidence-based medicine and apply them in their own practice. Such indirect benefits could in themselves justify the conduct of a study in LMIC, if the local authority determines that it outweighs the burden of research for the population (see 4.3.1)

"WHEN?" While it seems reasonable to perform clinical evaluation of health interventions where the conditions and capabilities are best suited to do so, there are instances when this must be done in locations where the conditions may not be ideal, particularly when local genetic, environmental and/or social factors may have an impact on the medical value of the health intervention under study (see 5.1.1).

Conversely, it is also important to recognize that not all research in resource-limited settings has added value. Increasingly, regulatory authorities require local clinical trials as a condition for registration of medicinal products, even if they have already been registered in other jurisdictions (see section 3.4). Local registration trials and other special regulatory requirements should only be imposed if there is a solid scientific rationale, and should not be taken as a mere formality.

"WHAT?" This document aims to encourage and facilitate good clinical research in low-resource settings across the range of clinical trial activity as a means to improve health and wellbeing. Clinical research encompasses a broad range of activities across a range of disciplines. In low-resource settings the range is the same, but the context is often different, and the health structures which support research are usually weaker.

Today a larger proportion of clinical research overall in those settings is on maternal and child health, infectious diseases and nutrition, and most are observational or implementation studies conducted post-registration (see Box 1 on page 18). There is a need for more pre-registration studies in low-resource settings.

"HOW?" The basic requirements and the ethical and scientific standards guiding research should be the same everywhere, but the priorities and needs depend on the context. Pre-registration studies need extensive and detailed documentation, but post-registration studies and other forms of clinical investigation often less so. Extensive documentation requirements for all clinical investigation have hampered clinical research in low-resource settings where the available human and financial resources

are limited. The requirements of good clinical practice should match the needs without compromising the essential principles.

1.6 Problem statement

Although substantial progress has been achieved in past years in conducting relevant, good quality clinical research in resource-limited settings, more such research is needed to address the health needs of people living in these settings. The persisting research gap contributes to the health disparity between high- and low-resource settings.

Lack of conducive environment

Many LMICs still lack effective ethical and regulatory frameworks [32] and implementation strategies for clinical trials with human participation, as well as legal structures to address the potential legal issues. There is also a lack of suitably trained staff and well-resourced centres to conduct non-commercial research. Health care infrastructures are usually weak and poorly resourced both with manpower and technical equipment. There is limited recognition of the value of research, and few LMICs have effective and well supported national research institutions. Building a more enabling and conducive environment for ethical and scientifically solid clinical research is essential.

Challenges in implementing international standards

Trial regulations are often very complex as they represent a stringent standard of international good clinical practice (GCP). An overly strict, literal interpretation of GCP requirements may present insurmountable obstacles in conducting clinical research in many resource-limited settings (see the example in section 3.5). There is a need for rethinking these one-size-fits-all requirements and for defining essential standards that are applicable globally and adaptable to the study type. Many guidelines and standards allow for some flexibility, without compromising on ethical principles, quality and validity of the research and the advancement of public health. A focus on essential standards is important across economic settings wherever resources to conduct clinical research are limited, *e.g.* in academic institutions, investigator-initiated trials or research for diseases for which competitive funding is scarce. As an example of this flexibility, the updated ICH E6 R2 guidelines [17] encourage the implementation of risk-based approaches to quality management and the use of less complex, efficient trial designs.

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

resource-limited settings and should be supported, including in outbreaks (Appendix 3). Studies conducted in line with good clinical practice will yield results that can improve the health and well-being ecosystem, and thereby increase the social acceptance of clinical research in these settings.

Objectives of this report

Pursuing earlier work initiated at CIOMS,[34] this report aims to provide recommendations on *why*, *when* and *how* to conduct clinical research in resource-limited settings in compliance with GCP standards. It builds on the CIOMS ethical guidelines [1] as well as existing publications on aspects of promoting good quality research in these settings (*e.g.* [5,35]). It provides a comprehensive overview of the main ethical and scientific issues, with examples and references where readers can find further details. The report includes pragmatic recommendations for governments, researchers and funders. It is of interest for all parties involved throughout the clinical trial life cycle, *i.e.* in policy-making, planning and funding, designing, assessing and carrying out clinical research in resource-limited settings, notably by ministries of health, ethics committees, regulators, health technology assessors, industry, public-private partnerships, academia and civil societies in all parts of the world.

CHAPTER 2.

THE RESEARCH ENVIRONMENT: OBSTACLES AND ENABLERS

This chapter describes the obstacles to clinical research in resource-limited settings, together with suggested enablers to reduce or overcome them, and cross-references to subsequent chapters where the issues are discussed in more depth.

- **The context of clinical studies in resource-limited settings differs from that in resource-rich settings in many ways (section 2.1).**
- **A more conducive environment with funding opportunities would advance clinical research in resource-limited settings, with benefits for public health (section 2.2).**
- **Infrastructure and capacity should be built to make research in resource-limited settings more sustainable (section 2.3).**

2.1 Clinical studies in resource-limited settings

The factors to consider in clinical research in resource-limited settings, as suggested from the experience of the CIOMS Working Group members in developing this report, are outlined in **Box 1**. These explain some of the difficulties and obstacles encountered.

2.2 Creating an research-friendly environment

An enabling environment is essential for good clinical research, and countries, institutions and organizations should take responsibility for creating this. The ability to conduct appropriate clinical research is dependent on several factors. These are institutional and community support, the clinical and logistic opportunities, the degree of scientific, financial and laboratory support, and the operational environment.

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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5 In December 2020, PubMed searches with country names as search terms and restricted to "Clinical trials" and the year 2020 yielded the following: "Nigeria" (population 200 million): 55 publications, of which only one was related to a preregistration trial—a phase 2 Ebola vaccine study. "Indonesia" (population 270 million): 23 publications, two of which were related to pre-registration studies, *i.e.* a phase 2 typhoid vaccine study and a long-term follow-up of a phase 3 trial on chronic myeloid leukaemia chemotherapy.

6 Of 331 completed trials in Uganda reported in the clinicaltrials.gov registry as at 2 February 2021, most were on aspects of managing patients with HIV, tuberculosis, malaria and other infectious and parasitic diseases (241 trials), followed by studies on reproductive, maternal and child health (35 trials), social and environmental issues (18 trials), and management of acute and post-operative conditions (14 trials). Only two trials were on cancers, both HIV-related.

7 The median number of patients enrolled in completed studies reported in the clinicaltrials.gov registry as at 2 February 2021 was 390 in Uganda (n=329 studies), compared with 99 in Denmark (n=5,080 studies).

From a researcher's or product developer's perspective there are far too many obstacles to clinical research in resource-limited settings, both in disease outbreaks and in general circumstances. Most of these obstacles—such as unsafe and unreliable roads, frequent power cuts and fluctuations, and ineffective systems to maintain safety and security— are consequences of limited resources, but others are organizational or bureaucratic, and these obstacles are potentially readily remediable.[43] It should be emphasized that many public institutions in resource-limited settings do create an enabling environment, but many also do not.

2.2.1 Role of host governments

Governments or communities in resource-limited settings may be neutral or hostile to clinical research, regarding it as unnecessary, interfering or problem-creating rather than problem-solving. Good clinical research is beneficial to health, both directly through a better understanding, diagnosis, prevention or treatment of disease, but also indirectly through training, support and better standards of health care. Governments should therefore view research as an important component of health improvement, which is necessary for achieving development goals and meeting the objectives of universal health coverage. Collaboration *e.g.* among governmental institutions, research institutions and/or public-private partnerships favours a conducive environment for research.

2.2.2 Conflict and discrimination

National or regional conflicts can cause exclusion, stigma and discrimination preventing people from getting the healthcare they need.[2] Under-resourcing or denial of health services can be used to weaken or suppress minority groups, thereby worsening the disease burden (notably of nutritional and infectious diseases). Investigation may be needed to identify causes and propose solutions. At the international level, geopolitical factors may influence research priorities and funding (see 2.2.6).

There are real concerns related to working with displaced populations such as in conflict-affected settings or in refugee camps where participants may be vulnerable to coercion or retribution, and there may be need for psychosocial interventions. Open or latent conflict may create humanitarian crises and new medical emergencies, and may put responders and researchers at risk.[40] (See also Appendix 3A.)

2.2.3 Corruption

Corruption in health care systems and the entire chain of agencies responsible for the supply of quality medicines and ancillary supplies is a major impediment to health care delivery and to development. Corruption (or the euphemism "weak governance")

is often not acknowledged openly, or it is actively concealed.[44] Corruption in various forms is ubiquitous and may feed on health inequity. It may prevent research, or it may affect the clinical trial process and threaten the quality of its outcomes.

Fighting corruption is urgent for the future of health globally. Corruption is embedded in health systems, and is sustained by both corrupted and corruptors. Therefore, everyone engaged in or supporting the health sector should recognize the threat of corruption, and encourage honesty and transparency and support law enforcement.[44]

2.2.4 Legal and regulatory issues

Ultimately, much of a regulatory agency's effectiveness and independence is determined by its country's political leaders, who have a responsibility to create a conducive environment that allows the regulatory system to function.[45] However, regulatory weaknesses and other legal uncertainties in resource-limited settings are significant obstacles to research.

- There is often a lack of clear guidelines for the ethical and regulatory authorization of clinical trials (*i.e.* what body is responsible for approving what type of research). For children, migrants, ethnic minorities, refugees and displaced persons there may be no responsible bodies competent to approve research protocols.
- Immature and under-resourced medicines regulatory authorities sometimes make unreasonable or inappropriate demands, resulting in excessive bureaucracy and lengthy delays in processing applications for clinical research (see also 3.4 and 4.4.3). In a systematic review this emerged as a recurring concern: the length of the delays was not usually described, but one study stated that it was not uncommon for grants to expire before all approvals were in place.[43] In some LMICs regulatory processes are linked to trade agreements (*e.g.* between the U.S. and Central American countries), potentially influencing marketing authorizations. Corruption can also be a factor (see 2.2.3 above).
- Ethical review is of prime importance in resource-limited settings, but the regulatory requirements are often unclear and review capacity is weak (see section 4.4).
- Specific legal uncertainties exist in some countries *e.g.* regarding the age or marital status at which independent informed consent can be provided, the legal status of guardians, the age of majority, or the law in relation to unregistered medicines.
- Drug importation can be very difficult, expensive and slow. Export of clinical samples to another country may be prohibited or difficult. The associated bureaucracy is often extensive. These factors are major potential threats to the quality of clinical research.

2.2.5 Public distrust

The environment for conducting clinical research in resource-limited settings is often characterized by a lack of awareness of and confidence in the social and health value of clinical research among the general public, health care workers, health authorities and policy-makers. Some individuals and some communities distrust medical research and are unwilling to participate in it.[41] If people do not participate in clinical research, new effective public health interventions specific to the population's health problems may be delayed or not materialize at all.

In some instances the distrust results from excessive research demands, and in others from misunderstanding or insufficient knowledge to appreciate the potential individual or community benefits of research—as in the case of anti-vaccine movements— or previous cases of corruption or direct harm. Local news channels and social media may nurture this distrust for many reasons. Sensitive and culturally appropriate community engagement through community advisory boards, community activities and education can overcome distrust (see section 4.5). Responsible dissemination of study information and results helps to increase public trust in research (see section 5.2).

2.2.6 Funding

Financing of research is a complex issue with many dimensions and challenges, not least the need for transparency and accountability in the allocation and utilization of funds. Financing and coordination of research and development, and proposals to stimulate research and development addressing the needs of people in resource-limited settings, have been examined at the behest of the World Health Assembly.[35] Two aspects related to funding were considered in the recommendations made at the beginning of this report.

Funders' research agendas (see Recommendation 18)

First, given that medical research is very poorly funded in most low-resource countries, financing comes from international donors, foundations, or the pharmaceutical industry in the majority of cases. At the same time there is a lack of national capacity to approve and oversee clinical trials. In some cases, funders impose their domestic ethical judgments upon the disbursement of funds to LMICs. At the international level, research may be affected when certain countries are denied access to funding or resources for geopolitical or ideological reasons. For example, since 1984, under all Republican administrations, the U.S. government has enforced the so-called Mexico City policy that bans the use of U.S. funding for research on the grounds that it appears to support abortion,[46] even in cases when research on potential teratogens is necessary (*e.g.* research on miltefosine for leishmaniasis) and when appropriate measures are taken to mitigate any risks associated with unintentional pregnancy (see also Appendix 1B). Relevant local authorities should be

empowered to protect the rights and interests of local populations in research (see section 4.4). This could include capacity-building on negotiation of fair research agreements. Useful guidance is available from the Fair Research Contracting Initiative of the Council on Health Research for Development (COHRED)[8].[47,48]

Sustainability (see Recommendations 9 and 16)

Second, funders seem more willing to support initiation rather than continuation of research projects or platforms in resource-limited settings, and historically have not invested in laboratory quality assurance schemes, despite their critical importance. One-off funding offers, *e.g.* for laboratory components or data management and analysis systems, are sometimes at the core of North-South research collaborations without considering longer-term sustainability. Efforts to build research capacity should be supported (see section 2.3).

2.2.7 Access to new health interventions

The social value of clinical research is grounded, among other things, in its contribution to the creation or evaluation of interventions, policies, or practices that promote individual or public health.[1, Guideline 1] Access to health products is a major problem in the developing world for many reasons, including cost,[9] and is an increasing problem globally both due to the rising costs of health technologies and the lack of new tools to tackle emerging issues such as antimicrobial resistance.[2] A UN high-level panel has called for more transparency about the aims and interests of all parties involved, and has called on governments to negotiate global agreements on the coordination, financing and development of health technologies to complement existing innovation models.[2] The COVID-19 pandemic has highlighted the urgent need for a global framework to facilitate an effective response (Appendix 3B).

Creating a research-friendly environment — Recommendations

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders* *Find examples of these categories on pages 4-6.

▶ Governments should realize their obligation to create an enabling environment for medical research, and appreciate the benefits this will bring to the quality of the health systems and practitioners, and the health (and economic status) of the people they serve.

(continued)

[8] See https://www.cohred.org/FRC/

[9] On average, total health spending per person in 2017 amounted to USD 37 in low-income countries, USD 84 in lower middle income countries, USD 486 in upper-middle income countries and USD 5243 in high-income countries.[9]

Creating a research-friendly environment — Recommendations (continued)	
▶ ▶ ▶	Funders, investigators and research councils should work with government bodies to facilitate public engagement and public understanding of the value of research for health.
▶	International agencies and NGOs providing aid in conflict areas should be open to the need to conduct or facilitate research benefitting people affected by conflict and discrimination, while staying impartial and being careful to support and not undermine relevant local health initiatives.
▶ ▶ ▶	The global community should develop and test new models that could work to fight against corruption in global health, and funders should support this effort. This task is urgent; corruption is arguably the biggest threat for the future of health globally, as it limits access to health services, and it debilitates all dimensions that determine good health systems performance—equity, quality, responsiveness, efficiency, and resilience—affecting outcomes and lives.[44]
▶ ▶ ▶	All stakeholders should actively reduce unnecessary bureaucracy, ensure transparency—including by disclosing conflicts of interest—and accountability in their operations, and build capacity for management and accounting where necessary.
▶	Ministries of Health should aim to strengthen regulatory processes and improve efficiency, including by allocating adequate funding, and clarify legal uncertainties. Clinical trial agreements, uniform shared templates for material/data transfer agreements, and other mechanisms enabling researchers to achieve the study objectives within agreed timelines while respecting national guidelines, should be encouraged.
▶	Researchers should improve their communication with local communities, including policy-makers and clinicians, about the benefits of clinical research.

2.3 Building research infrastructure and capacity

The need to strengthen research capacity in LMICs has been well recognized. The Special Programme for Research and Training in Tropical Diseases (TDR), which is co-sponsored by UNICEF, UNDP, the World Bank and WHO, has been working since 1975 to address diseases of poverty through research and innovation. In itself, conducting clinical trials in resource-limited settings can contribute to strengthening health system functions and equipping health services;[49] and in addition TDR is working to strengthen research capacity.[50] This section provides recommendations in some of the main areas that need strengthening in low-resource settings.

2.3.1 Human resources

The role of skilled manpower is central in any efforts to maintain research infrastructure in resource-limited settings. These include for example scientists/ clinical investigators, research nurses and support staff, as well as trial pharmacists to

manage the investigational products and study materials using the necessary IT resources for labelling and inventorizing. Career structures are needed to attract and retain good investigators and thereby strengthen research capacity. Investigators need to see a future in clinical research in their own countries.

Funding for training is required to build up a sustainable pool of researchers in resource-limited settings. Specific training requirements include research ethics, grant proposal writing, clinical investigation, research methodology, statistical analysis, communication, and publication (see Chapters 4 and 5). Mentoring of researchers in these settings is essential to strengthen their research capability, enhance research quality and alleviate an unnecessary sense of inadequacy which may impede due recognition of the importance of their research.

2.3.2 Data management and monitoring of trials

Recording and reporting of measurements and adverse events in clinical trials can be a labour-intensive process. In academic trials safety reporting is sometimes restricted to unexpected events, while all events (also those unlikely to be related to new treatment) are reported in industry-led trials. Clinical trials require independent monitoring to ensure compliance with GCP.[51] While in industry-led trials this is often done by commercial contract research organizations (CROs), these are usually beyond the budget of investigator-driven research. Strengthening capacity for clinical monitoring in academic groups is important. Many clinical researchers in resource-limited settings also lack access to training on research methodology and medical statistics, and do not have access to statistical support.

Data management

To minimize the need for resources and potential for errors, collection of unnecessary clinical or laboratory data should be avoided, especially in trials of later phases. As a rule, data that are essential for the particular intervention or question should be collected, although it can be an effective approach to collect certain related data or samples to be used or shared for future analyses (see also section 5.2). Where possible integration of clinical research into everyday practice should be attempted, taking care that the needs of local health care systems are respected (see also 4.3.1) and double recording avoided. Data repositories should be created to match the expectations of the research sponsors and/or regulatory authorities.

Data and safety monitoring

The draft revised ICH E8 guideline calls for safety monitoring of clinical studies conducted at any point in a medicinal product's lifecycle using an approach that reflects the risks to the study participants and what is known about the drug and the study population, and for setting up data safety monitoring committees that review accumulating data to determine whether to continue, modify, or terminate a study.[52] These committees should include representatives of the country in which the trial is conducted, and all members should be adequately trained. Cooperation among

clinical research centres in training local research personnel can facilitate clinical trial initiation, management, and data and safety monitoring.

Use of new technologies

Using the potential of modern IT facilities or mobile devices can simplify clinical research, save human resource and increase data quality (see Appendix 2A). Their use in data and safety monitoring and in post-approval studies could constitute a way for LMICs to leapfrog existing technology. For example, data could be collected in master datasets (*e.g.* patient records, laboratory databases, registries) and then transferred to study-specific databases. Alternatively, data could be collected by patients or carers at home using wearables or mobile devices, an approach that is explored in Europe by the Trials@Home Centre of Excellence, supported by the Innovative Medicines Initiative.[53] New technologies can also be used for remote monitoring, which is increasingly accepted by regulators particularly in emergencies such as the COVID-19 pandemic.[54,55]

Electronic health records

There is an increasing trend towards setting up different types of e-health records and registries. A major asset for any country wishing to create a research-friendly environment would be an electronic health record system that can be used for research. As many LMICs are now introducing electronic health records (EHRs) for the first time, there is a unique opportunity for governments and donors to consider the lessons learned in other countries (see Appendix 2B).

2.3.3 Laboratory capacity

Most clinical research requires laboratory measurement. This ranges from standard clinical haematology, biochemistry, immunology and microbiology through to specialized assays. In many resource-limited settings laboratory support is rudimentary, offering limited facilities for pharmacokinetic studies and therapeutic monitoring. Necessary computer programmes for laboratory data management, statistical analysis and mathematical modelling are also often lacking. Donors commonly provide laboratory equipment that cannot be maintained, or worse, drains precious resources away from other aspects of health care *e.g.* by burdening recipient countries with storage and disposal costs. In a survey on compliance with WHO guidelines for donations it was estimated that 40-70% of donated medical devices—including healthcare and diagnostic equipment—were not used as they were not functional, inappropriate, or because staff were not trained to use them.[56]

Using local laboratories

Although some investigations may require samples to be shipped to specialized laboratories, where possible laboratory measurement should take place locally or regionally. Local or regional laboratory capacity will minimize delays and risks to samples due to lengthy transport to distant laboratories. They are also a valuable source of locally appropriate reference ranges that are established on the basis of tests conducted in local populations.

Strengthening laboratory capacity

Laboratory capacity and training need to be improved. Adequate laboratory infrastructure would include trained laboratory technicians, availability of reagents, equipment with repair and servicing support, and constant-voltage electricity supply. Planning and institutional commitment is required to ensure that salaries are provided and equipment is maintained.

Laboratory capacity may be better sustained through regional strengthening.[57] Integration across programmes and sectors (avoiding "silos", fragmentation and duplication of systems and services), country ownership (avoiding excessive dependence on donor funding), partnerships and respect for local context and needs are useful guiding principles.[58] One approach is for governments to consider regulations and/or incentives for the use of local laboratories as a strategic means to support a sustainable local laboratory infrastructure.

Example: In India any biomedical and health research to be carried out in an international collaboration must comply with applicable guidelines [59-62] and must be registered with the ICMR Clinical Trial Registry.[63] There are provisions for exchange of biological material between laboratories and international collaboration, but transfer of all samples to a foreign laboratory is not permissible. If required, representative samples (about 10%) can be transferred to the foreign collaborators for quality assurance/quality control purposes.

While using local laboratories is a useful principle for routine laboratory investigations, specialized assays may require very specialized techniques for which it does not make sense to build local capacity. Thus, restrictions on the export of samples should always be considered very carefully as there is a risk that such rules do more harm than good.

External quality assurance

Participation in external quality assurance schemes is essential and empowering.[64] Such schemes help to identify problems and enable laboratories to demonstrate the validity of their results both to the health care workers and their patients, but also to external bodies supporting and conducting research. In some areas, notably serodiagnostics, qPCR, antimicrobial susceptibility and drug measurement, international quality assurance schemes with provision of essential reagents or standards can enable local or regional laboratory capacity development, as occurred for example in Latin America.[65]

Laboratory qualification

According to ICH GCP guidance, before a clinical trial starts, investigators should document the competence of the laboratory to perform required tests and support reliable results; this may involve information on certification, accreditation, established quality control and/or external quality assessment, or other validation.[17] Laboratory accreditation can be onerous and costly to maintain. Regulatory requirements should allow for acceptance of laboratory quality systems that match the requirements of the research to be conducted.

2.3.4 Standing research networks

Cooperation between researchers can facilitate exchange of experiences and can have benefits at various levels that enhance the quality of clinical research.

Example: The INDOX cancer research network,[66] a partnership between the Institute of Cancer Medicine at the University of Oxford and nine comprehensive cancer centres in India, builds capacity for locally relevant clinical research by training local investigators, site coordinators and research support staff, and developing and implementing uniform SOPs to ensure compliance with GCP.

Efficiency gains

Cooperation enables sharing of experience and resources, which can lead to more efficient conduct of trials.[33] Standing clinical networks offer well-established research infrastructures and enable career development for local scientists.

Community engagement

It is essential that community members (including disease-related communities or patient representation groups) are actively engaged in clinical research. Standing clinical research networks can provide important background information on clinical epidemiology and local practices, and allow formation of community advisory boards (see section 4.5). Cooperation between researchers can also lead to clearer common messaging *e.g.* on the benefits of clinical trials in generating evidence for health care, and potentially facilitate the negotiation of agreements to ensure that new health interventions become available to the patients after the trial ends.

Building research infrastructure and capacity — Recommendations

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders*

*Find examples of these categories on pages 4-6.

