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The CIOMS consensus report on clinical research in resource-limited settings

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Background. Responsible clinical research drives the advancement of healthcare. Despite tremendous improvements in the global research and development environment since the 1950s, low- and middle-income countries (LMICs) are often left behind. There are several reasons for this. Firstly, operational, social, ethical and regulatory challenges in LMICs make it difficult for researchers to conduct clinical studies in those settings in line with international requirements. Secondly, many people living in low-resource settings distrust research because some past studies have not benefited the participants or the communities involved.
Objectives. To present the consensus recommendations by a Council for International Organizations of Medical Sciences (CIOMS) Working Group on how to advance good-quality, ethical clinical research in resource-limited settings.
Methods. CIOMS convened a Working Group of senior scientists from drug regulatory authorities, the pharmaceutical industry, public-private partnerships for product development, and academia.
Results. This article summarises the Working Group's report.
Conclusion. The report recommendations can foster the creation of a more enabling ecosystem for clinical research and promote collaboration between policymakers, regulators, researchers and funders.

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The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organisation. Its mission is to advance public health through guidance on health research and policy, including ethics, medical product development and safety. CIOMS convened a Working Group comprising senior scientists from various stakeholder groups, with the objective of proposing pragmatic consensus recommendations to advance clinical research in resource-limited settings.

In March 2021, the draft report was posted on the CIOMS website for comment for 5 weeks, and Working Group members actively invited comments from their peers working in low- and middle-income countries (LMICs). The final report was published in June 2021.[1] An overview is provided below.

Backdrop and problem statement

Good-quality, ethical research is essential to identify and address unmet health needs, including those of women and children. LMICs bear the highest burden of preventable diseases globally.[2] While resource limitations can exist in any country,[3] they are more common in LMICs. They affect disadvantaged groups and individuals, migrants and displaced persons in particular. The situation is aggravated in global emergencies and in conflict areas.

Although new partnerships have emerged that address some of the health issues in low-resource settings, most clinical research is still conducted in the more conducive environment of high-income countries (HICs). Many people in resource-limited settings view research with distrust because they do not know what to expect, or have had earlier negative experiences with research or treatment. And instances of exploitative research in resource-limited settings initiated by entities from high-income settings – so-called 'ethics dumping' – continue to occur.[4] Lack of good-quality local research is one of the reasons why entire communities are deprived of new interventions to address their specific health needs.

The CIOMS report

The CIOMS Working Group's consensus report provides a framework to advance clinical research in low-resource settings. Key issues are outlined below. The report builds on the 2016 CIOMS International Ethical Guidelines for Health-related Research Involving Humans,[3] but is not intended to supersede those guidelines.

Challenges to the research environment in LMICs

Research funders' agendas do not always address the most pressing problems in LMICs, and corruption, autocracy, legal uncertainties and regulatory weaknesses create loopholes for players with undue interests. Excessive bureaucracy and limited public funding are major obstacles, which are often compounded by a lack of human resources and necessary infrastructure, such as safe road transportation and security.

Investments must be made in training and career structures, data and safety monitoring, laboratory infrastructure and quality assurance, robust technologies, and an adapted digital regulatory and research framework. Researchers should learn from each other's experiences, for example by sharing locally derived information,

guidance and resources through collaborative platforms.[5] Researchers and sponsors should collaborate to create and maintain standing clinical research networks that could serve both academic and industry-led clinical trials.

Guiding principles for clinical research

Current, internationally accepted requirements for pharmaceutical product pre-registration studies are reflected in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)'s good clinical practice (GCP) guideline.[6] The World Health Organization[7] recommends that the principles of GCP should be applied in all clinical trials, including the post-approval and clinical practice studies that account for most research currently being done in resource-limited settings. Although the principles of GCP hold true generally, some of the ICH GCP requirements were developed for pre-registration studies in HICs and may be difficult to implement meaningfully in resource-limited settings. The ICH has become more global, and a revision of ICH GCP is under way. It has also been recognised that for sustainable regulation at the global level, there is a need for more regulatory co-operation and reliance, where each authority concentrates on those functions for which it has capabilities.[8] The CIOMS consensus report makes recommendations to improve regulatory capacity, co-ordination and reliance in LMICs.

Ethical considerations

Protecting vulnerable research participants

Rather than considering entire classes of individuals as vulnerable, it is useful to examine the specific characteristics that may render research participants vulnerable, and to identify adequate protections to safeguard their rights and wellbeing.[3] Special attention should be paid to informed consent procedures, compensation for participation in research, indemnity in the event of research-related harm, and caring for participants' health needs during and after the study. As the benefit-risk balance of research may differ between studies, and between sites participating in a multi-site clinical trial, researchers and sponsors should do a tailored analysis for each study and site.

