Ethics of health research priority setting

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Prioritizing rare inherited diseases research in lower and middle income countries: the ethical dilemmas of Cochrane Evidence Synthesis

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Note: the author is a Cochrane member, author, and trainer. The views shared here completely belong to the author and do not represent Cochrane.

Brief description of case study context

Rare Inherited Diseases (RID) present significant challenges for healthcare research priority setting in lower and middle-income countries (LMICs) due to limited resources and a high burden of disease, particularly with limited access to healthcare services and a higher prevalence of consanguineous marriages. Evidence synthesis, such as systematic reviews, can help to address this gap by providing a comprehensive and critical summary of existing research on RID, identifying gaps in knowledge, setting research priorities, and promoting their inclusion in healthcare research priority setting. By synthesizing available evidence, researchers and clinicians can gain a better understanding of the disease, develop effective interventions, and contribute to a more equitable and patient-centered approach to healthcare research in LMICs.

Cochrane, as the gold standard for evidence synthesis, has been supportive of RID. Author's study up to May 2020 showed *Cochrane Database of Systematic Reviews* (Q1 journal) published 331 systematic reviews reporting on 1,181 clinical trials (January 2003 – May 2020). However, it was apparent that around three quarters of these reviews were produced by researchers based in high-income countries (HICs) (Europe, Americas and Australia). The proportion of diseases has been relatively balanced where intervention reviews on cystic fibrosis (mostly prevalent in Europe) occupied 39% of them and hemoglobinopathies at 31% (mostly prevalent along the tropical belt of LMICs) (unpublished).

Reduced stream of resources to Cochrane, especially since the pandemic, has forced the organization to transform its editorial decision-making process, which might include decisions on which research topics and review questions are approved. The transformation, fortunately, includes a plan to set up at least an evidence synthesis unit (ESU) in LMICs.

Given the limited resources available for RID research in LMICs, it is important to prioritize research questions that address the greatest unmet needs of patients, such as non-pharmacological interventions, and considerations of LMICs unique social, economic, and cultural background. Cochrane evidence synthesis can play an important role in helping to identify these research priorities by setting more inclusive priority setting process, and providing high-quality and up-to-date systematic reviews that can inform clinical practice and policy decision-making.

Ethical issues

There are several ethical challenges in prioritizing research on RIDs in LMICs for Cochrane evidence synthesis.

(1) *Inclusion and fair processes.* RID research may be more prevalent in HICs than in LMICs due to differences in healthcare access, resources, and funding. This may lead to a lack of representation of RID in LMICs in Cochrane evidence synthesis and raise questions of fairness in the systematic review process. This may be related to ethical considerations around the governance of Cochrane evidence synthesis. For example, the composition of review groups and the extent to which they reflect the diversity of stakeholders, including those from LMICs.

(2) *Criteria and goals for selecting RID research questions.* Selecting research questions for RID in LMICs involves careful consideration of limited resources and the delicate balance between scientific rigor and addressing immediate patient needs. Ethical implications must be weighed, especially in resource-constrained settings. For instance, while gene therapy holds promise for treating rare inherited diseases, it may be prohibitively expensive and inaccessible in LMICs. Prioritizing more affordable treatments like improved blood transfusion protocols or chelation therapies may be deemed ethically sound in LMICs, even if less relevant in high-income countries (HICs).

(3) *Global and local settings in which RID research priorities are developed.* Additionally, it's essential to consider the global and local settings in which RID research priorities are developed. Concerns may arise regarding the cultural appropriateness of research questions and the alignment with LMIC priorities. International organizations and funding agencies, typically situated in HICs, might prioritize advanced therapies or genetic testing, potentially overlooking the basic needs emphasized by patients and providers in LMICs, such as access to blood transfusions and chelation therapy. Bridging this gap between global and local priorities is essential to ensure that RID research effectively addresses the unique needs of patients in LMICs.

(4) *Cochrane's roles.* There have been relatively balanced LMICs vs HICs disease topics and underrepresentation of LMIC authors. It means, HIC authors have been working on many of the LMIC disease topics. While Cochrane has a dedicated priority setting method group that advises various other Cochrane disease groups, decisions have been much to the freedom of the disease groups. Representation of the LMICs in setting priority topics has not been well institutionalized. While the intention to establish an LMIC-based ESU is appreciated, challenges lie ahead include scarcity of locally sourced funding and other resources, acceptance of the local policymaker/authorities, and engagement with local public/interest groups.

Conclusions and recommendations

The challenges include inclusion and fair processes, criteria and goals for selecting RID research questions, global and local settings in which RID research priorities are developed, and governance issues such as capacity building and ethical justifications for allocating scarce resources to rare diseases.

Recommendation 1*: Ensure inclusivity.* Review groups should reflect the diversity of stakeholders, including those from LMICs. Capacity-building programs are required, which will promote the development of local LMIC expertise in evidence synthesis and to ensure that ethical justifications are in place for allocating scarce resources to rare diseases. It is also important to involve local communities and stakeholders in the development of research questions and to ensure that the research addressed culturally sensitive aspects.

Recommendation 2*: LMIC-sensitive selection of review questions.* Careful consideration of the ethical implications of different research questions and the potential impact of research on patients' lives is required. There may also be concerns about the cultural appropriateness of research questions and interventions in LMICs, as well as the impact of research on local communities and cultures.

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