▶ ▶ ▶	Governments, international organizations and sponsors should support the development of local research career structures as well as training schemes in research ethics (see Chapter 4), methodology, analysis and practice.
▶ ▶ ▶	Governments, international organizations and sponsors should invest in creating and maintaining local laboratory infrastructure, resources and staff capacity to support clinical trials wherever possible. Participation in external quality assurance schemes should be encouraged and supported.
▶ ▶	Researchers and funders should consider working together and sharing their experiences, methods and resources.
▶ ▶	Researchers and funders should collaborate to establish and maintain standing clinical research networks.
▶ ▶ ▶	Clinical trial centres should consider working with various forms of CROs, including academic equivalents, with training for monitoring both academic and industry-led trials.

CHAPTER 3.

GUIDING PRINCIPLES FOR CLINICAL RESEARCH

This chapter describes the ethical and regulatory principles for clinical research as reflected in international documents, the current globally recognized regulatory standards, and challenges with their implementation in resource-limited settings.

- **Ethical and regulatory principles for clinical research have evolved in response to rapid technological advances and increasing globalization (section 3.1).**
- **ICH good clinical practice (GCP) standards have been developed in the industrialized world to govern clinical trials for the development of new drugs (section 3.2).**
- **The principles of GCP for conducting and evaluating scientifically sound and ethical clinical research also hold true in emergencies (section 3.3).**
- **Regulatory capacity-building, harmonization and mutual reliance are indispensable in all settings (section 3.4).**
- **GCP principles should be applied to all clinical research, at a level of detail that is proportionate to the nature of the study and sufficient to answer the scientific question (section 3.5).**

3.1 Origins

The ethical and regulatory basis for the conduct of clinical trials evolved in parallel as national and international authorities recognized the need to protect human research participants and ensure the efficacy and safety of health interventions. Some of the main events are outlined below.

1940s-50s: Aftermath of the Second World War

1947: Nuremberg Code [67] promulgated as part of the judgment of the court that tried the Nazi physicians who had conducted experiments on non-consenting prisoners and detainees during the Second World War (*"The Doctors' Trial"*).[68]

1948: Universal Declaration of Human Rights [69] adopted by the United Nations General Assembly in the wake of the judgment on *The Doctors' Trial*.

1950: Beginning of World Medical Association (WMA) process of articulating a set of duties for physicians conducting medical research.

1960s: Stricter standards for control of health products

1962: In the wake of the thalidomide tragedy, Drug Amendments Act passed in the U.S. requiring the FDA to approve all new drug applications and, for the first time, demanding that a new drug should be proven to be effective and safe, with study subjects required to give informed consent.

1964: WHA Declaration of Helsinki adopted (subsequently revised nine times, most recently in 2013),[16] setting out ethical guidelines for physicians engaged in both clinical and nonclinical biomedical research.

1966: International Covenant on Civil and Political Rights [70] approved by the UN General Assembly to give the 1948 Declaration legal and moral force. Subsequent human rights instruments for the protection of women [71] and children [72] reinforce the connection between human rights and the ethical principles that underlie international guidelines for research with human beings.

1967: CIOMS work in bioethics started.[73]

1970s-80s: Ethical standards implemented in regulation of research

1979: Belmont Report [74] published in the U.S., identifying three core principles (respect for persons, beneficence and justice) and their application in informed consent, assessment of risks and benefits, and selection of research participants, and introducing the concept of vulnerability. The report formed the basis of regulation of research in the U.S.

1982: CIOMS ethical guidelines on biomedical research [75] published. (Subsequent guidelines issued in 1993,[76] and in 2002,[77] and for epidemiological studies in 2009;[78] most recent revision published in 2016, see below).

1990s: Regulatory harmonization in industrialized countries

1990: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) founded by regulatory authorities and the pharmaceutical industry of the United States, Europe and Japan.

1995: First international guideline on good clinical practice (GCP) published by WHO.[79]

1996: ICH GCP guideline [80] published, International Standards Organization (ISO) guidelines on clinical investigation of medical devices [81] published.

1997: Convention on Human Rights and Biomedicine (the "Oviedo Convention") [82] adopted in Europe to address the potential threats posed by the rapid advancement in biomedicine.

2000s: Accelerating advances in biomedicine

2000: Joint United Nations Programme on HIV/AIDS (UNAIDS) guidance on Biomedical HIV Prevention Trials [83] published (revised WHO/UNAIDS guidance published in 2007)[84]

2005: Pan American Health Organization (PAHO)'s Pan American Network on Drug Regulatory Harmonization (PANDRH) GCP guidelines published.[85]

2005: Protocol on Biomedical Research [86] opened for signature to implement the research-related principles of the Oviedo Convention; ratified by 12 Member States of the Council of Europe to date.[87]

2005: UNESCO's Universal Declaration on Bioethics and Human Rights [88] published, enshrining the principle of respect for human vulnerability and personal integrity as a bioethical value of universal concern.

2007: U.S. Clinical Trials Transformation Initiative (CTTI) established. This multi-stakeholder public-private partnership has issued a series of recommendations and tools to drive adoption of practices that will increase the quality and efficiency of clinical trials.[89]

2010s: Increasing global regulatory harmonization

2015: ICH organizational structure changed towards a more global outreach. Brazil and the Republic of Korea joined as regulatory members in 2016, China in 2017;[10] India became a regulatory observer in 2016 and may soon become a regulatory member.

2016: CIOMS/WHO *International Ethical Guidelines for Health-related Research Involving Humans* published,[1] providing internationally vetted ethical principles and detailed commentaries on how universal ethical principles should be applied, with particular attention to conducting research in low-resource settings [90].[11]

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10 As of October 2020 ICH counted 17 members and 32 observers, including the regulatory authorities of Europe, the United States and Japan (founding regulatory members), Canada and Switzerland (standing regulatory members), Brazil, Singapore, Republic of Korea, China, Turkey and Chinese Taipei (regulatory members), as well as three international industry associations. ICH observers include WHO and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) as standing observers, legislative or administrative authorities of Argentina, India, Cuba, Mexico, Israel, Colombia, Jordan, Moldova, Lebanon, Kazakhstan, Malaysia, Iran, Russia, South Africa, Armenia, Saudi Arabia and Australia, seven harmonization initiatives from all regions of the world, and seven other international organizations including CIOMS. Source: https://www.ich.org/page/members-observers

11 The CIOMS ethical guidelines are issued jointly with the World Health Organization (WHO) to complement the Declaration of Helsinki throughout its revisions. They are freely available from https://cioms.ch/publications/ in all six UN languages as well as in Japanese, Portuguese and Ukrainian. The 2016 revision includes four significant changes in response to challenges that have emerged in the past decade,[90] and that are all relevant in the context of this report. First, they place increased emphasis on the scientific and social value of research, second, they recognize that resource-limited settings can occur in all countries including high-income ones (see section 1.2 of this report), third, they include a new guideline on community engagement (see section 4.5), and fourth, they no longer label entire classes of individuals as vulnerable but define vulnerability as context-dependent, requiring specific safeguards to protect the rights and interests of research participants (see section 4.1).

3.2 Good clinical practice (GCP)

Definition

Clinical research is necessary to establish the safety and effectiveness of health and medical products and practices. Much of what is known today in this regard comes from randomized controlled clinical trials that are designed to answer important scientific and health care questions and form the foundation for evidence-based medicine. However, such research can be relied upon only if it is conducted according to principles and standards collectively referred to as Good Clinical Research Practice (GCP), *i.e. "a process that incorporates established ethical and scientific quality standards for the design, conduct, recording and reporting of clinical research involving the participation of human subjects"*.[5]

GCP principles

The GCP principles issued by ICH in 1996 (**Box 2**) reflect a number of ethical and quality principles found in other internationally accepted documents. They are very similar to the principles in WHO GCP guidelines,[79] as some experts were common to the respective WHO and ICH working groups.

Box 2. Principles of good clinical practice (GCP)

Source: [80]

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

ICH harmonized guidelines

Based on the GCP principles, the ICH harmonized guidelines started emerging in the 1990s and became the regulatory standards applied by most countries where significant drug development took place. The guidelines are divided into four topics: quality, safety, efficacy and multi-disciplinary.[12] In response to the increasingly global face of drug development ICH initiated a series of organizational changes in 2015 to expand its outreach and now includes members and observers from both well-resourced and resource-limited countries. Today, most countries have either implemented the ICH guidelines or follow most of the underlying principles.

ICH guidelines relevant to clinical trials

The ICH efficacy ("E") guidelines are those of interest for the conduct of clinical trials, *i.e.* investigations conducted in human subjects with the object of ascertaining the safety and/or efficacy of investigational products.[17] The ICH E6 *Guideline for good clinical practice* (GCP)[17] and related guidelines (**Box 3**) have been widely implemented by ICH members and observers. This means that data submitted to support applications for medicines registration (marketing authorization) in these countries must come from trials that have been conducted in compliance with ICH requirements. Accordingly, ICH standards are used as the basis for most companies' standard operating procedures governing the planning, conduct, analysis and reporting of clinical trials for the development of new drugs.

Box 3. Selected ICH guidelines relevant to clinical research
Source: https://ich.org/page/efficacy-guidelines

E3 – Clinical study reports
E4 – Dose response studies
E5 – Ethnic factors
E6– Good clinical practice [17] and draft updated principles [18]
E7 – Clinical studies in geriatric population
E8 – General considerations for clinical trials
E9 – Statistical principles for clinical trials
E10 – Choice of control group in clinical trials
E11-11A- Clinical trials in pediatric population
E17 – Multi-regional clinical trials
E18 –Genomic sampling
E20 – Adaptive clinical trials

Note:
Not all of these guidelines are necessarily relevant to all types of research in resource-limited settings. In general however, they can serve educational purposes and provide a sound basis for the planning and execution of many types of clinical research in resource-limited settings.

12 **Quality** guidelines (Q1A–Q14) harmonize guidelines for pharmaceutical quality based on Good Manufacturing Practice (GMP). **Safety** guidelines (S1A–S12) aim to uncover potential risks like carcinogenicity, genotoxicity and reproductive toxicity in preclinical studies. **Efficacy** guidelines (E1–E20) are concerned with the design, conduct, safety and reporting of clinical trials, and also cover novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines. **Multidisciplinary** guidelines (M1–M13) cover topics which do not fit uniquely into one of the other categories, *e.g.* the ICH Medical Dictionary for Regulatory Activities (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

The ICH Guidelines are available at: https://www.ich.org/products/guidelines.html

3.3 Benefit-risk assessment in emergencies

Past public health emergencies have demonstrated the value of clinical research as part of an epidemic response. They have also shown that there is a need for the international community to be better prepared and to use the phases between epidemics to strengthen capacities in research, health care systems, regulations, communication, community involvement and international coordination and collaboration. Comprehensive analyses of the lessons learnt have been conducted by WHO, the National Academy of Sciences and others.[91-94] This section sets out some basic principles of benefit-risk assessment in emergencies.

Principles of benefit-risk assessment

Regulatory decisions are in principle based on a comprehensive benefit-risk assessment in the local context. This takes into account the overall knowledge of science and technology, past experiences as summarized in regulatory guidance documents, and the anticipated benefits and risks of conducting a study, or of authorizing an investigational medicinal product. The inherent complexity of assessing benefits and risks[13] makes it impossible to calculate a simple ratio, illustrating the need for comprehensive and scientifically sound discussions.[95, 96] These principles also hold true in emergencies.

Assessing research applications

In reviewing applications for clinical research, the aim is to assess whether the proposed studies are scientifically sound and ethical. The WHO Research Ethics Review Committee has documented lessons learned in an outbreak situation and made recommendations for future public health emergencies.[97]

In emergencies, public health authorities are responsible to coordinate national surveillance activities with the aim to limit morbidity and mortality. This has come to the fore in the COVID-19 pandemic, and WHO has provided guidance for Member States.[98] In low-resource settings, where outbreaks are more common, public health surveillance activities can be an accelerated path to gather clinical data in emergencies. This is a useful option for local regulatory authorities and RECs to consider when evaluating research applications.

Assessing products

In evaluating applications for registration (marketing authorization), the aim is to assess all available evidence about a candidate intervention and the surrounding situation to determine whether the intervention is effective in preventing or treating the disease, and to establish whether its expected benefits outweigh its potential risks to patients. In a public health emergency, such information is often not readily available in sufficient quantity or quality to adequately support evidence-based decision-making, and the urgency of the situation magnifies the potential consequences of action or inaction.[99]

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[13] An example of this complexity is the evaluation of rotavirus vaccine, where the benefit of reduced mortality from rotavirus gastroenteritis and the risk of intussusception were not balanced equally in LMICs and in HICs.[96]

Unregistered interventions

The use of unregistered interventions may be deemed acceptable in particular circumstances under strict conditions. An example is compassionate use of investigational products to help patients who cannot otherwise be treated. The scientific and ethical considerations around this topic in an outbreak situation have been intensively discussed.[100]

Accelerated processes

In an outbreak response, decision-makers must perform benefit-risk assessments under time pressure. While the principles remain the same, well-defined fast-track processes are needed to provide the best response in a given situation in order to save lives. Examples are the WHO Emergency Use Listing Procedure (EUL), which is based on an essential set of available quality, safety, and efficacy and performance data,[101] and the so-called rolling review approach, where regulators review data as soon as they become available from ongoing studies.

Good research practices

When conducting a clinical trial in an emergency, sponsors and investigators should consult early with the responsible regulatory and ethics to arrive at a comprehensive understanding of the situation and the planned trial. During the trial they should secure the safety and the rights of the participants by following the ethical and regulatory principles of GCP within the context of an epidemic response. After the trial is completed they should fulfil all obligations, e.g. with regard to safety monitoring, and allocate sufficient time and resources to evaluate and document the lessons learnt.

Clear communication is crucial in emergencies to maintain trust in the information provided, and thus enable an effective response. Sponsors and investigators should devote sufficient time and resources to sharing results with the public (see section 5.2) and documenting lessons learnt.

When decision-making in the face of high uncertainty cannot be avoided, post-approval monitoring of the safety and effectiveness of new therapies or repurposed medicines approved for a new indication is critical. This could include phase 4 clinical trials, observational studies, manufacturer-run patient registries, patient support programmes, patient focus groups and proactive adverse reaction monitoring strategies.[99]

Benefit-risk assessment in emergencies — Recommendations

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders*

*Find examples of these categories on pages 4-6.

▶ Regulatory authorities should maintain solid, scientific and evidence-based principles and best practices to ensure that a proper review of research applications and benefit/risk assessment of potential new health interventions is conducted in emergencies.

(continued)

Benefit-risk assessment in emergencies — Recommendations (continued)	
▶	Wherever possible, regulatory processes should be accelerated to enable a timely response in an emergency situation. Regulators should cooperate effectively, and should rely on each other's decisions as much as possible.
▶ ▶	Sponsors and regulatory authorities should monitor the safety and effectiveness of new therapies e.g. through phase 4 clinical trials, observational studies, manufacturer-run patient registries and/or patient support programmes, patient focus groups and by implementing proactive adverse reaction monitoring strategies. (See also 2.3.2).[99]
▶ ▶ ▶	All stakeholders should follow best practices for communication and provide information that is timely, accurate, credible, understandable, actionable, consistent, and empathetic.[99]

3.4 Regulatory capacity, cooperation and reliance

3.4.1 Access to health products

Conditional and fast-tracked approvals

Since the inception of ICH in 1990, regulatory requirements have increased to address the complexities of developing novel technologies and treatments and optimizing their scale-up, manufacturing productivity and cost-effectiveness in downstream processing. This has increased the time and cost of product development. To speed up access to new products, new regulatory pathways have been created enabling conditional marketing authorization of products while further research is being conducted, as well as fast-tracked approval of products for use in public health emergencies.

Additional pathways for equitable access

To support good quality health care in resource-limited settings, regulatory authorities have created mechanisms for assessment of products to be used outside their borders, such as the EMA's Article 58 procedure [102] and the FDA approvals under the PEPFAR programme.[103] Both EMA and FDA also provide scientific advice that is not necessarily linked to a specific application. In addition, the WHO prequalification programme [104] has opened up an additional avenue for faster and more equitable access to stringently assessed safe and effective health products.[105]

Persisting bottlenecks

Regulatory legislation differs from country to country, and decisions are made separately and independently within each jurisdiction, resulting in delays for researchers and manufacturers who must navigate multiple regulatory systems to register the same health technology across countries.[106] Many authorities in LMICs require a local clinical trial and/or have other special regulatory requirements as a condition for registration, without considering whether this is scientifically justified (see

5.1.1) or whether it does in fact lead to gathering information from the relevant ethnic groups in the country. In this context, relevant research questions and appropriate study design (section 5.1) as well as sharing of data and results of clinical trials (section 5.2) are important.

3.4.2 Regulatory capacity

Global benchmarking

Implementation of GCP principles in national or regional regulations is very much dependent on a fully functional regulatory system. In resource-limited settings, many ethics committees and regulatory agencies still lack the requisite legislative and regulatory frameworks to regulate clinical trials of medicines to internationally accepted standards and to provide scientific advice for product-related clinical research.[107-109] WHO's regulatory capacity-building work led to the development of a Global Benchmarking Tool (GBT) to rate the maturity of the regulatory framework,[32] for self-assessment or external assessment of regulatory authorities.[14] The GBT indicators and fact sheet for clinical trials oversight give an overview of what a functional system would look like.[110]

Persisting gaps

The capacity of regulatory authorities worldwide varies greatly. According to WHO, only 50 of 194 countries assessed have what are considered to be mature regulatory authorities (the top or second-highest level on the four-point GBT scale); 99 countries are at the lowest level of maturity and have only some elements of a regulatory system.[32] Many agencies in resource-limited settings do not have sufficient specialist knowledge to ensure effective oversight of clinical trials. Strengthening national regulatory capacity requires long-term commitment and significant resources.[111] The health and economic value of effective regulation should be analyzed more systematically and communicated to governments and funders to make the case for sustained investments.[112]

Linking scientific and ethical aspects

An aspect that is sometimes overlooked is that scientific and ethical aspects cannot be separated completely. Regulators and ethics committees should invest more time in achieving a common understanding on the reasons why *e.g.* a particular study design should be used or specific data collected, and how this can be achieved in the context of the research. Regulatory requirements should be "ethics-proof" (see also **Chapter 4**).

[14] The WHO GBT indicators and fact sheets for each component function of regulating different types of health products (i.e. medicines and vaccines, blood products, and medical devices) can be freely accessed from: https://www.who.int/medicines/regulation/benchmarking_tool/en/

3.4.3 Towards harmonization and cooperation

Good regulatory practices

Consistent regulatory frameworks could encourage the investments needed to bring appropriate and affordable products to market and lead to harmonization of regulatory practices. WHO has developed guidelines[15] on good regulatory practices to support countries in this regard,[113] and has adopted a guideline on quality management systems for national regulatory authorities, with an aim to promote consistency in regulatory practices as a basis for mutual reliance and recognition.[114] Lessons learned from the new regulation adopted in Europe to harmonize the oversight of clinical trials, once it becomes applicable,[115] may also be useful for regional harmonization initiatives in developing countries.

Regulatory reliance

Given the ubiquitous resource limitations globally, the need for more reliance among regulators has been well recognized.[4, 116] In resource-limited settings, WHO regulatory support has led to collaboration and reliance initiatives such as the African Vaccine Regulatory Forum (AVAREF),[117] which has demonstrated its value in harmonizing and accelerating regulatory and ethics reviews in relation to Ebola vaccines,[118] and the collaborative registration initiatives that arose from the WHO prequalification programme.[119,120] More recently it has been proposed that the WHO GBT ratings of regulatory system maturity could be used to evaluate and publicly designate regulatory authorities as "WHO-listed authorities", as a basis for reliance decisions by the international regulatory and procurement community.[121]

Regulatory capacity, coordination and reliance — Recommendations

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders*

*Find examples of these categories on pages 4-6.

▶ Regulatory authorities in resource-limited settings should harmonize their practices with those in neighbouring countries, and should engage with more mature authorities to share information and resources.

▶ In line with the newly developed WHO guidance on good reliance practices,[122] regulatory authorities in source-constrained settings should focus on essential in-country activities such as oversight of safety monitoring, local manufacturing and distribution while relying on assessments made by well-resourced authorities for most other functions wherever possible.

(continued)

[15] The WHO guidelines on norms and standards for pharmaceuticals are found at https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines.

Regulatory capacity, coordination and reliance — Recommendations (continued)	
▶	Regulatory authorities should only require local clinical trials or set other special requirements if they are scientifically justified (see section 5.1), and should consider whether any remaining research questions could be investigated after marketing authorization has been granted.
▶ ▶	Governments and funders should allocate greater financial and human resource support for training and continuous education enabling regulatory authorities to improve compliance with rules and ethical guidelines for clinical research and to provide scientific advice

3.5 Implementing GCP

Role of ICH GCP

The principles of good clinical practice (listed in Box 2 on page 32) reflect internationally accepted ethical and quality principles for clinical research. The ICH GCP and related guidelines were originally designed for pre-registration studies. In the European Union, they only apply to interventional studies, but in many regions—in the absence of a widely accepted alternative—they are now applied to a broad range of research.

Applicability in clinical research

WHO recommends that, to the extent possible, the principles of GCP should apply to all clinical research involving human participants, not only clinical trials to develop new products.[5] However, implementation of ICH GCP guidelines involves a copious documentation effort that needs significant on-site resources, often in the form of research nurses, trial pharmacists handling the investigational product, and other healthcare professionals, as well as off-site manpower for clinical trial monitoring at the CRO or pharmaceutical company involved. In resource-limited settings well-trained healthcare providers are scarce at all levels, so that the research may compete with patient care, and trained research nurses are usually not available in the facilities where clinical research is conducted.

The current level of detail required for regulatory submission is often unnecessary for clinical trials of registered products or other types of clinical investigation. Insistence on full, literal application of the current ICH guidelines for all types of studies, regardless of context, can hinder research.

Example: Impact of ICH GCP guidelines in different settings, as described at a joint workshop held in 2018:[123]

(Outbreaks) — "One speaker described the challenges of meeting ICH GCP guidelines in the setting of an Ebola outbreak. For, example, all materials had to be sterilised before leaving the treatment tent and so researchers had to photograph consent forms on a tablet in a protective case that could later be dropped into bleach. She and others expressed concern that such stringent requirements are hampering research, particularly in low and middle-income countries. In a survey of over 5,000

researchers in these countries, respondents overwhelmingly said that they would be unable to conduct a vaccine trial because of the difficulty and cost."

(Community-based trials) — "One example was a cluster-randomised trial in Pakistan… In such trials, obtaining informed consent from every individual as required by ICH GCP is not possible."

(Innovative trial design) — "The ICH GCP guidelines do not anticipate or acknowledge this type of approach. One speaker… pointed out that the guidelines assume the use of frequentist statistical analysis; rather than prescribing a particular school of statistics, he suggested simply requiring that a protocol specifies criteria for success and so allows for use of different trial designs."

ICH GCP renovation

Recognizing these challenges, ICH has initiated a GCP renovation process with an aim to "provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of clinical trial designs and data sources that are being employed to support regulatory and other health policy decisions".[3] The international research community is providing active input to this process.[123,124] In April 2021 ICH published a draft, work-in-progress version of the updated ICH E6 principles on its website to facilitate transparency and a common understanding.[18]

Implementing GCP — Recommendation

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders* *Find examples of these categories on pages 4-6.

▶ ▶ ▶ Good clinical practice (GCP) standards should be applied meaningfully to suit the ethical and scientific requirements of the study. The level of detail required should be proportionate, and sufficient to answer the scientific question.

Note

The CIOMS Working Group determined that for all clinical research the following elements should be considered.

- Respecting needs and priorities in low-resource settings
- Addressing a relevant question
- Choice of the most appropriate study design
- Appropriate choice of study population
- Assessment of potential benefit and harms
- Ethics and informed consent
- Community engagement
- Post-trial access to study medication
- Payment/benefit for participation
- Monitoring and addressing study-related adverse effects

These elements are further discussed in Chapters 4 and 5.