Avoiding exploitative research

In recent years, HIC organisations and companies have been conducting clinical trials in LMICs to an increasing extent. Such partnerships can be highly advantageous for both parties, but they can also pose risks of exploitation. Adherence to the Global Code of Conduct for Research in Resource-poor Settings[4] will support long-term equitable research relationships between partners in lower-income and high-income settings.

Ethical review and capacity-building

Research ethics committees (RECs) have a central role in ensuring that the general ethical principles of clinical research are followed, including in public health emergencies. In LMICs several constraints threaten the RECs' ability to function to an acceptable global standard. Capacity-building, including training and resource allocation for ethical review, should be supported by governments, funders and RECs themselves.

Community engagement

Community engagement is critical in any clinical research, and more so in resource-limited settings, where the realities of life and the understanding of medical science are often very different from those of the researchers or sponsors. Community engagement is indispensable to build trust, manage expectations, facilitate communication of research outcomes to participants, enable negotiations for investments in research projects and infrastructure, and facilitate implementation of research findings. The community advisory board is an example of a useful approach. Importantly, sponsors have a duty to inform clinical trial participants and their communities about the research being conducted. Formal communication plans that address how a researcher will encourage, moderate and sponsor community engagement are essential.

Scientific considerations

Conceptualising and designing research

In clinical research, ethical considerations cannot be divorced from scientific considerations. Clinical trials should be designed to answer research questions that are relevant to the local community, taking into account health system capabilities, comorbidities, nutritional specificities and relevant host genetics. Scientific quality cannot be compromised. Adaptive study designs and statistical and pharmacometric modelling can improve the efficiency of clinical trials. Clinical studies should be of sufficient size and detail to yield valid data that lead to robust conclusions. Standardised methodologies, data sharing and meta-analyses should be encouraged. Investments to improve the local research environment (see above) should be planned for whenever possible.

Information sharing

Information sharing supports transparency and collaboration in research. While this is increasingly the norm in HICs, information sharing is insufficient in LMICs. Information is shared through clinical trial registries, patient- or disease-based databases and scientific publications, and raw data are also increasingly shared. However, controlling and curating data effectively requires significant resources.

The COVID-19 pandemic: Lessons learned

Many of the problems confronting the conduct of clinical research in low-resource settings were magnified in COVID-19. There was a dire lack of funding, equipment and supplies. Regulatory and ethical approval processes were delayed, and research was hindered by bureaucracy, politicisation and unclear leadership. Insufficient global incentives and high-level support 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 because of the fierce competition that prevails in the scientific and medical community.

Despite these challenges, effective vaccines were developed in record time. A major concern remains how equitable access to effective medical products can be ensured. What is clear, however, is that a conducive environment, collaboration, effective communication and engagement with local communities all underlie an effective research response at the international level.

Recommendations

The CIOMS consensus report[1] makes 20 high-level recommendations targeted at specific stakeholder groups, summarised below.

To governments and regulatory authorities

1. Invest in infrastructure, security and health systems, support research networks.

2. Consider lessons learned in other countries when planning electronic health record systems that could support research.
3. Combat inefficiency and corruption as a priority.
4. Incentivise recruitment, training, career building and collaboration of research personnel.
5. Harmonise, simplify and expedite regulatory requirements and processes, including for ethical review.
6. Ensure appropriate protection – which does not mean exclusion – of vulnerable research participants.
7. Support patient and community engagement.
8. Implement relevant research findings in national health systems.

To researchers

'Researchers' includes researchers from academic institutions, the healthcare industry, contract research organisations, and non-commercial entities.

9. Understand and respect the local context, including social, cultural, epidemiological, administrative and technical aspects.
10. Apply the principles of good clinical practice.
11. Engage local study participants and communities throughout the research, from an early stage. Do not divert resources from already overstretched local healthcare systems.
12. Plan in advance how to communicate with research participants and communities; be transparent about the aims and interests of all parties involved.
13. Investigate scientifically justified questions, using robust methods.
14. Consider the use of innovative, adaptive study designs and novel digital technologies.
15. Ensure data integrity, transparency and confidentiality, adequate dissemination of study results, and adequate reporting.

To international organisations and funders

16. Support policies and coalitions that facilitate a conducive research environment.
17. Support collaboration for ethical and regulatory oversight.
18. Prioritise research that answers locally relevant questions.
19. Support patient and community engagement.
20. Make agreements mandating collaboration, data sharing and adequate dissemination of study information and results.

Conclusion

Although regulatory systems and the conduct of major stakeholders have improved, more is needed to support clinical research in LMICs and remove the obstacles – many of our own making. Although documented evidence has been cited in the CIOMS report wherever possible, one limitation is that it describes many of these obstacles based on personal experience.

As with all guidance, the challenge is in the implementation. By bringing together the different stakeholders' perspectives, the CIOMS consensus report may prove a basis for constructive collaboration. The 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 indeed critical to build clinical research capacity in resource-limited settings, as part of sustainable development globally.

Declaration. None.

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Conflicts of interest. None.

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