CHAPTER 4.

ETHICAL CONSIDERATIONS

This chapter highlights some of the issues arising in clinical research because of social, cultural, medical, political, financial and infrastructural constraints in resource-limited settings, and possible solutions to protect the rights and welfare of research participants in these settings.

- **The determination in what ways an individual is vulnerable must be made with an understanding of the local context (section 4.1).**
- **This understanding must inform the measures taken to protect research participants in resource-limited settings (section 4.2).**
- **To counter exploitative research, equitable research relationships between partners in low- and high-income settings should be strengthened and supported (section 4.3).**
- **Ethical review in resource-limited settings needs to be strengthened (section 4.4).**
- **Community engagement is essential for ethical, good quality research in resource-limited settings (section 4.5).**

While this report builds on the 2016 CIOMS *International Ethical Guidelines for Health-Related Research Involving Humans*,[1] it is not intended to supersede those guidelines.

4.1 Vulnerability[16] in the context of resource-limited settings

The 2016 CIOMS ethical guidelines describe the characteristics and circumstances that may render individuals vulnerable—such as limited capacity to consent, subordinate position in a relationship, institutionalization, or being a refugee—and additional measures that can be taken to protect vulnerable persons individually or collectively in research. This involves judgments about both the probability and degree of physical, psychological, or social harm, as well as a greater susceptibility to deception or having confidentiality breached.[1, Guideline 15]

[16] In this report the term "vulnerable" describes persons or groups who may have an increased likelihood of being wronged or of incurring additional harm in research. In contrast, the term "special populations" is used to describe populations with physiological characteristics that warrant their being considered separately in clinical research, such as children, pregnant women and the elderly (see Appendix 1). The two categories may overlap.

The determination in what ways an individual is vulnerable must be made with an understanding of the local context of each study, and at each site in a multi-site clinical trial. The circumstances in resource-limited settings can impact potential research participants' decisions in various ways and render them more likely to be wronged or to incur additional harm. Researchers and sponsors should do a tailored analysis of benefits of a study and the burdens for trial participants in the specific context.

Poverty

Extreme poverty closely aligns with low levels of literacy, little or no access to healthcare, acceptance of authority without question and social stigmatization and discrimination. Poverty also severely impacts the social determinants of health *e.g.* due to lack of housing, living in informal settlements and slum-like conditions and little or no access to water and sanitation. In addition, systemic injustices —ranging from economic marginalization to discrimination of ethnic groups in healthcare systems— have given rise to, or perpetuated, vulnerability in some resource-limited settings.

Marginal-ization

This vulnerability can be heightened for particular groups such as sexual minorities, sex workers, persons with mental illnesses, patients suffering from a terminal illness, ethnic or linguistic subgroups, people in riots or conflict areas and people who are refugees, migrants or institutionalized. It is ethically imperative that their health problems are studied towards yielding evidence-based implementable outcomes. In resource-limited settings such groups can be particularly at risk of being sidelined, intimidated, manipulated, exploited or subjected to undue pressure.

Special groups, notably women, and children, are also at risk of being more vulnerable in resource-limited settings for many reasons (see Appendix 1).

Disproportio-nate impact of disease outbreaks

This vulnerability is further heightened in disaster situations. For example, the 2010 earthquake in Haiti had a far worse impact than the earthquake and tsunami that struck northern Japan in 2011,[125] and the lockdown measures during the COVID-19 outbreak disproportionately affected the poor and vulnerable who had less access to health care and social protection.[126] Informal traders and migrants were left with no source of income, resulting in rampant hunger in these groups, and overcrowding in cities, informal settlements, refugee camps and prisons allowed for rapid spread of the virus.

4.2 Protecting research participants

Particular health problems arise in resource-limited settings, and some of these are specific to particular vulnerable groups, *e.g.* migrants and those that are dispossessed. The main aspects that should be considered to protect the rights, welfare, safety and well-being of research participants in resource-limited settings are discussed below. Two examples of how the rights of women can be safeguarded in clinical research are provided in Appendix 1.

4.2.1 Informed consent

The process of obtaining informed consent—and assent in the case of children (see Appendix 1A) and of adults incapable of giving informed consent—should be carefully designed so that potential research participants truly understand the nature and the risks of the study and the fact that they are free to refuse participation or withdraw at any time. It should be made clear that the participants are not offered a new treatment but invited to participate in a clinical study (a common misunderstanding). Participants must also be informed how their privacy will be protected, how their data will be used in the context of the research,[1, Guideline 22] to what extent their biological samples and data will be stored for future uses,[1, Guidelines 11 and 12] and how the study results will be communicated to them (see also sections 4.5 and 5.2). The information should be approved by the REC before being provided to participants.

Obtaining truly informed and culturally relevant consent is particularly challenging in resource-limited settings.[127] These challenges may result in scenarios where participants are asked to sign consent forms that appear to be designed to protect researchers rather than participants, or to sign a sheet of paper, which is symbolic rather than an actual consent process based on understanding and voluntariness. Such practices can act as a disincentive to research participation or even access to health care. Verbal information, and the opportunity for an individual discussion about the benefits and risks of study participation, must be an integral part of the consent process. This discussion should include available options for contraception, if required for the study (see Appendix 1B).

Language barriers

In some cases participants are asked to sign lengthy and detailed forms that they may not understand because of educational, language or cultural barriers. Adequate time and resources should be allocated to ensure that use of local language and translation of information sheets and consent forms are done properly, aiming for consistent translation of key terms (such as “risk”) within and across trials. Translations into the participant’s own language should be proportionate to the original text, and can be supported by visual images or videos.

Illiteracy

Obtaining consent from persons who cannot read or write is challenging. Taking oral consent or asking for thumb impressions in place of signatures has social implications and may instil fear of the unknown in the person giving the consent. Information should be given in the presence of an impartial witness, and understanding must be ensured. The person serving as an impartial witness must be clearly instructed not to influence the participant and to respect confidentiality.

Family and group involvement

Informed consent decisions may not be individual but woven into the family and the community. Also there is often a limited ability to question authority or the caregiver, especially if it happens to be the treating physician. Permission of gatekeepers, which could be the head of the village, leader or other culturally appropriate persons, may be required along with the authorized representatives when dealing with vulnerable individuals. There may be situations that additionally require group consent before individual level consent.

4.2.2 Appropriate indemnity

Research participants should be compensated for the costs that they incur. This can be monetary or non-monetary but must not induce potential participants to participate in the research against their better judgment ("undue inducement").[*1, Guideline 13*] In low-resource settings even a small payment can become an undue inducement. For example, college students and the homeless are well known to be a ready source of research participants globally because of their urgent need for cash. There are situations where individuals in resource-limited settings participate in high-risk studies because of the financial inducements offered.[**128**]

Financial incentives

It has been argued that research participants from both industrialized nations and from limited resource settings should be compensated equally since they suffer the same burdens and equally contribute towards the study by contributing the same product, namely data.[*128*] At the other end of the spectrum, in an investigator-initiated trial in Cameroon the national ethics committee did not agree to any financial compensation being offered because it could hamper future research with less funding, induce participants into trying to satisfy the researchers introducing a possible study bias, and cause patients to come for unscheduled visits if they will get transport money.[**129**] A middle-ground approach would be to aim for compensation that is proportionate to usual income. Community advisory boards (see section 4.5) can provide advice.

4.2.3 Caring for participants' health needs

Researchers have an ethical obligation to care for participants' health needs during research and, if necessary, for the transition of participants to care when the research is concluded. Even though such care may be an incentive for participants in low-

resource settings, it should not be considered an undue influence.[1, Guideline 6] In addition, clinical trials sponsors, researchers and host country governments should make provisions for post-trial access to an intervention identified as beneficial in the trial for all participants who still need it. This information must also be disclosed to participants during the informed consent process.[16]

Post-trial access to interventions

Information gained from clinical trials conducted efficiently and expeditiously may allow early registration of drugs in LMICs, thus considerably enhancing profits for sponsors. It does not seem irrational to expect them to share these benefits with the research participants in LMICs by continuing to provide them with a proven treatment after the completion of the trial. The provisions for continued care should be described in the study protocol. Sponsors and researchers may no longer have an obligation to provide continued access when the intervention becomes available in the public health system. Moreover, sponsors, researchers and community members may agree before a trial starts that any intervention that has demonstrated significant benefit will be provided only for a predetermined period of time.[1, Guideline 6]

Post-trial access to other benefits

According to the Declaration of Helsinki, "*At the conclusion of the study, patients entered into the study are entitled to... share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits*".[16] There may be cases when the participants ultimately do not gain access to the study intervention, even if the company has had it approved and commercialized. In such cases there should be a system whereby participants in low-resource settings derive some other benefit, for example continued access to an established effective intervention that was provided as part of the standard of care or prevention to all participants during the research.[1, Guideline 6]

4.2.4 Compensation for research-related harm

Provisions for compensation in case of research-related harm are not only just but also pragmatic, as a lack of such provisions may disincentivize people from participating and undermine trust in the research enterprise.[1, Guideline 14] This is particularly important in resource-limited settings, where the livelihoods of many research participants and their families are precarious and the efficiency of local insurance mechanisms cannot be taken for granted.

Responsibilities for compensation must be agreed before the research begins, and should involve insurance coverage of the researcher, the sponsor and government.[1, Guideline 14] The ICH GCP guidance has this requirement in its point 5.8.1,[17] and it is now implemented in most regulations worldwide. Provisions for compensation are proposed for example in the Indian national ethical guidelines.[59]

Protecting research participants — Recommendations

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders*

*Find examples of these categories on pages 4-6.

▶ Researchers should allocate adequate time and resources for measures and materials to obtain true informed consent. If written informed consent is appropriate, forms should be as concise as possible. Innovative options for obtaining informed consent using new technologies, such as audiovisual models to ensure better understanding, should be considered where appropriate.[130]

▶ ▶ ▶ Communities should be engaged (see section 4.5) to help design effective measures to protect research participants' rights.

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.

4.3.1 Justifying the burden of research

Clinical research has not only benefits (see 1.5), but also represents a burden for the study population. It exposes study participants to a degree of inconvenience and potential risks, and may absorb scarce individual or health systems resources. In a fair collaborative partnership, the host country should determine for itself whether these burdens are offset by the expected benefits for the community's health,[131] or by other benefits such as the provision of ancillary medical care or the donation of medical equipment, although weighing such indirect benefits requires a great degree of effective independent oversight by RECs.[132]

Local and foreign REC approval

Externally sponsored research must be approved in the country of the sponsor as well as locally. The ethical standards applied locally should be no less stringent than they would be for research carried out in the country of the sponsoring organization. Local committees must be fully empowered to disapprove a study that they believe to

be unethical.[1, Guideline 23] Review by both the local and the foreign REC ensures that the protocol complies with all relevant requirements (see page 91 for an example), and is an opportunity to highlight and discuss any differences between the underlying standards.

Integrating research with routine patient care

In resource-limited settings, integrating clinical research with local health care services can be a rational, ethical and effective approach, provided that the input of local ethics committees and institutions is considered, sponsors acknowledge their ethical obligations, and patient care is not subordinated to scientific gain.[133] Many studies in resource-limited settings are conducted in busy hospitals, where doctor-to-patient ratios are often very low. Beyond the relevance of the research question itself, ethical review should also consider the impact of the study on patient care. For example it would be unethical for a researcher to reserve resources for use in study patients while turning away patients in need of basic healthcare services. Research must be adequately provisioned with personnel so that there is no diversion of human resources from routine care.

4.3.2 Standard of care

An often debated matter is the appropriate standard of care to be offered to participants in clinical trials. Ideally, participants in clinical trials should be offered the best standard of care available globally for the disease being studied. However, for most diseases and conditions such a 'universal standard of care' is routinely available to only a small proportion of the world's population.[134]

Sustainable standard

Health care in low-resource settings is limited. In the past, clinical trials comparing an intervention to a low standard of care (the current practice in many settings) have been challenged as unethical. Yet providing an unaffordable or unsustainable level of care in a trial, which cannot then be continued after completion of the trial, may provide a misleading result, thereby denying the opportunity for improvement.

Locally relevant interventions

The CIOMS ethical guidelines state that research must be responsive to the health needs and priorities of the community in which it is to be carried out.[1, Guideline 2] This means that research should aim to identify interventions that are locally relevant and will be used to benefit the community. Examples are rectal instead of parenteral artesunate in severe malaria for patients in rural environments en route to transferral clinics,[135] or relatively affordable and more feasible shorter courses of zidovudine given to pregnant women in developing countries to reduce the risk of mother-to-child transmission of HIV.[136]

Standard of care in the control group

In some circumstances it may not be possible to adopt a universal standard of care in national health care systems. In other circumstances, providing a universal standard of care to the control group in a trial may not provide results that are relevant to the

country in which the research is conducted. Sponsors of research or investigators cannot, in general, be held accountable for unjust conditions prevailing where the research is conducted, but they must refrain from practices that are likely to worsen unjust conditions or contribute to new inequities. Where it is not appropriate to use the best internationally available interventions because they would not be sustainable in the local context, the Nuffield Council on Bioethics recommends that:

> *"... the appropriate standard of care to be provided to members of a control group in a research project can only be defined in consultation with those who work within the country in which the research is to be conducted. It must then be justified to the relevant research ethics committees. Wherever appropriate, participants in the control group should be offered a universal standard of care for the disease being studied. Where it is inappropriate to offer such a standard, the minimum that should be offered is the best intervention currently available as part of the national public health system."*[134]

The World Medical Association's Declaration of Helsinki is also clear on this issue. For compelling and scientifically sound methodological reasons it can be necessary to use an intervention that is less effective than the best proven one to determine the efficacy or safety of an intervention; however, in such cases the patients who receive that intervention must not be subject to serious or irreversible harm as a result of taking part in research.[16]

The CIOMS position

The CIOMS ethical guidelines take the stance that any potential new intervention should be tested against an established effective intervention, and that researchers may only deviate from this rule when withholding or delaying such interventions is methodologically necessary and exposes participants to no more than a minor increase above minimal risk.[1, Guideline 5]

A controversial 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.

4.3.3 Countering "ethics dumping"

In recent years, organizations and companies from high-income countries (HICs) have been increasingly conducting clinical trials at study sites in resource-limited settings. Possible motivations for this include the desire to redress unmet health needs and develop research capacity in low-resource settings, but sometimes also the prospect of speeding up drug development, or of conducting cheaper research with easy availability of human participants with communicable and non-communicable diseases.[142] The inequalities and differences that exist between HICs and LMICs pose significant risks of exploitation during the conduct of externally sponsored research.[143] Inappropriate research practices can also occur in cases where external researchers are unaware of local ethical guidelines or fail to adhere to all the requirements.

Persisting inequities

While ethical standards and governance mechanisms to ensure compliance with them are well established in HICs, the same is not necessarily true in LMICs. Many LMICs may have established ethical standards at the national level, but ensuring compliance with these standards is resource-intensive and not always possible (see section 4.4). These inequities continue being of major concern in international collaborative research. Unequal North-South collaborations, while not generalized, continue into the 21st Century, with researchers conducting investigations in LMICs that would not be allowed in their home countries because they are unethical.[144-146] Such studies serve the scientific goals and profit motives of researchers from HICs, while impeding the host nations' ability and/or attempts to raise their standards to internationally acceptable levels.[144] The European Commission has termed this practice "ethics dumping".[145,146]

Reasons for ethics dumping

Ethics dumping can occur in two main ways.[144] Firstly, there can be intentional exploitation of research participants and resources in LMICs. This could occur when the research is prohibited in HICs (*e.g.* invasive experiments on wild-caught non-human primates.[147]) Secondly, there can be insufficient ethics awareness on the part of the researcher, while at the same time the capacity for effective research governance in the LMIC may be low. Either way, ethics dumping equates to the practice of double standards in health research.[148] Although it has been criticized for many years there is still evidence of its continuing existence.[144]

Global code of conduct

In an attempt to remedy the situation, the European Commission has commissioned the development of a *Global Code of Conduct for Research in Resource Poor Settings*,[6] making it a condition for all new research funding applications that undertake research in LMICs. Other research organizations have followed suit. The Code opposes double standards and prioritises equitable relationships between partners in HICs and LMICs based on the values of fairness, respect, care and honesty.[149]

Fair research partnerships

Achieving fairness in research partnerships is, in essence, a complex policy and management challenge. The COHRED Research Fairness Initiative (RFI) provides a framework and reporting system to promote fair and equitable research partnerships throughout the research endeavour.[150]

Avoiding exploitative research — Recommendations

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders*

*Find examples of these categories on pages 4-6.

▶	The priority-setting exercise for clinical research should involve the relevant local bodies, and should take into account vulnerable groups. Before approving the study the local authorities may wish to negotiate with the sponsors how the benefits will be shared with the local population.
▶	Ethical review should consider whether sufficient resources are available at the study site to avoid any negative impact on routine patient care.
▶ ▶ ▶	Research projects initiated by sponsors from HICs should be approved by a REC in the host country, wherever this exists, as well the REC in the high-income setting.[6]
▶ ▶ ▶	Adherence to the Global Code of Conduct for Research in Resource Poor Settings [6] will oppose double standards in research and support long-term equitable research relationships between partners in lower-income and high-income settings.

4.4 Ethical review and capacity-building

Research ethics committees (RECs) have a central role in ensuring that the general ethical principles for clinical research are followed. All proposals to conduct health research where humans are involved must be submitted to a competent REC for review of their ethical acceptability. Ethics review by RECs is required by international ethical governance standards [1 *Guideline 23; 16*] and by local law in most regions and countries.[74,151] WHO has provided guidance on the standards and their implementation in Member States.[152,153] REC approval or clearance is mandatory before research begins. Ethics review is also requisite for publication of results, as most journals will not publish research that has not received REC approval. This section describes the responsibilities of RECs and shortcomings in resource-limited settings, and approaches to strengthen ethical review in those settings.

4.4.1 Responsibilities of RECs

Ethics review must be independent, unbiased, objective and informed, and REC members must conduct themselves without fear or favour during the review process. While the main responsibility of RECs is to protect potential and enrolled research participants, potential risks and benefits for the communities in which the research is

to take place must also be taken into account. The ultimate goal of an REC is to promote high standards of ethics in research. The ethical acceptability of a study includes, among other things, its social value and scientific validity.[153] The main responsibilities of RECs are shown in **Box 4**.

RECs may operate on an institutional, regional or national basis. The advantage of institutional RECs is that they are familiar with local conditions and can engage in closer monitoring of ongoing studies; the main disadvantage is that they may feel constrained in rejecting or requesting major modifications to studies due to institutional financial interests in attracting external funding. While regional and national committees are further removed from the site at which research is being conducted, they may provide greater consistency and may have greater legitimacy in the eyes of the research communities and the public.

Box 4. Responsibilities of research ethics committees (RECs)

- Reviewing research protocols and proposals to ensure that research will be conducted in the spirit of endeavouring to promote health and to prevent or cure disability and disease.
- Ensuring that research participants are treated with dignity and that their safety and well-being are not compromised.
- Ensuring conformity to internationally and locally accepted guidelines and standards.
- Ensuring that true informed consent is obtained to the research throughout its phases. This involves evaluating the process and materials to be used for early community engagement, recruitment and enrolment of participants, updates about ongoing research, and sharing of outcomes once the research is concluded.
- Assessing incentives to be given to participants.
- Identifying and weighing risks and potential benefits of research.
- Evaluating risks to participants' confidentiality and related risks of discrimination.
- Evaluating the adequacy of confidentiality protections.
- Ensuring that participants and communities receive fair benefits.
- Ensuring that participants will receive adequate care and treatment (if medical interventions are used).
- Ensuring adequate provisions for research-related injuries (medical, psychological and social).
- Granting approval when research protocols and supporting documentation meet scientific and ethical standards.
- Reviewing amendments to research protocols according to national regulations
- Providing ethics oversight for approved research by monitoring studies once they have begun.
- Taking part in follow-up action and surveillance where relevant.

Other functions of RECs include:

- Setting policies.
- Offering opinions on ongoing ethical issues in research.
- Assessing the investigator's qualifications to perform the proposed research.
- Keeping researchers updated of ethical and regulatory requirements, and ensuring compliance.
- Protecting researchers from unjustified criticism *e.g.*by local individuals or groups.

4.4.2 Accelerated review

Accelerated reviews have two main uses.

Low-risk studies

Firstly, they can be a way to focus limited REC capacity where it is most needed. Accelerated review (sometimes called expedited review) allows for studies that carry no more than minimal risk to be reviewed and approved promptly by an individual REC member or a designated subset of the full committee.[*1, Guideline 23*]

Emergencies

Secondly, at times of emergencies ethics review must occur very rapidly to enable a quick response to emerging research needs.

RECs should innovate in developing fast-tracked review processes. There must be clear standard operating procedures for expedited and rapid reviews. A useful source of information for the latter is the WHO *Guidance for research ethics committees for rapid review of research during public health emergencies*.[**154**]

4.4.3 Need for capacity-building

There are three conditions necessary for RECs to safeguard the rights of research participants successfully. Firstly, they must be capable of managing applications for research with human participants independently, based on their understanding of the relevant ethical aspects, the scientific rationale of the proposed studies and how the ethical aspects apply to different types of research. For this purpose they must have access to adequate resources including independent scientific advice if necessary. Secondly, they must be able to recognize culturally sensitive ethical issues in complex settings. Thirdly they must have mechanisms in place to ensure that researchers comply with the requirements established by the REC. An effective REC should be viewed as critical to the research process, not as just another "rubber-stamping" committee.

The reality in LMICs is that it cannot be taken for granted that the RECs can function to a globally acceptable standard. A recent survey among national ethics committees from 84 countries, including 38 LMICs, has revealed a general lack of resources and challenges influencing the committees' sustainability, effectiveness, impact, accountability and independence.[**155**] Capacity-building programmes exist, but trainees may encounter numerous impediments when they attempt to put the lessons learnt into practice.

Shortcomings in LMICs

Ethics guidelines in many LMICs do not reflect internationally recognized standards of ethics or, where they do, these standards are not implemented and enforced through mandatory legal and regulatory structures.[*144*] As a result, the process and requirements for the approval of clinical trials are very often not well defined, and there is often excessive bureaucracy. Requested documents and format, review and

response times can differ substantially between countries, and different approval processes can occur in the same country, with sequential or parallel submission to ethics and regulatory agencies. Sometimes approval processes involve five or more bodies; and ethics reviews are done in duplicate. There is usually no quality assurance of ethical review.

Constraints of RECs in LMICs

Some of the constraints reported from African RECs [144,156] are listed below. These challenges occur in most LMICs. Several of them also apply to HICs; however, they are more pronounced in LMICs.

- Resources being inadequate
- RECs being composed of scientists, with little or no effective participation by patient and community representatives
- REC members having insufficient or at times no relevant expertise
- REC members not participating actively or consistently
- The importance of REC functions not being recognized
- The REC receiving very little or no support from its institution
- REC members not being paid for their demanding and time-consuming work, which is a disincentive to otherwise busy good evaluators.
- Occasional interference with independent functioning due to corruption, pressure from researchers or sponsors, political or institutional conflicts or vested interests of REC members

Working language

In non-English-speaking countries, the above-mentioned constraints are reinforced by the fact that the large majority of ethics and regulatory guidelines, international meetings, training courses and networking opportunities are in English. Non-English speakers remain excluded from these capacity-building opportunities.

Conse-quences

As a consequence of these constraints, there is a risk of reviewing practices not being uniform, applicants being treated unequally, inconsistent judgements, poor quality reviews resulting *e.g.* in approval of uninformative studies or rejections for reasons unrelated to critical scientific or ethical concerns. Significant delays of the approval process happen quite frequently and can impact clinical research: patient recruitment might be missed (*e.g.* during the malaria season), logistics are disrupted, drug supply is limited due to expiry dates, and staff turnover may require additional training and re-training. Prolonged study durations increase costs, and access to new or optimized treatments for patients is delayed. In some cases the anticipated bureaucratic obstacles prevent research from taking place at all.

The CIOMS ethical guidelines highlight the responsibility of external researchers to help establish and educate RECs according to their ability before the research is initiated,[1, Guideline 23] and to provide guidance on collaborative partnership and capacity-building for research review.[1, Guideline 8]

Ethical review and capacity-building — Recommendations

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders*

*Find examples of these categories on pages 4-6.

▶			Governmental authorities should consider setting up national ethics committees to promote consistency and avoid unnecessary duplication of work in regions where several RECs exist. Institutions could consider having joint RECs or common reviews for multicentre research.
▶		▶	Governments, international organizations and sponsors of research projects should invest in capacity-building for RECs in resource-limited settings, including training on scientific research, training for expedited and rapid reviews, and elements of follow-up, monitoring and evaluation.
▶			REC review should be based on the protocol and complete, up-to-date supporting information, and should include a determination whether the proposed clinical study is scientifically sound and justified.
▶			RECs should examine their internal processes to reduce unnecessary bureaucracy, streamline their functions, and harmonize processes with those of other RECs in the country or region.
▶			Reliance between RECs in national ethical frameworks should be encouraged to reduce duplication, except where separate reviews are needed to address local contextual factors.
▶	▶	▶	Ethics committees should be empowered to function independently of any institutional, external pressure or conflict of interest, and to take unbiased decisions.
▶		▶	International initiatives to strengthen ethical review, including those of WHO,[157] should be supported.
		▶	International organizations, sponsors and funders should make efforts to reduce the language barrier in capacity-building by providing documents and organizing events in languages other than English.

4.5 Participant and community engagement

The 2016 CIOMS ethical guidelines call for researchers and sponsors to engage communities in an early and sustained manner throughout all stages,[1, Guideline 7] and point to a successful example where this has built confidence and trust to gain the community's support of research.[158] In resource-limited settings, engagement of local stakeholders, including community members, study participants and family, is crucially important for researchers to consider how cultural norms and other local factors impact the research. The community's own leaders are key stakeholders in the community engagement process. Local researchers and clinicians also play an important role, as they facilitate recruitment of participants and are sometimes seen by the community as their gatekeepers.

4.5.1 Methods of community engagement

Community engagement measures undertaken by investigators should include meetings with local community leaders and health care providers to explain the research aims and answer questions and concerns voiced by the community. This requires upfront investments but can pay off by leading to more valid results and facilitating the uptake of the research findings. The investigators should also engage with prospective trial participants and family members to learn about their life circumstances, local practices and beliefs that might influence the conduct of the study.

Engagement with trusted persons

The successful implementation of a clinical trial is directly dependent upon a good relationship with the local community to keep stakeholders informed of the aims and objectives of the project and the possible outcomes. Local health care providers are important points of contact as they are consulted by people in the area, and may be involved in the research itself or in the implementation of its findings. In rural or semi-rural areas, village leaders, elders, and religious leaders are often seen as the most trusted authority figures. Engagement with such individuals is an important means of gaining the trust of the local community, explaining the project goals, describing the complexities of likely risks and benefits to prospective study participants, facilitating informed consent, and seeking advice on appropriate indemnities for study participation.

Community advisory boards

Community advisory boards are valuable in planning and implementation especially of large multinational clinical trials in resource-limited areas. A recommended method of community engagement is to have an initial briefing, followed by repeated consultations and progress updates, the frequency of which depends upon the level of information exchanged, stage of research, and issues or problems needing to be addressed.[159,160]

Need for sustained engagement

The process of setting up and maintaining a community advisory board takes considerable time and effort to be functional and effective. The relationship with community representatives begins with consultation and eventually leads to collaboration, as they contribute vital local knowledge on local factors that are relevant to the effective operation of the trial and how these factors might be addressed. Standing clinical networks (section 2.3) can provide a useful basis for sustained community engagement.

Community engagement plan

While researchers are often required to write an entire statistical analysis plan as part of their study protocols, there is often little or no mention of plans for community interaction. Community engagement and communication require special skills and financial resources. A formal plan for participant and community engagement before, during and after the study will help researchers to ensure that they are adequately equipped in this regard.[161]

4.5.2 Benefits of community engagement

Trust-building

Local community relationships are vital in understanding and dispelling myths, rumours or misconceptions that have the potential to undermine trust in the aims and potential benefits of this study. Two examples follow.

A Kenyan researcher mentioned that "Where blood, placenta or hair samples are collected, rumours always arise with the researchers labelled as devil worshippers."[17]

Media messages from different stakeholders about two Ebola vaccine trials in Ghana, gave rise to rumours that the trials were secret, that the vaccine could cause an Ebola outbreak in Ghana, and that improper incentives were offered to participants. This resulted in the trials being suspended.[162]

Community health workers can be especially helpful to explain the basic concept of a clinical trial, the scope and objectives of the study and its likely impact on the community and provide updates. This approach is instrumental in gaining and maintaining the trust of the local community and ensuring that the research respects its welfare and interests.[163]

Community education

Effective communication with potential participants as well as their family members is essential to explain the aims of the study, gain support for the research and obtain true informed consent (see 4.2.1). It also helps the researchers to understand the needs of the participants during study implementation better, to customize the research accordingly (section 5.1), and to communicate the findings of the research back to the participants (see 5.2.2).

[17] Personal communication J. Kimani, 14 December 2020

Secondly, community engagement provides a platform for wider information-sharing. It enables researchers to inform community leaders about the objectives of clinical research and of the specific study, to discuss topics of which there may be limited local awareness, such as patient autonomy and the voluntary nature of research participation, and to communicate the outcomes of the research to the public.

Adapting to local customs

Feedback from community representatives provides information on assumptions, customs and beliefs that are pertinent to the successful conduct of the trial. This helps researchers to adapt the study design and conduct to local circumstances, and can lead to adaptations and improvements to the trial protocol such as additional clarification on exclusion and inclusion criteria, inclusion of plans to ensure prompt follow-up, and specification of mitigation strategies to avoid loss to follow-up. Support from community leaders can be very valuable in conducting studies that have a cultural dimension.

Example: A male circumcision study was easier to implement when support from community leaders was sought and received in a non–circumcising tribe in Kenya.[18]

Negotiation of benefit-sharing

Community engagement enables a discussion of the expectations and perceived benefits from the trial. While it is the sponsors who decide where they would like to invest into clinical trials, local communities should be free to bargain for the benefits that they view as most valuable in exchange for allowing a trial to proceed.

Access to a new health intervention is the most obvious benefit from a clinical trial. A study intervention may not become reasonably available to the host population immediately once it has proven to be effective. However, this should not be a reason to consider participation in the study as fruitless. The new intervention may still become available in the longer term, as happened for example with antiretrovirals and hepatitis C products.

Communities might also derive indirect benefits from the research. The study participants may have access to basic health care which would not be available to them otherwise, or the community may benefit *e.g.* from local capacity-building or infrastructure development, although it is not always straightforward to appraise the effects of such indirect benefits [*132*] (see also 2.3.3). Communities may also wish to negotiate for longer-term benefits to improve their life circumstances as a way to address background injustices.[164,165]

[18] Personal communication J. Kimani, 14 December 2020

Participant and community engagement — Recommendations

- For governments and regulatory authorities*
- For researchers*
- For funders*

*Find examples of these categories on pages 4-6.

	▶	Where necessary, researchers should educate community representatives on basic knowledge of what a clinical trial is, how it differs from routine health care, and the specific protections provided for trial participants.
	▶	Researchers should develop formal plans on how they will communicate with participants and the local community throughout the clinical trial or study continuum in a meaningful way. (See also section 5.2)
▶	▶	Communities in resource-limited settings should be empowered to negotiate for fair benefits of clinical research. This will require support by an effective independent local REC (see section 4.4).

CHAPTER 5.

SCIENTIFIC CONSIDERATIONS

This chapter describes two of the main elements that are essential for advancing clinical research in resource-limited settings.

- **The social and scientific value of research depends on a relevant research question and good study design (section 5.1)**
- **Responsible sharing of information and data is essential to make the best possible use of limited resources and avoid unnecessary duplication of research (section 5.2)**

5.1 Conceptualizing and designing research

To justify the burden that clinical research represents for participants, clinical studies must yield robust conclusions on the efficacy, safety, benefits and risks of an investigation or intervention, that can be translated into health benefits and/or inform future research. Any health-related research must have a scientifically sound design and must offer a means of providing information not otherwise obtainable.[1, *Guideline 1*] The study design is important to establish data integrity and credibility of the findings. Common designs for medical studies and issues in their implementation, have been described in literature.[166] Randomized controlled trials are the gold standard in evaluating healthcare interventions.[167] They are increasingly complemented by so-called real-world studies, clinical practice observations and use of electronic health records [168] (see Appendix 2). Uninformative studies, *e.g.* poorly designed and underpowered studies, should be avoided.

Key questions The following questions should be asked when designing a clinical study in resource-limited settings:

▷ Will the study design answer an important medical question?
▷ Is the study population representative of the target population?
▷ Will the research findings directly or indirectly translate into benefits for the local population? (See also 4.3.1)

(continued)

(Key questions, continued)

- ▷ Is the study design feasible and adapted to the local needs and circumstances? Are sufficient resources and infrastructure available to make the appropriate measurements and store samples and study drug and documentation appropriately? (See section 2.3.)
- ▷ Is the design suitable, are the sample sizes large enough, and is the proposed statistical analysis adequate to answer the question?
- ▷ Where required, are there adequate randomization and blinding procedures that can be implemented in the environment where the study will take place?

5.1.1 Appropriate research question

Addressing local health needs

A clinical investigation in a resource-limited setting should seek to answer a question that is relevant to the disease or populations being studied. For example, the following aspects may need to be investigated in the local medical context.

- Diseases that affect people in resource-limited settings disproportionately (*e.g.* certain communicable, neonatal, maternal and nutritional diseases, neglected tropical diseases)
- genotypic differences between populations which would eventually allow for more targeted or more appropriate interventions [169] (see also Appendix 5);
- need for adapted products and approaches to diagnosis, triage and treatment for populations living in remote areas;
- local co-morbidities and nutritional specificities, which could impact outcomes and make the results of these studies hard to extrapolate to other populations; and/or
- traditional medicine practices,[170] which could be researched as health interventions in their own right, or in the context of a study intervention as they may either mitigate its results or augment its benefits.

5.1.2 Study population and sample size

Sample size estimation

Estimating the required sample size is a crucial part of study design to ensure that studies are sufficiently powered to detect clinically relevant findings without burdening an excessive number of participants. Conventional power equations can be an efficient approach for standard designs, but they are unavailable or unsuitable for many complex study designs. In these situations, computer simulation techniques can be a useful and flexible alternative.[171]

Representativeness

Strict eligibility criteria that generate a homogeneous study population make it easier to detect statistical differences between interventions, but may exclude important patient subgroups. A more heterogeneous population is likely to be more clinically relevant and allows better characterization of the factors affecting responses to the health intervention under study. On the other hand but it increases the sample size that is needed to show a treatment effect.[166]

Related to this, the design, conduct and interpretation of any clinical study will benefit from knowledge of the study population in terms of the epidemiological setting, key behavioural factors, economic status, relevant host genetics, *e.g.* pharmacogenetics (see Appendix 5), diet, anthropometric data, prevalence of infections and other diseases, normal laboratory values and other factors. Unfortunately much of this information is often unavailable.

Inclusiveness

It has been recognized that patients that have historically been excluded from clinical trials—*e.g.* children including neonates, pregnant women and the elderly—may have different pharmacokinetic and pharmacodynamic characteristics than other populations and should therefore be included (see Appendix 1). This is especially relevant to resource-limited settings. Local context must be taken into account when defining the inclusion criteria for research participants from a low-resource setting.

5.1.3 Adaptive study designs: less is more

In order to make clinical trials faster, less costly and more successful, novel strategies in study designs have been implemented in recent years.[172] In conventional clinical trials, the protocol of a study is determined before the first patient is enrolled. Newer methodologies are more flexible. With adaptive designs, researchers can monitor the incoming data and adapt the protocol based on pre-established criteria as the study unfolds, for example by dropping or adding doses, adapting the size or duration of a trial, or enriching the study population by adding more of the types of patients who respond to the treatment being investigated.

Adapting to local context

Elements that can substantially enhance the value of a clinical trial in a resource-limited setting also include:

- Relevant genotyping (patient, infective organism);
- measurement of drug levels – particularly heat-stable, dry blood spot filter paper-based; new micro-sampling technologies are valuable especially for use in children, where collection of blood is limited for ethical reasons (see Appendix 1A)
- adaptive methods of data collection, such as mobile phone app-based data gathering;
- use of recent technology such as wearables during trial conduct where appropriate (see Appendix 2); and
- use of portable analysers.

Adaptive designs can benefit investigators as well as patients, since the sooner it is proven that a drug or a dose of a drug either works or doesn't work, the sooner that drug can either be advanced or its evaluation in patients can be stopped. On the other hand adaptive designs require much greater attention from statisticians and data safety monitoring boards, as they rely on rapid analysis and data transmission. This may be possible in the context of well-supported industry-led pre-registration

studies, or with the exceptional support made available in public health emergencies of international concern,[173] but in resource-limited settings the support required to run adaptive trials is often lacking. The discussion on the utility of adaptive designs is ongoing.

Regulatory perspectives

At this time, regulatory agencies tend to review proposals for adaptive designs with greater scrutiny than they give to conventional designs, possibly because adaptive designs are a new approach. As with any research, there must be a clear design rationale, a demonstration of statistical validity, simulation-based operating characteristics, and a comprehensive charter for the data and safety monitoring committee that addresses both the interim decision rules and the manner in which operational bias will be prevented.[174] Regulatory agencies have opined favourably on adaptive designs,[175,176] and an ICH expert working group is developing harmonized principles for regulatory review.[177]

Conceptualizing and designing research — Recommendations

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders*

*Find examples of these categories on pages 4-6.

▶	Funders and institutions conducting research should recognize the value of information about the study population and its importance in assessing the potential impact and benefit of medical research. Community engagement may provide access to valuable information (see section 4.5).
▶ ▶ ▶	Research to address the health needs of children and women, including pregnant women, should be actively encouraged (see Appendix 1).
▶	Both industry-sponsored and academic research in resource-limited settings should focus on relevant research questions that will help to achieve a clear health benefit.
▶	Researchers should consider the use of adaptive study designs and data collection, where possible and appropriate.
▶	As a rule, to minimize the burden on the local infrastructure and population, data collection should focus on those variables that provide needed scientific information for the study.
▶	Research protocols should be adapted as much as possible to local clinical practice, e.g. regarding frequency of visits and sampling.
▶ ▶ ▶	Governments, international organizations and sponsors should support education on research methodology and study designs in resource-limited settings, as well as building the necessary infrastructure (see section 2.3).

5.2 Responsible information-sharing

The CIOMS ethical guidelines underline the importance of public accountability for realizing the social and scientific value of health-related research, and call for prospective registration of health-related research and timely publication of the outcomes.[1, Guideline 24] Sharing of information on clinical trials, data and samples where relevant can maximize their use to support safe and effective health care and sound regulatory decision-making. Information-sharing can also increase accountability in the design, conduct, analysis, and reporting of clinical trials.

These considerations are particularly important in resource-limited settings, where communities are at a greater risk of being disadvantaged, and where many people are unwilling to participate in studies due to limited knowledge about research, distrust and safety concerns.[41] At the same time, transparency and collaboration are particularly challenging to achieve in resource-limited settings, as data management and information-sharing require adequate human resources, infrastructure and sustained support.

5.2.1 Trend towards information-sharing

Industry, academia, sponsors, and regulatory authorities are increasingly encouraging information-sharing on clinical research and its outputs.

Regulators

Registration of clinical trials is required in some jurisdictions, including the U.S. [178] and the EU.[179] Both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) now provide public access to data submitted in regulatory applications [180,181] and EMA has an initiative to publish clinical trial study reports after a marketing authorization is issued, with a mechanism for sensitive information to be redacted.[181]

Scientific journals

Journals publishing study results also demand registration: the International Committee of Medical Journal Editors (ICMJE) requires disclosure of information on planned, ongoing, and completed clinical trials as well as protocol details and study results as a condition for publication.[182] Initiatives such as Cochrane, AllTrials, and the OPEN Consortium (To Overcome failure to Publish nEgative fiNdings) are advocating strongly for greater transparency in results reporting.

The research community

European and American industry associations have committed to principles of responsible data-sharing and to good practices in data-sharing with researchers, making clinical study information publicly available, sharing results with participants in clinical trials and publishing clinical trial results.[183] From the patients' perspective, TransCelerate has proposed three guiding principles for patient-based clinical trial registries of the future—accessible, informative and trustworthy—and presented a

wireframe concept of what a registry should look like.[184] The case for open data has also been made by major organizations representing global science.[185]

Information-sharing in LMICs

LMICs have been largely absent from the discussions on "open data"[19], as in many of them problems of slow internet connection speeds, out-of-date hardware and software, computer sharing and limited time to work online, lack of proxy servers, inability to access library resources off campus, and shortage of qualified technical support make it more difficult to implement an open data policy.[186-189] The recent increase in research funding and resulting data from LMICs has brought scientists from LMICs into discussions on open data, both as contributors and users, for example through the Africa Open Science Platform.[190]

Data protection

Most people do not object to their data being stored and used for research for the common good.[1, Guideline 12] Nevertheless there is a need for a regulatory and research framework to address individual data protection requirements and legal and administrative concerns. This is a challenge globally, and not all LMICs have effective such frameworks. While it is important to protect the privacy of research participants, overly strict privacy laws can also pose an impediment to data-sharing. This risk can be mitigated if the research community is consulted whenever data protection laws are designed or updated.

Example: South Africa's Protection of Personal Information Act (POPIA) [191] was modelled on an early draft of a the EU's General Data Protection Regulation (GDPR),[192] and while the GDPR was later modified to make exceptions for research, the POPIA was not.[193] The POPIA is restrictive in that it states that personal information, including genetic data, must be collected for a "specific, explicitly defined and lawful" purpose, and that data subjects need to be "aware of the purpose." This could mean that sharing of data for future research would be unlawful in terms of the POPIA.

The bottom line

The incremental costs and resources to support and sustain the data-sharing component of clinical studies should be weighed against the potential benefits from improved regulatory and public health decisions, which will translate to more effective allocation of resources for health interventions and further research. Nuanced solutions will be needed to incentivize data-sharing activities and strengthen data science capacity in the highly complex and varied environments of LMIC research settings.[186]

[19] "Open means anyone can freely access, use, modify, and share for any purpose (subject, at most, to requirements that preserve provenance and openness)." Source: http://opendefinition.org/

5.2.2 Forms of information-sharing

Clinical trial registries

A clinical trial registry is a platform for entering information on clinical trials. It is a key tool to support transparency and sharing of results—which are essential to make the best possible use of limited research funding and resources— and to inform patients and their health care providers of the opportunities to participate in these trials. Registries are often searchable, *e.g.* by disease/indication, drug, study size, sponsor, or location.

Global platform

Most registries accept national or international trials from all over the world. ClinicalTrials.gov, run by the U.S. National Library of Medicine, was the first online registry for clinical trials and is the largest and most widely used today. To enable transparency and disclosure WHO created in 2005 a global registry platform, the International Clinical Trials Registry Platform (ICTRP), which provides a consolidated view of clinical trials globally. Researchers can register their trials in any of the registries in the World Health Organization (WHO) network.[194]

Common elements in clinical trial reporting

Re-affirming the ethical imperative of registering clinical trials and reporting their results, the signatories of a joint statement have agreed to include the following elements in research institutions' policies: (1) Registration of clinical trials in a registry complying with WHO's international agreed standards before the trial starts, and regular updates thereafter; (2) publication of the results in the registry within a year from primary study completion and/or in a journal within two years, including the trial's registry identifier for easy linking; and (3) reporting past trials and their status, for consideration in the assessment of subsequent funding proposals.[195]

Local and regional registries

Easily accessible and user-friendly local clinical trial registries that are adapted to local needs are a useful entry point for patients and healthcare professionals to access information about clinical trials and other clinical research being conducted in their region. Local registries with a multi-lingual interface can facilitate registration of trials in languages other than English.[196] Where available and applicable, researchers should consider registering their trials in a local or regional clinical trials registry meeting ICTRP criteria [197].[20]

Patient- or disease-based registries and cohort studies

Patient- or disease-based databases are being increasingly implemented in clinical research. They enable collecting data from patients with rare and uncommon diseases and are excellent tools for post-licensure long-term follow-up of studies and

[20] In April 2021 the WHO ICTRP criteria for accepting trial records were met by registries in Africa (PACTR), Australia and New Zealand (ANZCTR), India (CTR-I) Brazil (ReBEC), China (ChiCTR), the Republic of Korea (CRiS), Cuba (RPCEC), Iran (IRCT), Japan (JPRN, with four network members), Lebanon (LBCTR), Peru (REPEC), Sri Lanka (SLCTR), Thailand (TCTR), as well as five regional or global registries predominantly containing trial records from Europe and North America. (The full names of the registries are shown on the WHO ICTRP website.)[*197*]

for identifying rare treatment-related side effects. They can also be used in assessing the effectiveness of new treatments in various populations. At present most disease-based registries are owned by academic institutions, learned societies or disease-specific consortia; they can be national or international, and they can include all patients or just specific groups of patients.

Disease-based databases can be managed with limited resources by integrating data collection into everyday clinical practice. For example, the WorldWide Antimalarial Resistance Network (WWARN) has a database containing individual patient data from over 70% of all antimalarial drug trials conducted in the modern era. In HIV infection several databases of patient cohort studies have been developed, mostly but not only in industrialized countries (**Table 1**). Patient- or disease-based databases can be implemented in resource-limited settings at reasonable costs.

Table 1. Examples of disease-based databases: Selected HIV cohort studies

A. Swiss HIV Cohort Study,[198] started in 1988
B. The United Kingdom Collaborative HIV Cohort (UK CHIC),[199] started in 2001
C. The HIV-Brazil cohort study,[200] started in 2003
D. Swedish InfCare HIV Cohort,[201] started in 2003, national registry from 2008
E. Australian HIV Observational Database (AHOD),[202] started in 1999, expanded to New Zealand from 2014
F. AFRICOS, Kenya, Nigeria, Tanzania, Uganda,[203] initiated in 2013, 15-year study

	Population	Main objective	Data collection methodology
A.	People living with HIV (PLWH) in Switzerland, including Swiss Mother and Child HIV Cohort Study (MoCHiV) > 20000 participants end of 2018	To provide optimal patient care, to reduce HIV transmission, to conduct research on HIV treatment, pathogenesis, co-infections, immunology and virus-host interactions	Informed consent needed. Annual data collection from centres based on general study protocol (demographics, clinical data with risk assessment, and antiretroviral therapy)
B.	PLWH aged ≥16 years presenting in collaborating centers > 50,000 records end of 2020	To investigate the clinical outcomes, response to treatment and epidemic dynamics of HIV-1 in the UK	Annual electronic data collection: demographics, AIDS diagnoses and deaths, results of various laboratory tests, antiretroviral drug use and hepatitis co-infection.
C.	PLWH followed in 26 public health care facilities (convenience choice) 6109 HIV-infected adults at the end of 2012	To analyze the effectiveness of combination antiretroviral therapy (ART) and the impact of this treatment on morbidity, quality of life and mortality	Data collected every 6 months using routine clinical care data and self-reported quality-of-life questionnaires
D.	PLWH receiving care in Sweden >7600 participants in August 2018 (>99% coverage)	To create good, equable care regardless of method of infection, gender and care provider by identifying problems and improvement potential	Annual data collection from centres based on study protocol
E.	Patients at 30 HIV clinics throughout Australia and 2 sites in New Zealand 4466 patients at the end of 2017	To describe the treatment environment for HIV positive people in Australia. Supports State and Commonwealth Health Departments planning of HIV care	Collation of routinely recorded HIV treatment and clinical data
F.	Ongoing study, will recruit 3500 HIV-infected and 700 uninfected participants. Conducted by the U.S. Military HIV Research Program.	To longitudinally assess the impact of clinical practices, biological factors and socio-behavioural issues on HIV infection and disease progression in an African context. Evaluation tool for U.S. PEPFAR program.	Volunteers are enrolled at total of 12 clinical treatment sites. Evaluation of demographics, treatment regimens, long-term outcomes, social and behavioral risk factors, aspects of adherence; co-morbidities

Publication in scientific journals

Quality of reporting

Clinical trial results should be considered for publication in peer-reviewed scientific journals and/or presentation at scientific conferences and meetings, irrespective of whether the results are positive or negative. In particular, all phase 3 clinical trial results and clinical trial results of significant medical importance should be submitted for publication. The CONSORT (Consolidated Standards of Reporting Trials) statement provides guidance for clear, complete, transparent reporting of randomized controlled trials.[167]

Open-access

Publication of clinical research results in open access journals should be preferred to make the results more accessible to researchers, clinicians and policy-makers in low-resource environments. However, the fees associated with open-access publishing can be difficult to cover from limited research budgets. Some journals grant waivers or discounts, and the support for open access is growing.[204]

Language and geo-graphical bias

As English is the predominant language of science, language barriers can prevent non-English-speaking researchers from publishing their work; and in LMICs this effect may be increased by a geographical bias in favour of articles from HICs.[205] Financial support for writing publications in English could help to reduce this bias.

Quality of information

With increasing competition both among researchers and among journals, and with increasing amounts of information being generated and published online, it has become challenging for editors to ensure good quality peer-review of the articles submitted to them. In the COVID-19 pandemic, research has become politicized and standards have fallen as illustrated by the example of hydroxychloroquine in COVID-19 (see Appendix 3B). This has prompted a call to action to researchers, scientific journals, governments, regulatory authorities, research funders, editors and those responding to the media, with recommendations for accurate, measured and responsible scientific communication.[206]

Expanded access to data

Benefits

Increasingly, researchers are sharing not only summarized results as published in scientific journals, but complete raw datasets, *i.e.* de-identified individual participant data (IPD). Access to IPD offers many potential advantages, both statistically and clinically. Thus, raw data from multiple studies can be pooled for meta-analyses, providing a better chance to detect differences in treatment effects than if aggregate data were used.[207]

Risks

Expanded data-sharing can have unintended negative consequences. Firstly, there are risks of breaching confidentiality and privacy, as it can be difficult to de-identify participant-level data completely without rendering them useless. For example, information on age, race, sex, education, and occupation might be triangulated with other databases, or information on diagnosis of a rare disease might be linked to

public knowledge, health records, or research data sets that include names or personal identifiers. This risk is growing as more and more data become available electronically.[208]

Secondly, open access to raw data may lead to flawed analyses being published by others, and even if the methodologies are also disclosed, such publications could still mislead health care providers and patients.

Thirdly, mandatory disclosure of detailed clinical trial data could allow competitors to misappropriate the data to seek approval of their own products elsewhere, learn about other companies' scientific or commercial strategies, or inundate regulatory authorities with additional data analyses and requests for reconsideration of decisions.[209]

Lastly, with data science opening up new avenues in medical care,[210] health data have become a sought-after resource. As digital health data begin to be generated in resource-limited settings, they may be exported for use or monetizing by others. Researchers and governments in LMICs should consider how these data can be subjected to good governance.

Grace period

Investigators in resource-limited settings, who often lack the means to analyse and interpret their data rapidly, may be rightly reluctant to share data for analysis by others, even after the results have been published in a scientific journal. Determining equitable grace periods before controlled release of data is still a subject of debate.

Models for expanded data-sharing

It has been proposed that all scientists have a responsibility to aspire to make their research data FAIR, *i.e.* findable, accessible, interoperable and re-usable.[211] The pharmaceutical industry has committed to a number of best practices for proposals to be submitted by requesters of data sets, evaluators of such proposals, and researchers who are provided access to the data.[183] In practice, however, expanded data-sharing is complicated and there is no one-size-fits-all model. Four different approaches to sharing participant-level clinical trial data sets and the disadvantages of each, have been described, ranging from a completely free model without any control to a highly controlled model where an independent intermediary entity would review requests for data and grant access subject to specified conditions on the use of the data.[209]

Cost of controlled data-sharing

Maintaining a data-sharing system requires funds and human resources. It could involve paying a technical team to set up and maintain databases and facilitate use of data sets, experts to evaluate data requests and correspond with applicants, and legal teams to prepare and ensure compliance with data-sharing agreements. This model would only be suitable for resource-limited settings if a funding mechanism can be developed to meet the financial obligations associated with it. Although ideally

there should be some level of public funding to support data-sharing systems, it is unlikely that this can be made available in LMICs given their financial constraints.

Sharing results with participants, communities and policy-makers

Sponsors have a duty to inform clinical trial participants, their communities and the public about research and its outcomes.[1, Guideline 24] Dissemination of results to the community is particularly important in resource-limited settings, where it can support confidence in research and facilitate implementation of research findings.[131]

De-briefing meetings

A useful step in data-sharing with participants is to hold a de-briefing meeting with community peers and study participants before the final results are released. The study participants and community members are partners in research [212] and can often point out interesting nuances or offer useful insights into the interpretation of the results from their perspective.

Clear, non-technical language

Publications in scientific journals are usually written in technical jargon and are not geared towards study participants and communities. Researchers must disseminate study information to participants and communities using a local language and in a non-technical form. What constitutes effective communication will depend on the type of study and the local context. Useful guidance is available on how researchers, with the involvement of community stakeholders, can plan and perform dissemination activities, including by social media.[161]

Sharing results with clinicians and policy-makers

Communicating research results to clinicians and policy-makers, who will act on those results, is important to bridge the "know–do gap" and achieve better health.[213] In resource-limited settings, decision-making is particularly complex. Available evidence suggests that LMIC researchers rarely transfer the knowledge they have gained to decision-makers because of a wide range of individual and institutional capacity constraints, that knowledge transfer can be improved by collaboration and networking with target audiences and by conveying tailored and targeted messages, and that researchers need more training and funding to produce relevant research and to communicate its outcomes.[214]

Social media

Social media are increasingly used to communicate information about research to the community. While this is a useful mechanism, unrealistic expectations may sometimes be raised (see the example of hydroxychloroquine in Appendix 3B), or misleading information disseminated (see the example of Ebola trials in Ghana on page 56). Another example is the advertising of non-validated COVID-19 treatments of dubious origin as on social media in Latin America among the most economically deprived populations.[215]

While a large part of the population in resource-limited settings has access to social media, there may be insufficient access to concise, independent, validated

information that could counter the danger of misinformation, as is done *e.g.* by WHO through its COVID-19 "mythbusters" advice for the public.[216] This is a problem worldwide. An analysis of the use of a social media platform to find information about the Zika virus pandemic in the U.S. found that misleading posts were far more popular than the posts dispersing accurate, relevant public health information.[217] Guidance on social media-related benefits, risks and best practices is available from many health care institutions and professional organizations.[161,218]

Responsible information-sharing — Recommendations

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders*

*Find examples of these categories on pages 4-6.

▶		Researchers should minimize the risk of re-identification of individual participants from any data that may be shared outside the study, and should make both the plans for data-sharing and any risk of data identification clear to study participants as part of seeking informed consent.
▶	▶	Academic research institutions and hospitals should support appropriate management, analysis and publication of clinical research data and results, seeking support for writing and translation where necessary.
	▶	Funders are encouraged to accommodate the costs of data-related activities when funding clinical research (see also the recommendations on electronic health records in Appendix 2).
▶	▶	Funders and sponsors are encouraged to allocate dedicated human resources for communicating objective, validated information and research results to participants, communities, clinicians and policy-makers before, during and after research, as well as to the media and the general public. This is particularly important to combat the harmful consequences of misleading information that may be disseminated by parties with commercial or ideological interests.

CONCLUSION

In recent decades more and more research has been being conducted in LMICs with funding from entities based in HICs. International efforts to fight the priority diseases affecting people in low-resource settings have helped to reduce the global health divide, but more needs to be done to sustain these gains and close the gap further.

Despite the progress achieved, clinical research in resource-limited settings continues to be challenging to conduct. Regulatory systems and the conduct of major stakeholders have improved, but in general the ethical review systems and regulatory oversight remain fragile and need further support to become more effective. It must be acknowledged that some studies conducted in these settings have brought more burdens than benefits for the local population. Principles of research ethics and good clinical practice (GCP) have been developed to protect research participants and ensure credible data. These are now widely accepted; however the GCP requirements originated in a highly industrialized environment and are difficult to implement meaningfully in resource-limited settings. Moreover, each study is different, and researchers and sponsors have a responsibility to reflect on ethical and scientific aspects in context before submitting any new clinical research proposal for approval.

One limitation of this report is that it describes some of these challenges based on individual personal experience rather than scientific evidence, given that there is a dearth of published articles on the subject. Nevertheless, the Working Group agreed on a number of approaches on how researchers and funders can work together with governments and communities in low-resource settings to conduct research that will yield robust and meaningful results while building sustainable local research capacity.

The connection between health and wealth has once again become obvious during the COVID-19 pandemic, which has affected poorer people disproportionately, destroyed livelihoods and impacted national economies worldwide. Vulnerabilities have been heightened or have appeared for the first time. Much of the research on COVID-19 has been uncoordinated and inconclusive, with the notable exception of vaccine development. The pandemic has shown the importance of prompt, well-coordinated, credible research to identify safe, effective and affordable health interventions that will enable an effective global response.

In the longer term, reducing the persisting disparities between and within countries is a must for sustainable development. Clinical research in resource-limited settings has the potential to improve overall health care delivery, with cascading socio-economic benefits for patients, communities and the broader health care systems. However, these benefits do not come for free. Joint efforts are needed to remove existing barriers and mobilize sustainable investments in research.

This report is a call to action for funders, scientists, the pharmaceutical industry, community representatives, regulators and governments. Its recommendations are not just aspirational, but are achievable and critical to continued development of clinical research capacity in resource-limited settings. All these stakeholders should seek and maximize opportunities to collaborate in addressing the recommendations of this report.

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APPENDIX 1.

SPECIAL POPULATIONS

This appendix deals with two subpopulations that differ biologically from the population generally studied in clinical trials to the extent that they have to be considered separately in clinical research, namely children and women of childbearing age. Similar considerations apply to older people, who have been underrepresented in clinical studies due to frequent polytherapy and comorbidities;[219] this group is not further discussed here.

A. Children

Problem statement

The health of children and adolescents (here defined as individuals less than 18 years of age) is vulnerable to many factors. At the same time, the processes of growth, development and maturation make it difficult or impossible to treat children on the basis of experience and data collected from adults. Children and adolescents must therefore be included in health-related research unless a good scientific reason justifies their exclusion, with special safeguards and care including appropriate legal protection.[*1, Guideline 17*] Similarly, the ICH E11 harmonized guideline [220] draws attention to the ethical issues arising in paediatric studies, and states that children should only be enrolled in clinical studies when this is necessary to achieve an important paediatric public health need. The ICH E11 guideline underlines the urgency of paediatric studies to develop treatments for serious or life-threatening diseases in children, following an assessment of initial safety data or a detailed justification why such data in children are not available.

While regulatory initiatives in the U.S. and the European Union have stimulated the development and registration of paediatric medicines, many approved medications worldwide have not been studied in children, and research is lacking on interventions that are needed only in low-resource settings, such as pre-referral treatments, empiric therapies and mass treatments. In summary, children still do not enjoy the highest attainable standard of health in the same way as adults, as is their basic right.[221]

Importance of the problem in resource-limited settings

Disease burden

Clinical trials aimed at addressing the safety and efficacy of medicines and formulations in children are particularly important in LMICs, where children represent a high proportion of the population (up to 50%), and where the majority of preventable deaths occur in children. The main issues are neonatal disorders, infectious diseases and nutritional deficiencies, many of which are specific to children, but non-communicable diseases like childhood cancer [222] and neurological disorders are becoming increasingly important.

Clinical contributing factors

From a clinical perspective, many children in resource-limited settings have a low birthweight and may suffer from macro- and micronutrient deficiencies and chronic parasitic infections. Growth and development is often impaired by chronic infections and poor nutrition. Some may not have received childhood immunizations even if the general vaccine coverage is good. Dosing is a major problem, especially in infants. Doses extrapolated from adults are often too low, for example for antimalarials.

Vulnerabilities

Millions of children living in resource-limited settings face additional challenges due to their circumstances. They may be looked after by elder siblings or grandparents, as their parents are working elsewhere. They may be deprived of a home or education due to poverty, and they may suffer from physical, mental or social exploitation for example because they are regarded as cheap labour, which can cause emotional problems. They may be deprived of safe drinking water, good food and hygiene. Emancipated or mature minors or orphans may be living in the streets and forced into begging, facing violence and trauma and lacking access to health care services. Children from migrant, minority or rural populations, those who are institutionalized or those married underage may be exposed to additional health risks that need to be researched, and at the same time they may have additional vulnerabilities requiring special attention when they participate in research.

Role of children in epidemics

Children may play an important role in transmitting disease during outbreaks, even though they typically comprise only a minority of cases. This has been the case in Ebola virus disease,[21] and it is one of the aspects being considered among the lessons learned from the COVID-19 pandemic.

Lack of a conducive environment for paediatric research

Regulatory capacity

National competent authorities, even in countries with a functioning regulatory system for adult medicines, do not necessarily have the required competence to assess proposals for paediatric clinical trials, to evaluate paediatric medicines or to carry out

[21] In the Ebola virus disease (EVD) epidemic in West Africa the first suspected case is believed to have been a 2-year-old child in Guinea in December 2013. The index case for spread to Mali in October 2014 was also a 2-year-old child, and in Liberia, following the second declaration of no active EVD transmission, a 15-year-old boy with symptoms compatible with Ebola, subsequently confirmed to have EVD, was seen at a health care facility in Monrovia in October 2015, resulting in an alert to public health authorities.

pharmacovigilance in this area. This may result in refusal to accept appropriate trials or acceptance of inappropriate trials, and decisions are often delayed or withheld. To build needed capacity WHO has launched a Paediatric medicines Regulators' Network (PmRN) as a part of its initiative to "Make medicines child size". This network had sustainability problems at first, but was reactivated in December 2019.[223]

Legal issues

Trials in children can be complex from an ethical and legal perspective. Fear of liability issues can be an obstacle in some situations.

Example: Planned trials with rotavirus vaccine in developing countries were suspended after the vaccine was withdrawn from the market in an industrialized country due to a potentially life-threatening complication observed in a small proportion of vaccinated infants. Researchers were understandably hesitant to pursue the studies, even though most deaths from rotavirus occur in LMICs and the vaccine could have had significant benefits in those settings. It has been recommended that ethical issues related to the future development and testing of rotavirus vaccines should be identified early and resolved through dialogue among the involved parties under the leadership of international health organizations and ethical bodies.[224]

Research capacity and Infrastructure

Successful performance of quality paediatric clinical trials requires not only well-trained investigators and support staff but also appropriate equipment as required by the protocols. To ensure that the research findings will be valid in everyday practice, the resources should not differ dramatically from what is normally available at the setting of the trial. Integrating clinical research into everyday practice—using scavenging samples or laboratory leftovers for pharmacokinetic assessment, using patient registries in long-term follow-up studies, and/or integrating visits for clinical research with those conducted for patient care—is recommended.

Trained staff

A key bottleneck is the availability of investigators in resource-limited settings who are experienced in paediatric research and in working with children. Training of regulators, investigators and support staff is crucial. Such training must be developed and delivered in close international collaboration. Successful collaborative training and e-learning courses have been organized (*e.g.* the Global Research in Paediatrics (GRiP) Roadshows [225]); however, a framework is needed to make such courses sustainable. Paediatric research should also be included in the curricula of local medical and pharmacy schools.

Standing paediatric research centres

Establishing research capacity anew for each clinical trial is not optimal. Consideration should be given to establishing paediatric clinical trials centres, preferably networked ones, that may either be specialized in an important disease area or capable to run studies on many types of diseases. These centres should be able to perform drug assays that are sensitive enough to allow determination in newborns and young children. International cooperation of paediatric clinical trial centres and networks provide opportunities to learn from each other.

Ethical considerations

Over the years, ethical concerns about research participation by children have resulted in regulations based on three general approaches: 1) ensuring that the balance between risks and potential benefits of a research project be clearly favourable to the child; 2) for research projects that do not offer the expectation of a direct benefit, allowing child participation only if the risk can be considered minimal or no greater than a minor increase over minimal risk; and 3) requiring in all cases permission by a competent adult with parental authority, in addition to assent from the child when this is developmentally feasible.[226]

Informed consent, assent

Assent of a child [*1, Guideline 17*] should be based on information on the clinical trial and provided appropriately to their level of understanding (increasing with age), for example by using pictograms and cartoons-based informed consent forms. While there is no international agreement on the age when assent of the child is required, it is accepted that dissent from a child should be respected regardless of age.

Avoiding exploitative research

Trial sites in LMICs can be attractive for researchers from HICs mainly due to a high prevalence of diseases, commonly in treatment-naive form, and (perceived or real) lower trial costs. Such trials are not necessarily inherently unethical (see section 4.3), as long as they meet scientific and ethical standards and are responsive to local health needs. For new products intended specifically for resource-limited settings this is not a primary concern, although thought should be given to making these available as appropriate formulations that can be used in the local setting, i.e. they should not require unavailable infrastructure such as refrigerators, specialized laboratories or facilities for compounding.

Scientific considerations

Extrapolation

Not all research needs to be repeated in resource-limited settings. For diseases that exist globally, data could be generated in HICs and knowledge transferred to LMICs. However, in LMICs much of the disease burden in children is due to neonatal disorders, nutritional disorders, diarrhoeal diseases, lower respiratory infections, malaria and meningitis.[9] The prevention, diagnosis and treatment of these conditions need to be studied in the specific settings, including underserved and rural communities.

Extrapolation and modelling using data from older children or even young adults are increasingly recommended, if there are sufficient data to support it. Drug development is increasingly supported by pharmacometrics, an emerging science that quantifies drug, disease and trial information, and has traditionally focused on drug models *i.e.* concentration-effect, dose-response or PK/PD relationships.[227] However, while these approaches can help in planning studies and better inform clinical programmes, they still can only rarely be used without at least some confirmatory or safety trials, and cannot currently replace clinical trials completely.

Defining developmental subgroups

International regulations for paediatric drug development have evolved. The recently adopted ICH E11 guideline [220] recognizes that chronological age alone (or weight bands as a surrogate for age groups) may not always be an adequate basis to define developmental subgroups in paediatric studies.[228] For some conditions, arbitrary division by chronological age may limit the study population unnecessarily, thus delaying the development of medicines for children, including for serious or life-threatening diseases. The ICH E11 guideline [220] suggests that depending on factors such as the condition, the treatment and the study design, it may be justifiable to include paediatric subpopulations (adolescents) in adult studies, or adult subpopulations in paediatric studies. In resource-limited settings this may be imperative, considering that the WHO Essential Medicines List for Children (EMLc) only applies to children up to the age of 12 years;[229] after that they fall under the WHO Essential Medicines List (EML) for adults.

Age-appropriate scientific methods

Scientific methods need to be adapted for use in children. For example, the small physical size of newborns makes all interventions, including taking blood samples, challenging. In addition, the small blood volume of a newborn severely limits the quantity safely available for sampling. Venous blood sampling is difficult and may not be allowed in some societies. These factors allow for only a minimum number of carefully planned samples to be taken and require very sensitive assay methods for analysis of samples; however, there is a lack of assays using small volume capillary blood, notably for drug level measurement. Assessment of subjective symptoms, which in adults is done through questionnaires and interviews, is not possible until a child reaches a level of development where s/he can communicate in an understandable way and express subjective feelings. A good example is the assessment of pain related to interventions or in trials of analgesics.

Paediatric formulations

The ICH E11 guideline [220] highlights the importance of formulations to permit safe and accurate dosing and enhance adherence to therapy. In resource-limited settings additional considerations may be needed to ensure that the products are heat-stable, well accepted (*e.g.* in mass treatment campaigns) and can be safely administered by uneducated care-givers such as illiterate persons or older siblings.

Conclusions

This appendix shows the dimensions of paediatric research gap in resource-limited settings, where infectious diseases and nutritional deficiencies cause a significant burden of disease in children, rapid access to health care is poor, and dosing is a major issue, particularly in infants. This means that there is a real need for good quality clinical research in children in these settings.

Special populations: Children — Recommendations

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders*

*Find examples of these categories on pages 4-6.

▶	▶	▶	Clinical studies in children in resource-limited settings are needed not only in hospitals but also in communities, including in remote areas.
▶	▶	▶	The requirements of good clinical practice should focus on implementation of the essential principles, with documentation requirements that match the needs and context of the studies.
	▶	▶	More pharmacometric studies and pharmaceutic formulation studies should be conducted to support the development of safe and effective medicines for children.
▶		▶	Governments and funders should support initiatives to strengthen regulatory expertise for paediatric medicines as well as academic expertise and capability for paediatric clinical trials.

B. Women of childbearing age

The CIOMS ethical guidelines make a compelling case for inclusion of women in research.[1, Guidelines 18 and 19] The fact that a population is considered vulnerable should never be a reason to exclude it from participation in clinical research where the results may be beneficial to that population, so long as everyone involved in the research is aware of the risks involved and appropriate safeguards and protective health measures are in place.

Vulnerabilities

In resource-limited settings, women may need special protection in research for a variety of reasons. Women and the girl-child in some settings may be exposed to a range of social, cultural, economic, educational and political challenges that limit their freedom to make their own life and healthcare decisions. Risks to female children include those of being unwanted, uncared for, abused, rejected, and threatened in their bodily integrity including that of being sexually exploited and assaulted. Adult women may be denied personal autonomy because they live under the patronage of their fathers or husbands. Where wives outlive their husbands, they may be abandoned by their families and society. Migrant women and women affected by war, which is commonly seen in some LMICs *e.g.* in Africa are especially vulnerable to abuse.[230]

Research needs

The specific research needs regarding women of childbearing age should be given attention, such as the study of the treatment of infections and nutritional deficiencies in pregnant women. This is particularly true in low- resource settings, where the burden of these conditions as well as maternal and neonatal disorders remains high.[9] Practical issues should be considered, including the antenatal care needs of pregnant women. In addition to evidence from clinical research, pregnancy registries play an important role as an information resource for clinicians.[231]

Special populations: Women of childbearing age — Recommendations

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders*
*Find examples of these categories on pages 4-6.

▶ ▶ More research should be conducted to address the research needs of women of childbearing age in resource-limited settings.

▶ ▶ Researchers and ethics committees should ensure that the cultural context is respected when studies are conducted in women of childbearing age.

▶ ▶ ▶ The establishment and use of pregnancy registries in LMICs should be encouraged.

The remainder of this appendix illustrates some of the issues of conducting clinical trials in resource-limited settings involving women of childbearing age, and pregnant women, based on two published papers.

1. Inclusion of women susceptible to and becoming pregnant in preregistration clinical trials in low- and middle-income countries

Source: [42]

Women of child-bearing age during a clinical trial are seldom considered a specific population in literature on therapeutic clinical development, and there are no guidelines for this population. The paper summarized here looks at women of childbearing potential with a negative initial pregnancy test and access (or not) to adapted, safe contraception provided by the sponsor. In theory, these women should not become pregnant during the trial, but in practice several of them will start an "unauthorized" pregnancy. Some reasons for this that may be more frequent in resource-limited settings than elsewhere include: (1) Poor access to contraception or insufficient compliance with contraception by the patient or her partner; (2) interactions between contraceptives and certain concomitant treatments widely used in some resource-limited settings, such as anti-tuberculosis medicines, antiretrovirals or antifungals and (3) the desire to have a child despite the investigator's advice. In some trials, the treatment or associated care may improve the participant's health status, increasing her willingness to become pregnant or the likelihood of this happening.

Understanding the limitations of contraception in resource-limited settings, DNDi has proposed two risk-based algorithms to ensure that women of child-bearing age are represented as far as possible in trials in line with scientific and ethical standards. One algorithm applies to inclusion of women at the start of a trial, while the other applies to keeping women in trials after they have unexpectedly become pregnant. The stepwise decisions are made in response to the following questions (more details are found in the published paper):

For inclusion in a clinical trial:

→ Are available data from prior use of the drug in pregnant women, or from animal studies? *(Human data will have more weight than animal data)*
  → Is the use of the drug safe, based on the available data?
    → Is the disease under study life-threatening, or chronic and debilitating, or non-serious? *(Inclusion will be more acceptable for a serious than a non-serious condition)*
      → Does an alternative safe treatment exist? *(If so, inclusion is acceptable only for life-threatening diseases and provided there is safe prior use in pregnant women)*
        → Is effective and safe contraception available? *(If not, inclusion may still be considered but possibly postponed)*

Example: In a study for a life-threatening disease where an alternative treatment exists, inclusion would not be acceptable if only data from animals are available, but inclusion in Phase 3 studies would be acceptable the drug has been used safely or only non-serious events have been observed in pregnant women.

For continuation in a clinical trial if an unexpected pregnancy occurs:

→ Is the disease very serious without alternative treatment for pregnant women, or is it non-serious without a safer alternative, or is there a safe but not user-friendly treatment alternative?
  → Is there well-established safe use of the drug in pregnancy? *(If yes, continuation acceptable from Phase 2;)*
    → If safe use in pregnancy has not been established, continuation may only be acceptable for a very serious disease with no alternative treatment. The decision depends on the severity of the risk for the embryo/foetus in humans or, if no human data are available, on the type of toxicity in animals (whether only teratotoxicity or also other toxicity has been observed and if so, which) and the stage of the pregnancy.

The paper also emphasizes the need for collection of data on the use of new drugs after approval to inform the benefit/risk assessment in field conditions. Such data could come from adverse event spontaneous reporting, cohort studies or pregnancy registries.

2. Example of ethical safeguards in research conducted in pregnant women in Africa

Source: [232]

The World Health Organization recommends intermittent preventive treatment of pregnant women in African regions with moderate to high malaria transmission. However, there is growing resistance of the malaria parasite to the antimalarial that is currently recommended for this type of treatment. It is therefore important to conduct studies with alternative drugs in this population.

This multi-centre study was conducted in five African countries representing both East and West Africa (Benin, Kenya, Malawi, Tanzania and Uganda) to evaluate the efficacy and safety of azithromycin-chloroquine vs. the current standard treatment in 5,044 pregnant women. It was sponsored by Pfizer Inc. and Medicines for Malaria Venture (MMV). A number of safeguards were put in place to ensure that the rights of these vulnerable participants were respected and their health and welfare were ensured at all times:

- Input and advice were sought from recognized experts. Very early in the programme various international bodies were engaged, including malarial and maternal health experts of the World Health Organization and the Malaria in Pregnancy Consortium. Advice was also sought from the London School of Hygiene and Tropical Medicine. An Article 58 procedure was started with the European Medicines Agency (EMA) to ensure the scientific and regulatory validity of the clinical research project. Overall study design, study endpoints and treatment regimens were adapted to their recommendations to ensure study results would be applicable to the local populations and acceptable from a clinical, regulatory and guideline perspective.
- The Steve Biko Centre for Bioethics of the University of the Witwatersrand in Johannesburg was engaged to ensure ethics input in study planning and implementation of extensive training of all site personnel in ethics of clinical research, with special emphasis on clinical research involving pregnant women.
- Special attention was given to the informed consent process, including evaluation of literacy and whether a written form was available in the participant's preferred language. Engagement was sought not only with study participants but also with family members to be sensitive to local practices and beliefs which are especially important in pregnancy, taking care not to affect participants' individual decision-making and autonomy.
- Community health workers were hired to provide support and continuous follow-up for study participants, and ensure compliance with supportive measures such as the use of insecticide-treated bed nets which were provided as part of the study implementation.
- National and district-level stakeholders such as health ministers and regional/local community health workers were consulted and kept informed.
- Local meetings with community leaders were held regularly to update the community on plans and progress.
- Ethical approval was sought from, and granted by, all relevant authorities (eight in total).
- Standard ante-natal care and continued follow-up were provided in line with local guidelines.
- In order to minimize exposure to experimental treatment, early study termination for either superiority or for futility, based on a pre-specified interim analysis, was included in the study plan.

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APPENDIX 2.

DIGITAL TECHNOLOGIES AND ELECTRONIC HEALTH RECORDS

Globally, digital technology and tools are rapidly transforming the healthcare landscape. These advances in digital health are not limited to resource-rich settings. As there are vast inequities in disease burden and in research capacity between developed and developing countries, funding agencies and researchers are channelling resources to accelerate the implementation of innovative new health technologies that may help to bridge this gap. This appendix looks at the uses of digital technologies at the different stages of clinical research, and makes a call for the development of research-friendly electronic health records in LMICs.

eHealth

Technology advancements have revolutionized health-care delivery in many ways. This includes everyday health care service delivery using increasingly ICT-based applications. Individual patient data recording, processing and analytics are part of these developments for a variety of reasons. The World Health Organization (WHO) defines eHealth as "the use of information and communication technologies (ICT) for health" [233].[22] In its broadest sense, eHealth is about improving the flow of information, through electronic means, to support the delivery of health services and the management of health systems.[234]

Implementation in countries

In line with these WHO statements the Seventy-first World Health Assembly in 2018 acknowledged the potential of digital technologies to play a major role in improving public health. The delegates representing 194 WHO Member States agreed on a resolution on digital health, urging Member States to prioritize the development and greater use of digital technologies in health as a means of promoting Universal Health Coverage and advancing the Sustainable Development Goals.[235] A 2015 WHO

[22] The full definition given in World Health Assembly (WHA) Resolution 58.28 [233] is: "eHealth is the cost-effective and secure use of ICT in support of health and health-related fields, including health-care services, health surveillance, health literature, and health education, knowledge and research."

survey found that 58% of Member States had an eHealth strategy, 47% had national electronic health record (EHR) systems, 54% had legislation to protect electronic patient data and 83% had one or more national initiatives involving the use of mobile devices for medical and public health practice.[236]

Challenges

In low-resource settings, researchers and innovators face tremendous challenges, including the lack of technical training, basic infrastructure, research tools, financial resources, and up-to-date access to scientific information through the internet. Of note, the unchecked availability of scientific data, as recently observed during the COVID-19 pandemic, can also lead to an increasing risk of misinformation of scientists and the public alike. All these obstacles impede developing and implementing innovative and low-cost technologies. The availability of communication technology—ranging from basic cellphone coverage to 5G—and internet bandwidth has a major impact on the level of penetration of digital technologies.[237] Low internet upload/download speeds have been major impediments to date.

A. Digital technologies in clinical research

Digital technology can be a strong enabler for increasing clinical research in resource-limited settings by making such research more accessible for patients and more efficient for providers and health systems. The total enterprise of clinical research can be impacted by digital technology.[238] Examples relate to different stages of the clinical research process:

Clinical trial design and protocol development

One could assess the appropriateness of a specific design for a clinical trial with patients using telecommunication to crowdsource feed-back on study feasibility, endpoints and inclusion and exclusion criteria. Any improvement in collaborating with patients in the research process, easing patient access and reducing the burden of trial participation, will have a positive impact. The preparation of the study protocol can largely be automated, including with the use of natural language processing and artificial intelligence to interpret existing data.

Initiation of clinical research

Technologies exist today that can allow for rapid screening of potentially eligible participants in clinical research. Examples of such technologies are the automated mining of EHRs, but even in circumstances where no EHRs exist, registries and lab data to match patients with trials can be utilized to expedite recruitment.

Other examples are the use of digital consent, including through mobile technology, and the automation of workflows for investigator contracts and confidentiality agreements.

Lack of diagnostic methods often hampers patient recruitment. There are promising new tests—inexpensive, portable, easy-to-use diagnostics that are practical at even small, local health centres such as a recently acknowledged non-invasive malaria test that connects to a mobile app.[239] Mobile technology, even if not connected, provides great opportunities.

The problem of diagnostics is accentuated by a lack of health personnel in developing countries, particularly in rural settings. However, the training of health care workers in all aspects of clinical research and general capability development, both on broad research aspects, as well as specific to certain protocols, can now be done remotely through e-learning platforms.

Trial conduct

Retention of trial participants and in general adherence to treatment can be greatly enhanced through smart-phone alerts and messaging. This technology has been in use for many years now, for instance in diabetes management, including in rural areas in resource-limited settings.[240]

Mobile digital systems can also improve real-time study monitoring and digital end-point collection. Data can be entered at the point of care on a mobile device connected to the electronic data capture system assuming infrastructure is in place. The system could also integrate automatic detection of possible errors so that they can be corrected in real time. This could greatly accelerate the process of data accuracy and completeness review and the validation and sign off on the data. Furthermore, the use of wearables can further assist in assessing specific clinical parameters remotely and transmit these to the investigators, although it cannot completely replace more field-based, in-person monitoring methods.

Telemedicine holds great promise for researchers to gain access to specialized consultations without having to refer patients over great distances. This can now include relatively simple use of mobile phones to capture for instance pictures of lesions or microscopic images that can be quickly shared for remote assessment. Telemedicine's major constraints include the access to and cost of the higher bandwidth that is required for transmitting physiological data and complex medical images. These constraints are more severe in developing countries where even telephone-line-based access is limited, and broadband access is either not available or is far too expensive.[241]

Supplies and cold-chain tracking

As of the last few years, international organizations such as Gavi, the Vaccine Alliance have embraced digital technologies which could be extended and used for clinical research. For instance, Gavi works with Parsyl's advanced supply chain data platform to support Senegal and Uganda to track and monitor cold chain conditions while vaccines are being distributed. This provides near real-time visibility of the entire vaccine supply chain.[242]

Digital records

At the other end of the ecosystem, one can cite MasterCard expertise and technology, which is enabling ministries of health and authorized health workers to provide a card with a digital immunization record to each participating child's caregiver. Using this approach, one can strengthen the efficiency and reach of health services in developing countries.[243] However, as is the case in all countries, data governance and respect for privacy will be paramount for the continued acceptance of these tools by populations.

Use of digital health technologies in emergencies

The COVID-19 pandemic of 2020 has highlighted opportunities for the application of digital technology, including for research purposes. Such uses can include response planning, disease surveillance, patient testing, contact tracing, quarantine and clinical care. An interesting example is the internet-based CURE-ID repository, which lets the clinical community report novel uses of existing drugs for difficult-to-treat infectious diseases and has been updated to be a more effective tool in the COVID-19 public health emergency. As a pilot project, CURE-ID will be used as a single centralized source of curated publicly available information for COVID-19 and coordinated with the U.S. adverse event reporting system FAERS, with an aim to identify existing drugs that demonstrate possible therapeutic benefits and should be studied further in clinical trials.[244]

As mentioned above, many of these applications may require digital infrastructure that is not always available in low-resource settings. In addition, privacy infringement is often a real concern for some applications.[245]

Conclusion

There is no doubt that technology can substantially improve health but also ease the implementation of clinical research in resource-limited settings. As discussed above, many of these digital technologies are currently available and could be strong enablers of clinical research. We ought to strive to achieve an appropriate balance between investment in new technologies and in conventional strategies to bridge the gap in both the quantity and quality of clinical research conducted in resource-limited settings. One should also be reminded that, as research drives innovation in resource-limited settings, an added incentive for such investment is that this can drive adaptation of existing practices in more resource-rich countries. Important obstacles do remain though, including lack of basic tech infrastructure and financing.

B. Electronic health records (EHRs)

In the context of clinical research the potential use of data from appropriately designed EHRs is one of the major areas of interest amongst a variety of eHealth solutions. In its third global survey on eHealth, WHO has defined EHRs as *"real-time, patient-centred records that provide immediate and secure information to authorized users. EHRs typically contain a patient's medical history, diagnoses and treatment, medications, allergies, immunizations, as well as radiology images and laboratory results".*[246] This annex considers EHR data that are collected in routine health care by primary care physicians, in hospital settings or during specialist ambulatory services, as well as electronic prescribing systems and insurance claims, and discusses their potential use for research. An EHR system that yields data for research is a major asset for any country wishing to attract more clinical research to be conducted in its territory.

Adoption in national health systems

Globally

The 2016 WHO Global Observatory for eHealth noted a steady growth in the adoption of national EHRs over the past 15 years, and a 46% global increase in the past five years. Over 50% of upper-middle- and high-income countries (n=23) have adopted national EHR systems. Adoption rates are much lower in the lower-middle (35%; n=10) and low-income countries (15%; n=3); however this is changing rapidly. The most frequently cited barriers to the implementation of EHRs were lack of funding, infrastructure, capacity and legal frameworks.[246] The majority of WHO Member States with national EHR systems report integration of EHR systems with laboratory (77%; n=44) and pharmacy (72%; n=41) information systems, and with picture archiving and communications systems (56%; n=32).[246]

In LMICs

Integration of electronic health records (EHRs) in the national health care systems of low- and middle-income countries (LMICs) is vital for achieving the United Nations Sustainable Development Goal of ensuring healthy lives and promoting well-being for all people of all ages.

While the use of national EHR systems is increasing in LMICs, there is limited evidence for these systems being integrated into the national health care systems. This is confirmed by a recent comprehensive literature survey [247] that highlights a narrow focus of EHR implementation and a prominence of vertical disease programmes such as HIV in EHR adoption. Examples of EHR implementation in Sierra Leone, Malawi, and India support the vision that EHR are going to be rolled out in many more LMICs in years to come. The authors conclude that unless evidence-based strategies are identified and applied, integration of national EHRs in the health care systems of LMICs will be difficult.[247]

Emerging local solutions

On a background of hesitant government leadership and lack of affordable and practical EHRs solutions, local initiatives are under way in some LMICs.

Example: Stre@mline [248] is an EHR platform that has been developed in partnership by local clinicians and engineers in Southwestern Uganda and is used in two low-resource hospitals. It operates without internet access (which is unreliable at the hospitals), instead it is deployed via local area networks for a total of over 60,000 patients, with good user acceptance and plans for expansion. Local technical support is available, and the system is economically sustainable without international funding.

Problem statement

Although the adoption of electronic health records (EHRs) in patient care settings is increasing rapidly throughout the world, the use of EHR data in clinical research seems to lag behind. It seems that not only governments, but also donors who support strengthening of health systems in LMICs are already late in taking leadership. This may lead to the same problems as encountered in well-resourced settings years ago: fragmentation and many competing initiatives with different philosophies and standards. If EHRs are not designed in a research-friendly way from the start, it will be much more difficult and expensive to link them up with research databases and systems once they have been built.

Value of EHRs for clinical research and innovation

To what extent EHRs effectively succeed in improving quality of care and patient safety remains a matter of debate. Nevertheless an increasing number of publications, including from emerging economies and limited-resource settings, point out their value for the improvement of health services and also the health of individual patients.[249] Re-use of data from appropriately designed EHR systems for larger scale research can bring learnings for health systems, enabling them for example to make more informed decisions about the best treatment pathways, optimize resource utilization, or monitor patient safety more effectively. Contributing to larger scale research also has local value: It can bring in income from clinical trial sponsors, and the inclusion of local patients in a study will make the findings more valid for the specific country.

Versatile EHR designs

One of the most important ICT advancements in health care has been the gradual implementation of EHRs that are compatible with multiple tasks. This can bring significant benefits:

Supporting clinical research

Re-use of health care data directly for research purposes can bring significant value and accelerate learning in several key areas: streamlining clinical research processes at health institutions; improving data quality by minimizing manual transcription, thus reducing errors; evaluating the feasibility of research protocols and the availability of patients to participate in research; providing real world evidence; and, last but not least, enhancing drug safety and early identification of safety events.[250,251]

Ways to leverage EHRs for clinical research were explored at a recent multi-stakeholder think tank meeting.[252] Participants concluded that EHRs can be a major tool in the quest to decrease costs and timelines of clinical trial research, generate better evidence for clinical decision-making, and advance health care. Over the past decade, EHRs have increasingly offered opportunities to speed up, streamline, and enhance clinical research. EHRs offer a wide range of possible uses in clinical trials, including assisting with pre study feasibility assessment, patient recruitment, and data capture in care delivery.

Supporting "learning healthcare systems"

It has been suggested that continuing the 20th-century model of the dedicated research setting and relying (almost exclusively) on randomized controlled trials will not allow for translating the current pace of progress in the life sciences into timely access to new and better treatments for patients. New models are needed to enable decision-makers to navigate complex scenarios in the future, be they related to investment, regulatory, financing, or patient-level decisions. It is suggested that the future is with learning healthcare systems having EHRs at their centre and being able to offer complementary information to randomized controlled trials and long-term follow-up studies for decision-making purposes.[*168*] Current regulatory developments point in that direction (see below).

Planning for research-friendly EHRs

It is high time for a call to consider clinical research needs when setting up EHRs in resource-limited settings. We would like to urge all initiatives that are developing EHR for use in national health care systems to consider making them usable to support wide range of clinical research, including clinical trials with medicines and vaccines. Building this capacity into EHR systems from the start would save tremendous resources and make it more likely that local populations can rapidly benefit from clinical research, including faster access to new medicines and improved quality of health services.

Regulatory developments

In advanced settings EHRs are already frequently used for capturing patient-level data in clinical trials. Rapid advances in ICT, of which EHRs are an important part, and our understanding of disease, will likely lead to a major shift in how the health care systems think about the data, which will in turn challenge current regulatory frameworks. It is believed that in the future there will be a shift away from *milestone-based data* collected at defined time points towards *continuous, contextual data*. This shift will impact the current model of medical product regulation, with potential implications across the whole regulatory landscape, reflecting the convergence of clinical development and clinical practice.[253]

Regulatory authorities have recognized the value of Real World Data for generating information to support the efficacy and safety of new medicines,[254] and have issued regulatory guidance documents.[255,256]

Technical challenges

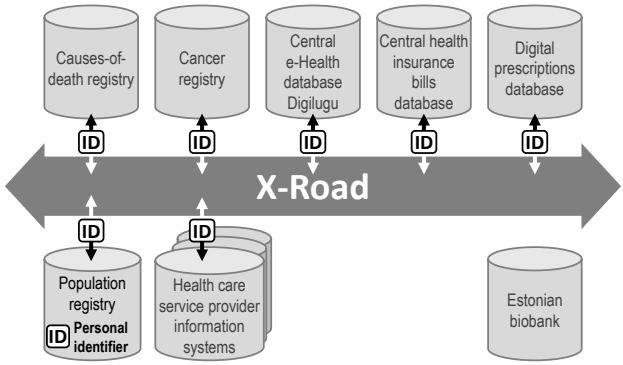
Inter-operability

To be useful for research, EHR must be interoperable,[23] *i.e.* it must be possible to link them to other datasets for analysis.[257] The Stre@mline system described above [248] has not been used for research, but given that it incorporates locally relevant standards and a medication inventory management component, the data may be standardized to a degree that enables them to be exported and mapped to other datasets. However, true interoperability between different electronic systems, including automated data transfers from EHRs to electronic data capture (EDC) systems designed to collect data in clinical research, is complex and has still not been achieved even in industrialized countries. Recent regulatory guidance points to this issue and suggests approaches to solving it.[256] An example of an interoperable data exchange system is shown in **Figure 2**.

Patient identifiers

A challenge more specific to LMICs is that in many of them there is no unique identifier for patients accessing services across the health care system. This makes it impossible to link data from different datasets to an individual. To enable the use of EHR datasets for research it might be necessary to introduce a master dataset that will be collected from every patient.

Figure 2. X-Road — IT infrastructure for linking databases in Estonia



Adapted from: [258]

X-Road is a national level secure data exchange layer. Its use is mandatory for Estonian state level services (99% of which are conducted online), and it is also implemented in Finland, Kyrgyzstan, Namibia, the Faroe Islands, Iceland and Ukraine. Most health-related databases in Estonia are exchanging data via X-Road. The personal identifier for each individual is provided by the population registry. Hospital IT systems are sending discharge summaries to a central e-health database, healthcare bills go to a central insurance bills database, and almost all prescriptions are made through a central prescription database. National level registries such as the causes-of-death registry and the cancer registry are connected to X-Road, and there are plans to link the Estonian population-based biobank to it.[259]

[23] Interoperability has been defined as "the ability of different information systems, devices or applications to connect, in a coordinated manner, within and across organizational boundaries to access, exchange and cooperatively use data amongst stakeholders, with the goal of optimizing the health of individuals and populations."[257]

Legal and ethical considerations

Industry, academia, sponsors, and regulatory authorities are increasingly storing, re-using and sharing health-related data, including complete raw (participant-level) data as well as information from EHRs (see also section 5.2 of this guideline). There are no specific regulations on the phenomenon of these "Big Data", including, in national and international legal frameworks. However, there is a complete regulatory framework for personal data protection in many legal jurisdictions, mainly in Europe, of which many rules can be applicable in the area of "Big Data", including EHRs.

EU General Data Protection Regulation (GDPR)

The EU's General Data Protection Regulation (GDPR) entered into force on 25 May 2018.[192] It relates to a new reality in the sense of quantity, analysis, accessibility, and application of "Big Data". Its principles have been adopted in other countries. It should be noted that EU regulations were designed for the European context and may not be entirely applicable in other jurisdictions. If they are not well adapted they could in certain cases make clinical research cumbersome or even impossible to carry out (see the example on page 64 of this guideline).

Statutory law provisions

Countries that have no specific laws on personal data protection can use constitutional and statutory law provisions as well as common law principles for the same purpose,[260] as is the case in most commonwealth countries. So there is not a lack of regulation but of specific provisions and perhaps of new principles that are adequate to regulate the new features of "Big Data".

Many of the regulations at the international level have been developed in the context of international data flows mainly due to trade in health services, which leads to cross-border data transfers. The United Nations Conference on Trade and Development (UNCTAD)'s 2016 *Data protection regulations and international data flows* is notable in this regard.[261]

International core principles

Agreement on the core principles of international regulations can be attributed to the United Nations General Assembly's *Guidelines for the Regulation of Computerized Personal Data Files* (1990), which contain principles to ensure protection of privacy and confidentiality that as a minimum must be provided for in national legislations.[262] These are the principles of purpose-specification and security. The guidelines also require countries to designate an authority that supervises the observance of these principles, sanction those in breach, and prescribe the need to protect privacy during the trans-border movement of personal data. The guidelines were meant to govern computerized and manual files that contain personal information (see paragraph 10 of the guidelines) but the principles can still be applied, to some extent, in the context of "Big Data".

Other non-legally binding guidelines that have shaped national legal frameworks are the World Medical Association's 2013 *Declaration of Helsinki* [16] and the 2016 *Declaration of Taipei on Ethical Considerations Regarding Health Databases and*

Biobank.[263] Lastly, the 2017 "Report of UNESCO's International Bioethics Committee (IBC) on Big Data and Health" [264] is a useful reference.

Implementation

While there is a broad consensus on the core data protection principles at the heart of most national laws and international regimes, the main challenge is divergence in the implementation of these principles as well as in the detailed data protection laws of the world.[261] This is an evolving subject, and only a high-level introduction into the matter has been presented here. In resource-limited settings, efforts should be made to find the right balance between individual data protection, research ethics and research needs.

Conclusions

Learning from past mistakes

The benefits of re-using EHR data for clinical research are numerous. Many respected organizations such as the U.S. Food and Drug Administration (FDA), U.S. Department of Health and Human Services/Office of the National Coordinator for Health Information Technology (HHS/ONC), Integrating the Health Care Enterprise (IHE), The Clinical Data Interchange Standards Consortium (CDISC), European Union (EU), Health Level Seven International (HL7), Innovative Medicines Initiative (IMI) in the EU, The European Institute for Innovation through Health Data (I~HD), Japan's authorities and others have encouraged the use of EHRs for research and continuous health systems improvement.[265] Resource-limited settings should not be left behind, and the donor community should take e-health, including EHRs, more on board. By learning from mistakes made in setting up EHRs systems in more advanced settings, LMICs can make considerable savings of time and resources in the long-term.

Potential benefits and challenges

A move towards leveraging EHRs in clinical research has potential benefits, as shown by the added value achieved in pilot projects and actual investigational trials used for regulatory submissions. It opens up opportunities to bring new therapies to patients sooner, potentially at a lower cost, and to learn more rapidly from healthcare information, thereby accelerating learning health cycles. On the other hand the remaining challenges are complex and will require stronger collaboration among all relevant stakeholders. Adoption and harmonization of global standards to make EHRs suitable for clinical research is a must.

Window of opportunity

With the increasing interest in and adoption of EHRs globally, it is the right time for all respective stakeholders in resource-limited settings— Ministries of Health, clinicians, researchers, the international donor community, sponsors and others– to collaborate. Only by working together is it possible to change the environment so that EHRs can be used more rapidly and readily for research. In parallel the capacity for research can be increased to provide high quality information that will contribute to improvement of public health in these countries. In the longer

term this could also pave the way for a smoother and faster establishment of continuous learning health systems for the benefit of all patients.

Electronic health records — Recommendations

▶ For governments and regulatory authorities*
▶ For researchers*
▶ For funders* *Find examples of these categories on pages 4-6.

▶ ▶ ▶	All stakeholders involved in conducting or supporting clinical research in resource-limited settings should promote quality use of EHRs for the benefit of patients, health systems and research.
▶	Ministries of Health, in cooperation with other stakeholders, should take leadership in introducing forward-looking policies favouring the introduction, development and maintenance of EHRs that meet unified (internationally recognized) standards for content and interoperability.
▶	The international community, including donors supporting development of health systems in resource-limited settings should intensify their efforts to support the implementation and sustainable use of EHRs in low- and middle income counties (LMICs).
▶	Forward-looking policies and strategies to introduce EHRs in resource-limited settings can consider a step-by-step approach, starting in individual health centres or regions, but should have the vision of multi-functionality and interoperability with other centres/regions and (health) databases.
▶ ▶ ▶	Best possible efforts should be made to protect the privacy of individuals and of groups of people, because the possibility of discrimination derived from the information obtained through EHRs data should be avoided. Ethical and legal basic principles of protecting individuals in health-related research using EHRs have been defined by several international organizations and should be adopted or adapted for use in respective national/regional settings.

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APPENDIX 3.

OUTBREAKS

Outbreak situations always challenging, and in resource-limited settings they are further compounded by weak systems and services. Outbreaks are difficult to forecast in advance and may quickly spread across countries and continents. Known or new pathogens may cause outbreaks at any time, requiring a rapid research response.

Outbreaks

The World Health Organization defines a disease outbreak as follows: "A disease outbreak is the occurrence of disease cases in excess of normal expectancy. The number of cases varies according to the disease-causing agent, and the size and type of previous and existing exposure to the agent."[266] An outbreak may occur in a restricted geographical area, or may extend over several countries. It may last for a few days or weeks, or for several years. The threat of rapid international spread was seen in the 2002/2003 outbreak of severe acute respiratory syndrome.[267] The 1918 influenza pandemic and the COVID-19 pandemic have shown the devastating effects of outbreaks of a global nature and sustained duration.

Research response

Conducting clinical research in outbreak settings is challenging, regardless of the socio-economic status of the location.[268] Recent history provides many examples of the challenges experienced in combatting cholera in war-torn Yemen, yellow fever in Angola, and Zika in South and Central America, which was met with a research response covering a wide range of aspects including product development.[269] The 2014-16 Ebola outbreak in West Africa sparked an immediate, unprecedented collaboration between researchers and started a global move towards more preparedness.[270] The need for a global coordinated response has now arisen on an unprecedented scale in the current COVID-19 pandemic.

This appendix describes the experiences and lessons learned from the Ebola outbreaks in West Africa and the Democratic Republic of the Congo, as well as the COVID-19 pandemic as it unfolded during the development of this Working Group report.

A. Ebola: Experiences and lessons learned

Obstacles

An incomplete list of obstacles in research on any outbreak includes lack of diagnostic assays and counter-measures, establishment of research protocols that can be readily implemented, selection of research sites and investigators, conducting scientific, ethical and data safety monitoring board reviews, and obtaining regulatory approval through national competent authorities. Well-intentioned research responders may also be challenged gaining an understanding of the sociology, culture, and political structures in the affected region. More often than not, these issues are layered and complex. Regardless, community engagement activities, usually conducted on a deliberate process, cannot be overlooked.[271] In the response to the recent Ebola outbreak in the Democratic Republic of the Congo this was extremely difficult, as the local population was disenfranchised from the central government and participated in armed resistance to responders, including researchers.[272]

The outbreak situation compounds the obstacles that complicate research in a resource-limited setting,[33] and adds complexity. Not only does the research team need to consider the availability of assays and countermeasures, they need to consider the logistics of transporting those items to the low-resource setting and the establishment of cold-chain facilities along the supply-line if required. Additionally, there may be differences in regulations between countries impacted by the outbreak for import/export permits, determination of genetically modified organisms for vaccines and lack of standardization in biosafety level classifications. All of these considerations further complicate the capacity of sponsors to initiate clinical research with investigational products.

Agreement on research protocols becomes somewhat more challenging due to the addition of multiple responders/contributors with good intentions who have competing ideas of approaches to clinical research and study design.[273] Selection of research sites may be driven by the availability of infrastructure that can support clinical research or based on ease of developing infrastructure if none exists.

Enabling principles

Overarching principles for the conduct of clinical research in an outbreak setting have been previously described.[270,274] These include ethical conduct, partnerships with affected countries, scientific validity, independent review and oversight, and transparency. The following are some enabling principles that are particularly relevant for conducting outbreak research in resource-limited settings.

Coordination of research efforts

Coordination amongst the international scientific community is typically initiated via the WHO research roadmap prioritization of disease threats and products needed to counter those threats. The roadmap also provides a framework for the establishment of public/private partnerships and to improve collaborative decision-making amongst the scientific community, pharmaceutical industry, regulators, donor country funders, non-government organizations, and most importantly, the potential communities where the research would be conducted.[275] Of note, regulatory agencies such as the U.S. Food and Drug Administration actively encourage sponsors and investigators to engage in trial design proposals for outbreak research as early as possible.[276] An additional factor emphasizing the importance of deliberate coordination is that of resource allocation. The very nature of the resource-limited setting demands efficient planning to avoid duplication of efforts and focus on answering questions that have the potential to address the challenges faced by the community at risk in the outbreak. The role of children in transmission and containment of outbreaks should not be forgotten, and the need for paediatric studies should be included upfront in any planning for clinical research (see also Appendix 1A).

Engaging local authorities and communities

Partnerships with investigators and officials from countries at risk of outbreaks in the process will not only facilitate the response to the pending threat, it will have the potential to better develop a research capacity within the country or region to have in place the human capital infrastructure to respond to future outbreaks. And while it is not feasible to provide an *a priori* ethical approval of a clinical research protocol, it is possible to engage the potential communities and ethical review committees of the general concept of planned studies such that their input on the relative risks and benefits of the possible interventions is taken into consideration early in the planning process.

Similarly, planners should anticipate whether the research may involve refugees and who should be involved in representing those groups regarding authority for approving research. And while it may not be possible to conduct the full range of community engagement activities, it is important to take into consideration the concerns of the community such that they are heard and incorporated in the research response.[277]

Data and privacy protection

Special consideration should also be given to explaining the process for protecting the private information of research participants and how data and samples will be used for the current outbreak and any future research that may come from the data and specimens provided.[*1, Guideline 11*] The research community has an overarching responsibility to outline the structure and function of independent oversight required to ensure that there is a coordinated effort at data and safety review responsibilities. Likewise, establishing well understood data-sharing principles amongst all collaborators will facilitate rapid reporting of results and may lead to earlier availability of effective and approved countermeasures.

Logistic considerations

Regardless of the best efforts to apply the principles described above, no amount of scientific planning will replace sound logistic planning. In this regard, the challenges are time and location. The time required to put all logistic aspects in place becomes a rate-limiting step.

Supplies and systems

Given that many items needed in an outbreak are potency-dated, warehousing these items for "just-in-case" scenarios may be financially unsustainable. Perhaps a "just-in-time" contingency contract to make supplies available at the outset of a response could facilitate better responsiveness. Likewise, the contingency contract approach can be used for large equipment such as laboratory and freezers/refrigerators that would otherwise take up warehouse space.

Plans for import permits and customs clearance of the material moving into an affected country should also be part of the planning process, and an area where strong partnerships with in-country ministries of health and local investigators will facilitate this process.

Having systems in place to support the research to include transportation, power generation, clean water, data management, laboratory functions, communication, and cold-chain monitoring systems is also an important consideration for readiness. Moving equipment and material to the location of an outbreak, while a challenge during the West Africa Ebola outbreak, was relatively easy compared to the distances involved in getting to the Ebola outbreak in the North Kivu Province.

Similarly, storage of biological samples in the region and considerations for future research with those samples needs to be discussed early with the country partners and if time permits, with the local community. Establishing material transfer agreements if complicated tests are required in well-developed laboratory settings should be part of early discussions.

Personnel and participants

Mobilization and/or hiring and training of personnel cannot happen overnight. Best efforts to provide regular training on good clinical practices and communicating potential scenarios to mobilization teams could enhance readiness. Furthermore, when hiring local medical staff, it is important not to deplete already strained health care delivery capabilities.[270]

Given that the outbreak at hand is one of many disease challenges in the community, consideration for the care of other illnesses that may complicate the treatment of the outbreak disease need to be part of the coordination between the research team and the team responsible for overall health care delivery.

Planning for housing, feeding, security and protection from the environment of study participants and research personnel on short notice cannot be overlooked in the

process. Additionally, protection of study personnel involves not only providing personal protective equipment inside the health care setting and security of the research site, but another consideration is appropriate resilience training before their deployment, checking on their well-being during their deployment, and follow-up upon return as the stress of working in an outbreak environment can manifest itself in unforeseen ways.

Finance

While this listing of logistic challenges is not exhaustive, planners need to consider financial management systems to demonstrate good stewardship of resources that are often donated or funded by governments outside the region.

Conclusion

The conduct of research during an outbreak can be a challenging and frustrating task. However, planning ahead can reduce the potential for frustration and lead to well-executed research that answers important public health questions.

B. The COVID-19 pandemic

The global pandemic caused by the SARS-CoV-2 virus has had the greatest societal and economic impact of any infection in modern times. Within a few months of its first official recognition in Wuhan, China, in December 2019, the infection—COVID-19—spread across the inhabited world. On 30 January 2020 COVID-19 was declared a public health emergency of international concern by the World Health Organization.[278] The pandemic has highlighted the global vulnerability to health threats. It has increased the risks of corruption worldwide.[279] and has had a disproportionate and heterogeneous impact in resource-limited settings [280] More effective ways are needed to counter this pandemic and similar future threats with a joint research response.

This appendix is based on information available at the end of May 2021.

Fragmented response

The WHO Blueprint

Research began immediately into all aspects of the virus and the disease in order to plan preventive strategies and to find drugs and vaccines. WHO activated a research and development Blueprint to accelerate diagnostics, vaccines and therapeutics for the novel coronavirus. The Blueprint aimed "to improve coordination between scientists and global health professionals, accelerate the R & D process, and develop new norms and standards to learn from and improve upon the global response".

Lack of coordination

As the epicentre of the pandemic moved from East Asia to Europe, and then to the Americas, nearly all the research initially was in these wealthier countries which made large financial commitments to the global fight against the infection. The impact in

low-resource settings varied substantially. South America was very badly affected, whereas in much of sub-Saharan Africa the impact was initially much less severe. The quality of epidemiological data also varied widely with some countries actively suppressing information. The research environment was pressurized, frenetic and, despite the statements from national and international agencies, remained generally uncoordinated. Preprints, press statements, television interviews and social media commentary dominated over the more traditional (but much slower) publication and engagement processes. All reports and communications came under intense media scrutiny. Use of the most widely prescribed drug, hydroxychloroquine, became heavily politicized. Within 6 months over 3,000 trials had been registered and over 20,000 scientific reports posted or published on-line. But none had provided definitive information on prevention or treatment.

Heightened financial and organizational obstacles

Although high-level commitment to accelerate research was often proclaimed, and there was a general willingness of large organizations to work together, on the ground the processes involved in obtaining funds, ethical review, and regulatory and import permits were generally as slow, or even slower than usual (particularly in low-resource settings, as many the key personnel were now at home rather than work). Although it was generally recognized that benefits from repurposed drugs were likely to be relatively small, and therefore that large trials would be necessary to provide sufficient statistical power to identify these small benefits, there were very few large studies and yet a proliferation of small studies – which were sadly destined to be inconclusive.

In the first year of the global COVID-19 pandemic the only clear policy directions for the management of hospitalized patients have come from multicentre adaptive platform trials—the UK RECOVERY trial, the WHO SOLIDARITY trial and the REMAP-CAP trial. These trials showed clearly that hydroxychloroquine, azithromycin, interferon, convalescent plasma and lopinavir-ritonavir were ineffective and that remdesivir did not reduce mortality, but that low-dose dexamethasone and interleukin-6 receptor antagonists reduced mortality in patients receiving oxygen or being ventilated.[281-284]

Limited evidence-base for action

Under intense public and political pressure to provide solutions Governments and their regulatory authorities often acted on the basis of very limited evidence to approve or endorse therapeutics, while containment and isolation measures ("lock-down") were often slow to be enforced.

The example of hydroxychloroquine illustrates the dangers of politicizing research, the lowering of scientific and reporting standards at a time of enormous public pressure and concern, and the vulnerability of responsible institutions to these factors. In resource-limited settings, these events have prevented needed further research that could have benefitted people in resource-limited settings.

Example: Chloroquine (CQ) and hydroxychloroquine (HCQ) in COVID-19

Tentative positive results led to premature recommendations

The first studies were conducted in China and then, as the pandemic spread westward, in Europe. In March 2020 preliminary data appeared from France, suggesting that HCQ combined with azithromycin could accelerate SARS-CoV-2 viral clearance in COVID-19 infections.[285] Although the evidence was far from conclusive, this news was given high-profile media coverage. Many countries included these drugs in their recommendations, and four (containing over 20% of the world's population) recommended HCQ prophylaxis for health care workers, although there was no clinical trial evidence at the time.

Unsubstantiated negative results led to halting of trials

Meanwhile numerous reports appeared warning of cardiovascular risks based on the well-described electrocardiographic QT prolongation associated with CQ and HCQ. In May 2020 a very large retrospective observational study claimed that these drugs increased mortality in COVID-19 and were associated with ventricular arrhythmias.[286] Although there were immediate concerns over the veracity of the data, several regulatory authorities stopped clinical trials in progress and did not allow new trials to start. WHO temporarily suspended the HCQ arm of its own multicentre randomized trial (the SOLIDARITY trial).

Data could not be verified, papers retracted

Soon afterwards the paper, as well as an earlier study that relied on data from the same company,[287] were retracted as the data could not be verified (and was likely fabricated). WHO resumed the HCQ arm of its SOLIDARITY trial.[288]

Negative findings in hospitalized patients

In June 2020 came negative results in the largest randomized controlled trial in hospitalized patients (RECOVERY)[289] and a much smaller study. WHO stopped the HCQ, lopinavir, and interferon arms of its hospital-based SOLIDARITY trial on 19 June, 4 July and 16 October, respectively.[283]

WHO recommendations against HCQ

In December 2020, the WHO living treatment guideline (version 3) strongly recommended against the use of HCQ and lopinavir-ritonavir for treatment at all stages of the disease.[290] However, the guideline did not recognize that therapeutic responses depend on the stage of disease progression.[291,292] Most (HCQ), or all (lopinavir-ritonavir), of the randomized controlled trial data came from hospitalized patients in whom inflammatory processes predominated. In contrast, antivirals would be expected to be of benefit in prevention or early disease. Accordingly, the guideline focused on prevention of death or need for ventilation, not on prevention of hospital admission, which should be the therapeutic priority in low-resource settings with very limited access to respiratory support and intensive care.

In March 2021, the first version of the WHO living guideline on drugs to prevent COVID-19 strongly recommended against the use of HCQ for chemoprophylaxis, based on results from three trials in pre-exposure prophylaxis (PrEP) and three in post-exposure prophylaxis (PEP).[293] The guidelines considered that mortality and prevention of hospital admission from COVID-19 would be the two main outcomes upon which to provide guidelines. However, there were only two COVID-19 admissions, and there were no deaths in the PEP studies (and 5 deaths in HCQ recipients versus 8 in those receiving no drug in the three PEP trials); yet the guidelines concluded that there was "high certainty evidence" that HCQ chemoprophylaxis neither reduced mortality nor prevented hospital admission. They also suggested that funders should "reconsider" continuation of the trials.

This unfinished saga has negatively affected the reputations of science, research, medical publishing, regulatory bodies and policy making — and shown how difficult it is to conduct good research in the face of intense media coverage and extreme politicisation.

Challenges in low-resource settings

Many of the COVID-19-related challenges affected low-resource settings disproportionately, and this increased the obstacles for conducting effective research. Some examples are given below.

Health system challenges

There were many questions which were specific to low-resource settings, notably how to maintain existing disease control programmes while COVID-19 dominated, how to keep up with obtaining and reporting new information despite limited access to internet and functional digital tools, who and where to test with very limited capacity, how to manage and triage patients and their relatives in busy overcrowded hospitals, how to obtain informed consent for research under these circumstances, and how to use oxygen most efficiently when there was limited supply. There were no ready and rapidly obtainable sources of funding to answer these urgent questions.

Lack of personal protective equipment (PPE)

From the beginning of the pandemic it was evident that front-line health care workers were at particular risk from the COVID-19 contagion. In countries where there was inadequate provision of personal protective equipment (PPE) initially (*e.g.* in the United Kingdom) rates of infection in health care workers were very high, but then fell rapidly as it was provided. On the other hand it was evident that fragile health systems in low-resource settings, which were unable to provide PPE to health care workers in often overcrowded facilities, and offered well supported intensive care facilities only in a few large urban centres, would be a difficult base for researchers to conduct their studies.

Limited testing capacity

Before the introduction of validated point-of care rapid tests, RT-PCR testing was the only way to verify COVID-19 and to distinguish it from other febrile respiratory infections. Testing is necessary to characterize disease epidemiology and thereby inform an evidence-based response. At the time of writing, testing is still inadequate in many settings and very limited in most low-resource settings. Unfortunately testing also became politicized, with countries using testing to control case numbers. Some countries even prohibited or reserved testing. This illustrates the importance of a standing laboratory infrastructure to support critical health research, and the dangerous politicization of medical research in times of medical emergency.

Focus on repurposed drugs

As the COVID-19 pandemic spread it was apparent that development of new therapeutics and vaccines by established industry or academic groups would take many months, so the focus of therapeutic research naturally fell on potential repurposing of existing drugs. But from a low-resource setting perspective, cost would be a major issue. Therefore, while the antiviral remdesivir, interferons and other biologicals were being trialled in wealthier countries, they were not under consideration for low-resource settings. Priority went to drugs which were already available and affordable. Unfortunately there was no coherent response, most trials

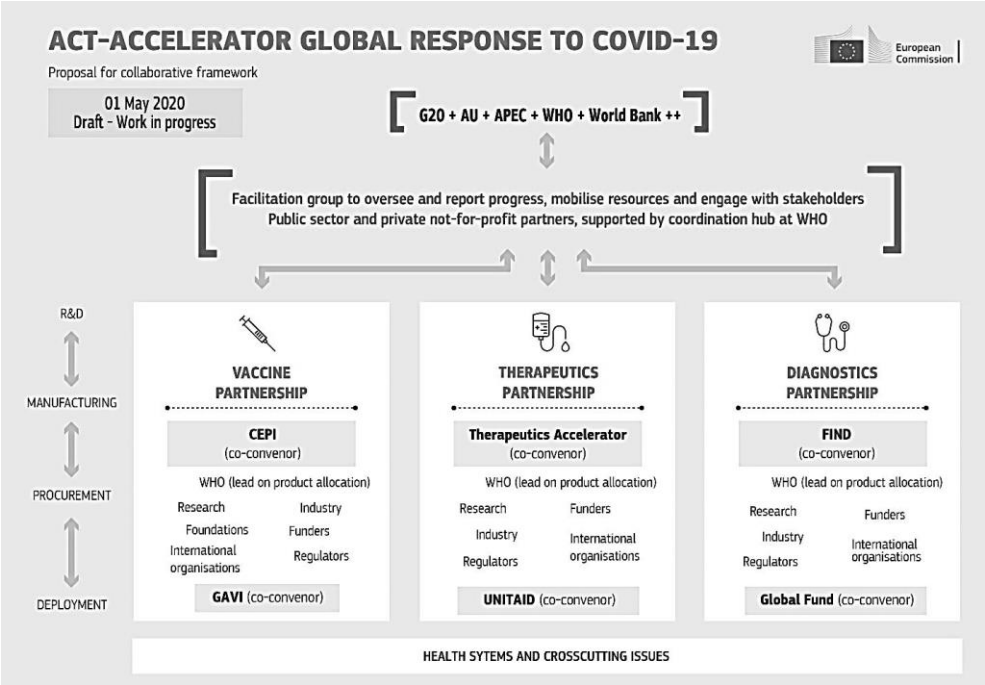
were small, and well over a year later, definitive answers in prevention and early treatment are still awaited.

Global frameworks for research and access to products

Recognizing that low-resource settings would be particularly affected by COVID-19 and that there would be research questions specific to these settings, a global coalition was formed to facilitate this research.[173] This coalition encouraged sharing of research protocols, case report forms and other trial materials and information relevant to the trials, and supported data-sharing and responsible reporting. Noting that much of the public and private COVID-19 research is being funded by governments and charities, it called for funding agreements that would mandate open collaboration and data-sharing while protecting the rights of study participants.

To assure equitable access to effective interventions, WHO in collaboration with partners launched a global framework supporting adequate production and deployment of effective vaccines, therapeutics and diagnostics for equal access by all participating countries, regardless of income levels (**Figure 3**).

Figure 3. COVID-19 Global preparedness pledging infographic



Source: [294]

The arrival of vaccines

The rapid development and testing of COVID-19 vaccines was a remarkable scientific achievement. In general, the protective efficacy of vaccines surpassed expectations. COVAX, the vaccines pillar of the ACT-Accelerator, convened by the Coalition for Epidemic Preparedness Innovations (CEPI), GAVI, the Vaccine Alliance and WHO, has supported the building of manufacturing capabilities, and buying supply, ahead of time with the aim that 2 billion doses can be distributed fairly and equitably by the end of 2021. However it has been acknowledged that there have been escalating bilateral deals for vaccines and suboptimal investment in global solutions. WHO has urged producers and countries with bilateral deals to be transparent and prioritize COVAX, and countries introducing vaccines to use only products with a stringent approval (*e.g.* WHO Emergency Use Listing).[295] WHO's COVID-19 Emergency Committee called for measures to promote global solidarity and equitable vaccine access.[296] The WHO Director-General warned that the world was "on the brink of a catastrophic moral failure" and pointed out that vaccine equity is not only a moral but also a strategic and economic imperative.[297]

The first generation mRNA vaccines require very low temperature storage and transport and will not be suitable for most low-resource settings, but the majority of current vaccines will be deployable using existing cold chains. Very little vaccine-related research has occurred in low-resource settings, and public attitudes and likely acceptance is unclear. This has been exacerbated by the unusual but serious procoagulant adverse effects associated with some of the modified virus vaccines. The emergence and rapid spread of more transmissible viruses with spike protein mutations, and the threat this poses to individual protection from current vaccines as well as the ultimate goal of herd immunity, are substantial. This emphasizes the importance of tackling pandemic threats globally, and reinforces the need to support laboratory infrastructure in resource-limited settings so that vaccines and therapeutics can be adapted rapidly to emerging threats.

Conclusions

Challenges for research

Many of the problems confronting the conduct of clinical research in low-resource settings were magnified in COVID-19 studies. Funding was available mainly in wealthier countries which were hard hit by the pandemic, while support for research addressing problems specific to low-resource settings was difficult to obtain. Despite excellent processes, such as the AVAREF joint review, having become available, regulatory and ethical approval were even slower than before in some countries, as governments and institutions closed or functioned less efficiently, and joint review decisions were not promptly implemented by national authorities. Rapid and effective action was often almost impossible with obstructive bureaucracy, intense politicization and unclear leadership. Effective mechanisms to support and facilitate research were not created by governments in low-resource settings. There were insufficient

incentives and high level support for the large definitive multi-centre, multi-country trials needed to change policy and practice. Laboratory infrastructure to support COVID-19 research was usually absent. Overburdened hospitals were unable to accommodate additional research, particularly as this required isolation and use of precious protective equipment. Lack of collaboration meant there were many small, underpowered, largely observational studies, but few large definitive studies. Lack of collaboration has also been an issue in well-resourced environments due to the fierce competition that prevails in the scientific and medical community.

Equitable access to health interventions

At the time of writing it is still too early to consider all the lessons learned from COVID-19. Effective vaccines have been developed in record time, and effective treatments will eventually be found. However, a major concern for the future is how equitable access to these products can be ensured.

Looking at the first year of the pandemic, a study found that countries' theoretical preparedness according to the Global Health Security Index did not predict their actual performance in terms of preventing COVID-19-related deaths. The study identifies ten factors related to political, economic and social contexts and the role of civil society to take into account in future preparedness assessments, and concludes that an effective response is more likely to be achieved in fair societies where people are socially and economically secure.[298] It stands to reason that similar factors as described in this report —a conducive environment, collaboration, effective communication and engagement with local communities—underlie an effective research response at the international level.

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APPENDIX 4.

CERVICAL CANCER SCREENING IN INDIA

The facts

The studies

The international standard for early detection of precancerous lesions is periodic Pap smear (cytology) screening. It requires infrastructure that is not available in all LMICs. Three clinical trials were conducted in India with funding from the U.S. and France [137-139] to investigate the effectiveness of alternative screening methods, primarily visual inspection with acetic acid (VIA), in high-risk women from socially disadvantaged backgrounds. The study protocols were reviewed and approved by the local institutional RECs in India, two of the studies [138,139] were also approved by the International Agency for Research on Cancer (IARC), the specialized cancer agency of WHO.

All participants were educated about cervical cancer and alternative screening methods, and were informed where these were available outside the study. They were randomly assigned to receive either screening (approx. 200,000 women) or standard care under the government programme in India, *i.e.* no screening (approx. 140,000 women). 294 women from the screened groups and 254 from the control groups died of cervical cancer during the long-term follow-up.[24]

The complaint

An American physician submitted a complaint about these studies to the U.S. Government's Office of Human Research Protections (OHRP), essentially stating that this research was pointless since the accepted standard of cervical cancer screening was already known, and that offering no screening to the women in the control group resulted in the needless death of 254 women.[140]

The OHRP findings

The OHRP investigated the study that had received U.S. government funding [137] (it had no jurisdiction over the other two studies). It found gaps in the translated materials informing study participants about available screening methods, as well as irregularities in REC functioning, and requested corrective action. It did not, however, determine that the no-screening control groups were unethical.[299]

[24] According to published results [137-139], and as summarized in [140]. There were more women in the screened arms than in the control arms because one of the studies [138] involved screening by Pap smear (cytology) and by HPV testing in addition to VIA.

CIOMS position on non-intervention control groups

The CIOMS ethical guidelines take the stance that any potential new intervention should be tested against an established effective intervention, and that researchers may only deviate from this rule when withholding or delaying such interventions is methodologically necessary and exposes participants to no more than a minor increase above minimal risk.[1, Guideline 5]

The debate

The table below shows some of the messages being exchanged as part of the controversial debate about these studies. It illustrates the complexity of the issues, and the dangers of creating and reinforcing mistrust of research, even with the best intentions. It may be added in this regard that the physician who lodged the complaint spent several years advocating for Pap smear screenings at the public health level to prevent cervical cancer in Viet Nam.[300]

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."

(continued)

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."

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APPENDIX 5.

PHARMACOGENETICS AND PERSONALIZED MEDICINE

Well-designed pharmacogenetics studies in LMICs, especially those that translate to clinical and public health benefits, have the potential to lead to better effectiveness and fewer side effects of drugs for individual patients, while offering savings in both time and cost of health care; however, LMICs have participated minimally in genomic research for several reasons including lack of coherent national policies, limited number of well-trained genomic scientists, poor research infrastructure, and local economic and cultural challenges.[31] This appendix provides an overview of pharmacogenomics and summarizes the experience of researchers of the Iberoamerican Network of Pharmacogenetics (RIBEF) with conducting studies in low-resource settings.

Personalized medicine

Every individual has a different genetic makeup. There is a global effort to apply genomic science and associated technologies to further the understanding of health and disease in diverse racial and ethnic populations. In particular, the Human Genome and International HapMap projects have opened the door for a new generation of diagnostic tools that could help to identify individuals and populations at risk for developing specific diseases. Personalized medicine (also called precision medicine or genomic medicine) is an emerging field in which the application of specific biological markers, often genetics, enables diagnosis and disease management to be more accurately targeted at the individual patient. Personalized treatment offers significant benefits but also many challenges, especially in areas where both the disease and available treatments are complex such as autoimmune diseases [303] and cancer.[304]

Pharmaco-genomics [25]

Genetic factors can influence drug metabolism, drug transport and drug targets responses to drugs. State-of-the-art genomic methods including whole genome genotyping and next-generation sequencing (NGS), and in particular the sequencing of highly polymorphic loci such as the HLA region, have increased our understanding of uncommon events in particular individuals or ethnic groups. Pharmacogenomics can enable the identification of optimal drugs and dosages for individuals and sub-populations based on genetic differences; taking into account the effect of growth in children, which involves variations in gene expression.

Drug metabolism is the most studied aspect in pharmacogenomics. It has been shown that plasma levels of drugs and their metabolites can vary among individuals even after taking the same dose, pointing to genetic factors.[305] These differences have clinical implications: ultrarapid metabolizers will have sub-therapeutic plasma levels of the active drugs with a risk of therapeutic failures, while poor metabolizers will have accumulating, supratherapeutic levels that may cause adverse drug reactions.

Some genetic mechanisms involve both the patient and the pathogen. For example, in studies in Burkina Faso and Zanzibar, the CYP2C8 status of patients with malaria influenced the long-term selection of treatment-resistant *P. falciparum*.[306,307]

The role of ethnicity

To a degree, the genetic factors influencing drug response correlate with ethnicity. Recent studies demonstrated differences in the frequencies of several alleles and phenotypes related to CYP2D6, CYP2C9 and CYP2C19 in Latin American populations, and molecular ancestry methods showed that the distinctive genetic structures associated with these differences were broadly consistent across ethnic boundaries.[308,309]

Most existing guidelines for personalized medicine are based on genotyping. However, available genotyping panels developed in one region of the world do not always reliably predict phenotypes in people from another region. For example, existing genotyping panels—developed for Caucasian populations—did not predict the phenotypes of metabolic capacity of major drug-related enzymes (CYP2D6, CYP2C9, CYP2C19, CYP1A2) in populations with an Amerindian genetic background.[310-312] This means that specific geno-phenotyping panels are needed to predict drug response in different populations.

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[25] The ICH E15 guideline includes the following definitions: **Pharmacogenomics** (PGx): The study of variations of DNA and RNA characteristics as related to drug response. **Pharmacogenetics** (PGt) is a subset of pharmacogenomics (PGx) and is defined as: The study of variations in DNA sequence as related to drug response.[313] In practice the two definitions are often used interchangeably.

A further complication is that, with increasing migration and admixture of people from different ethnic backgrounds, self-identified ethnicity and skin colour do not necessarily correspond to genetic ancestry.[315] This, too, has been shown in the studies carried out in the Latin American region.[309] An understanding of how geography and ancestry influence genetic structure can help to shape public health policies and clinical strategies in a globally diverse context.

Regulatory guidance

The uses of pharmacogenetics and pharmacogenomics have been well recognized by advanced regulatory authorities, who have developed various guidelines as outlined below. To ensure a consistent terminology and interpretation of existing and future regulatory documents the ICH E15 guideline was issued in 2007.[313]

Information from pharmacogenomics studies have enabled regulatory authorities to provide treatment recommendations for specific populations. A well-known example are the ethnic variations in CYP2C9 and VKORC1 genotypes that affect dosing of warfarin, prompting the U.S. FDA labelling update in 2007. Often referred to as the "poster child" exemplifying the approach, this exercise provided useful experience for subsequent labelling updates for carbamazepine, abacavir, clopidogrel and several other drugs.[314]

Recognizing that there may be important genetic and inter-ethnic differences in drug response, regulatory authorities generally require inclusion of patients from different ethnic groups in drug trials, as well as safety and efficacy analyses in terms of these groups.[315] Two relevant ICH guidelines are ICH E5 on ethnic factors in the acceptability of foreign clinical data,[316] and ICH E17 on planning and design of multi-regional clinical trials.[317]

DNA sample collection

Clinical trials provide opportunities to identify variations in drug response in specific patients or patient populations. DNA collection from all study participants will provide useful information for retrospective analysis in case of any unexpected adverse events, and will enable assessment of uncommon mutations in population samples to identify susceptible patients. The genetic specificity of trial participants may also be used to determine the inclusion and exclusion criteria and increase safety.

Pharmacovigilance also provides opportunities for sample collection. The international Serious Adverse Event Consortium (iSAEC) assembles sample collections for various types of adverse events, and is making anonymous clinical and genotyping data publicly available on its data dissemination website.[318] At the time of writing, datasets for more than 5500 patients (including cases and controls) were available. However, to date there is no involvement of researchers or institutions from LMIC.

Another flagship initiative is the 1000 Genomes Project, which has created a large public catalogue of human variation and genotype data.[319] Here, too, there is a low coverage of certain populations from LMIC, notably the very diverse African populations.

Genetic testing

Genetic factors can determine the individual susceptibility to both dose-dependent and dose-independent adverse drug reactions. Genetic risk factors have been identified for example for the severe cutaneous adverse reactions associated with the anticonvulsant carbamazepine,[320,321] and for the severe hypersensitivity associated with the antiretroviral drug abacavir in certain ethnic populations.[322] Genetic testing to prevent abacavir hypersensitivity reactions is currently one of the best examples of integrating pharmacogenetic testing into clinical practice and ensuring safer use of a medication.[323,324]

For certain medicines genetic testing is required before they are used. An example is the antimalarial primaquine, which can cause acute haemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[325]

Limitations

It should be noted that pharmacogenetic screening before prescribing a medicine is not always justified. Two examples are given below.

*The HLA-B*5701 allele is carried by about 7% of the population, and is strongly associated with drug-induced liver injury (DILI) secondary to flucloxacillin. However, DILI occurs in less than one of a thousand patients treated with flucloxacillin. Screening 1000 patients would thus identify 70 patients with the risk allele, but would only prevent one DILI case, while 69 patients may miss out on needed treatment. HLA-B*5701 testing would still be useful to support a DILI diagnosis in patients with unexplained liver injury after taking flucloxacillin.[326]*

*HLA-B*5701 is associated with abacavir hypersensitivity. Although HLA-B*5701 genotyping before prescription of abacavir is cost-effective in the U.S. and the United Kingdom, an analysis from Singapore showed that this would not be the case in all countries due to differences in cost structures and population genetics.[327]*

Benefits of pharmaco-genomics in LMICs

Pharmacogenetics and personalized medicine have been mostly developed for high-income countries; however its benefits should be made accessible to all people in the world. Given the large amount of genetic diversity in LMICs, there are significant opportunities where pharmacogenomic information can help to optimize research and health care. In clinical research, it can be used to stratify participants according to their pharmacogenetic profile. In routine clinical care, it will enable optimization of dosages and regimens of pharmacological treatments, including medicinal plants.[328] For example, inclusion of pharmacogenomic information that affects drug response in the WHO Essential Medicines List (EML) could contribute to a better use of essential drugs in different regions of the world. And in pharmacovigilance, adverse drug reactions can be evaluated according to patients' pharmacogenetic profiles,

Efforts are under way to promote the use of genomic medicine in LMICs. The H3Africa Consortium, which consists of a network of NIH-, Wellcome- and African Academy of Sciences (AAS)-funded research sites across Africa, establishes collaborations among African researchers and generates unique data that could be used to improve health both on the African continent and globally.[329]

Conclusion

Although it is not possible to test all drugs in all ethnic groups, knowledge about benefits and risks in specific groups can be used to improve clinical research and drug use in these groups. The right to health care applies to all people in the world, and autochthonous populations represent a growing sub-population in many countries. Universal Health Coverage by the year 2030 is one of the United Nations' Sustainable Development Goals.[330] To achieve this goal, these diverse groups must be considered.

Experiences of pharmacogenetic researchers working in Latin America

At a symposium held in October 2019 in conjunction with the 5th Meeting of the CIOMS Working Group on Clinical Research in Resource-Limited Settings,[331] researchers from the Iberoamerican Network of Pharmacogenetics (RIBEF)[26] discussed their experiences with conducting studies in resource-limited settings. RIBEF is a collaboration network that brings together more than 40 research groups with the aim to increase the pharmacogenetic knowledge in the multiethnic and multicultural in Latin American region.

The barriers encountered by the researchers mirrored those described in the Chapter on *Obstacles and enablers* of this report. Technical shortcomings, limited laboratory and biobanking facilities and gaps in ethical and regulatory processes, were experienced in the RIBEF studies. Local differences in diagnostic criteria, therapeutic guidelines, as well as diet and nutrition, co-morbidities and co-medication including widespread use of traditional medicines, made it challenging to define

[26] RIBEF Participants at the 2019 RIBEF/CIOMS symposium: **Adrián Llerena**, Extremadura University Hospital and Medical School, INUBE Extremedura Biomedical Research Institute, Badajoz, Spain; **Eva Peñas Lledó**, INUBE Universidad de Extremadura (UEx), Spain; **Félix Balboa Lezaún**, Fundación PHI, Acebo, Extremadura, Spain; **Eduardo Tarazona-Santos**, Universidad Federal de Minas Gerais, Brazil and Universidad Peruana Cayetano Heredia, Lima, Peru; **Shyam Diwakar**, Amrita University, Kerala, India; **Jose Pedro Gil**, Karolinska Institute, Stockholm, Sweden and Gulbenkian Scienfic Institute, Lisbon, Portugal; **Enrique Terán**, Universidad San Francisco de Quito (USFQ), School of Medicine, Quito, Ecuador; **Ronald Ramirez Roa**, Universidad Autónoma Nacional de Nicaragua (UNAN), School of Medicine, León, Nicaragua; **Isabel Hernández Guerrón**, Pontificia Universidad Católica, Nursing School, Quito, Ecuador; **Martha Sosa Macías**, Instituto Politécnico Nacional, Centro Interdisciplinario de Investigación para el Desarrollo Integral Regional, Unidad Durango, México; **Carlos Galaviz-Hernández**, Instituto Politécnico Nacional, Centro Interdisciplinario de Investigación para el Desarrollo Integral Regional, Unidad Durango, México; **Julio Lara Riegos**, Universidad Autónoma del Yucatán, Mérida, México; **Ignacio Verde Lusquiños**, Universidad de Beira Interior, Portugal; **Juan Molina Guarneros**, Universidad Nacional Autónoma de México, México; **Sujit Nair**, University of Mumbai, India; **Graciela Moya**, Universidad Católica Argentina, Buenos Aires, Argentina.

appropriate inclusion/ exclusion criteria and to interpret the study results. There were significant language and communication challenges. Explaining the nature and value of the research being undertaken, and obtaining true informed consent, was challenging. Not all studies were designed to yield results that could be directly used to benefit the local population, but even where this was the case, governments failed to implement the findings in public health policies. Mistrust of genetic research was therefore common.

The **Declaration of Mérida/T'Hò** was adopted at the symposium, highlighting the impact of **ethnicity** and **pharmacogenetic factors** on drug response, raising awareness of the fact that **traditional medicine** co-exists and interacts with allopathic medicine, and calling for **education** of the clinical researchers to effectively respond to the complex conditions of different sociocultural contexts. [331]

The researchers' recommendations, both in terms of pharmacogenetic studies and in terms of overcoming the barriers in low-resource settings, are summarized below.

Recommendations made by RIBEF researchers at the CIOMS/RIBEF symposium [332]

For pharmacogenetic studies

Methods:

- Obtain maximum information from the available material, *e.g.*: Use whole genome amplification for the quantitative enrichment of the sample; develop high sensitivity PCR nested systems or using Q-PCR for single nucleotide polymorphism (SNP) genotyping, if of interest; however, do not limit research to SNP-determining systems only; Use appropriate next generation sequencing (NGS) if available; sequence the full open reading frames (ORFs) of the genes of interest
- Use the least invasive methods possible, taking minimal volumes of blood. Base blood bio-sampling on finger prick systems, especially those associated with preservation in filter paper type of matrixes, with appropriate downstream laboratory technologies. Phlebotomy based on venipunctures can be challenging, in particular with small children. Also, researchers should take into account blood-associated cultural issues, for example the notion that one is born with a finite, fixed amount of blood, prevalent in some west African ethnic groups.
- When designing clinical studies in resource-limited settings, consider the ancestry of the population, the sociocultural context (*e.g.* interaction with traditional medicine), and the education needs of research teams for clinical research in vulnerable and autochthonous populations.

Age groups: Studies should focus on adults, unless the pharmaco-exposed group is paediatric (*e.g.* malaria in Africa), or there is a reason to believe that the presence of a certain pharmacogenomic marker is associated with increased pre-reproduction mortality in the population (potential example: G6PD mutants, haemoglobinopathies). In children, particularly neonates and young children, in addition to genetic information there is a need for data showing whether the genes that affect pharmacokinetics are expressed or not.

*Data***:** Maintain a repository for all clinical pharmacogenetics research data.

For any clinical research in resource-limited settings and/or culturally diverse groups

- Manage patients in their native language, with treatments based on their cultural-natural resources.
- Communicate with the patient or guardian in order to register any events during the treatment. This can be continued in a "vigilance follow-up" after the study, thereby compensating the patient for his/her participation, while making the bio-sample more valuable due to enrichment with eventual phenotype information.
- Build bridges between the dominant culture of health services and the different cultures of the population that receive those, to generate health programmes with an intercultural approach.
- Focus on attending to the health priorities in local health systems. Aim for sustainable collaborative research with hospitals that are focused on the community's health priorities. Involve local health care providers in the research projects so that patients will feel comfortable.
- Educate health care providers on the genetic markers associated with specific traits.
- Sensitize health policy makers to the usefulness of the results for the populations.
- Include social scientists in the conception and design of projects.

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APPENDIX 6.

CIOMS WORKING GROUP MEMBERSHIP AND MEETINGS

The CIOMS Working Group on Clinical Research in Resource-Limited Settings met in a series of six in-person meetings and three virtual meetings from November 2017 to August 2020. The draft Working Group report was further developed by an editorial group and was posted for comment on the CIOMS website in March 2021 before being finalized for publication. The members of the editorial team were: Samvel Azatyan, Ames Dhai, Luc Kuykens, Hubert Leufkens, Roli Mathur, Jerome Pierson, Lembit Rägo, Marie Valentin, Pol Vandenbroucke and Nick White, supported by Monika Zweygarth. The Working Group members and meetings are listed below.

Members of the CIOMS Working Group on Clinical Research in Resource-Limited Settings

Name	Organization
Puneet ARORA	Roche/Genentech
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Ruxandra DRAGHIA	Merck U.S.
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Name	Organization
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Raj LONG*	Bill & Melinda Gates Foundation
Irja LUTSAR	University of Tartu, Estonia
Roli MATHUR	National Centre for Disease Informatics and Research, Indian Council of Medical Research (ICMR)
Florent MBO KUIKUMBI	Drugs for Neglected Diseases initiative (DNDi)
Alambo MSSUSA*	Tanzania Medicines and Medical Devices Authority
Jerome PIERSON	NIAID, Division of Clinical Research, U.S.
Lembit RÄGO	CIOMS
Rosanne ROTONDO	Novartis
Aita SIGNORELL	Swiss Tropical & Public Health Institute
Honorio SILVA*	IFAPP (alternate for Gustavo Kesselring)
Nathalie STRUB WOURGAFT	Drugs for Neglected Diseases initiative (DNDi)
Marie VALENTIN*	World Health Organization (WHO)
Pol VANDENBROUCKE	Pfizer
Nick WHITE	Mahidol University, Bangkok, Thailand, and Wellcome Trust
Julian WOELCKE*	Novartis

* = Participated in fewer than 3 Working Group meetings

List of Working Group meetings

Date	Location	Host
November 2017	Geneva, Switzerland	CIOMS
March 2018	Geneva, Switzerland	Drugs for Neglected Diseases initiative (DNDi)
October 2018	Tallinn, Estonia	CIOMS
Preceded by	Open meeting: Using electronic health records (EHR) for clinical research: can we do better?	Ministry of Social Affairs, Republic of Estonia; State Agency of Medicines of Estonia (Ravimiamet)
February 2019	Geneva, Switzerland	CIOMS
October 2019	Mérida, Spain	University of Extremadura, Mérida, Spain
Preceded by	RIBEF-CIOMS Symposium on medicine and health research in indigenous populations of Latin America	Regional Government of Extremadura; Iberoamerican Pharmacogenetics Network (RIBEF)
April 2020	Virtual meeting	CIOMS
June 2020	Virtual meeting	CIOMS
August 2020	Virtual meeting	CIOMS

APPENDIX 7.

LIST OF COMMENTATORS

We thank the following persons for their comments on the draft Working Group report:

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(continued)

(List of commentators, continued)

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Evidence generated through responsible clinical research is one of the major pillars of the advancement of health care. In past decades there has been tremendous progress in the clinical research and development (R & D) environment globally, with increasing attention being paid to the health needs of people in resource-limited settings, where most of the preventable morbidity and mortality occurs. However, financial, social, ethical and regulatory challenges persist in low- and middle-income countries (LMICs), and most clinical research today is still being conducted in and for high-income countries (HICs). The aim of this report is to provide balanced arguments to promote scientifically sound good quality clinical research in low-resource settings.

The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization with the mission to advance public health through guidance on health research and policy including ethics, medical product development and safety. This report reflects the consensus opinion of the CIOMS Working Group on Clinical Research in Resource-Limited Settings, and was finalized in line with comments received during public consultation. The report is intended for governments and regulatory authorities, the research community and sponsors, as well as international organizations involved in funding or conducting research. The report provides a comprehensive set of recommendations to all major stakeholders. While it builds on the 2016 CIOMS International Ethical Guidelines for Health-related Research Involving Humans, it is not intended to supersede those guidelines.

Clinical research in resource-limited settings. A consensus by a CIOMS Working Group. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2021.

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