BMJ Global Health

Global health reciprocal innovation: ethical, legal and regulatory considerations

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To cite: Rid A, Aguilera B, Banda C, *et al*. Global health reciprocal innovation: ethical, legal and regulatory considerations. *BMJ Glob Health* 2024;**8**:e014693. doi:10.1136/bmjgh-2023-014693

Handling editor Helen J Surana

Received 28 November 2023
Accepted 5 May 2024

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ABSTRACT

Global health reciprocal innovation (GHRI) is a recent and more formalised approach to conducting research that recognises and develops innovations (eg, medicines, devices, methodologies) from low- and middle-income countries (LMICs). At present, studies using GHRI most commonly adapt innovations from LMICs for use in high-income countries (HICs), although some develop innovations in LMICs and HICs. In this paper, we propose that GHRI implicitly makes two ethical commitments: (1) to promote health innovations from LMICs, especially in HICs, and (2) to conduct studies on health innovations from LMICs in equitable partnerships between investigators in LMICs and HICs. We argue that these commitments take a significant step towards a more equal global health research enterprise while helping to ensure that populations and investigators in LMICs receive equitable benefits from studies using GHRI. However, studies using GHRI can raise potential ethical concerns and face legal and regulatory barriers. We propose ethical, legal and regulatory considerations to help address these concerns and barriers. We hope our recommendations will allow GHRI to move the global health research enterprise forward into an era where all people are treated equally as knowers and learners, while populations in both LMICs and HICs benefit equitably from studies using GHRI.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Global health reciprocal innovation (GHRI) is a recent and more formalised approach to conducting research that recognises and develops innovations (eg, medicines, devices, methodologies) from low- and middle-income countries (LMICs), especially in high-income countries (HICs). Legal and regulatory barriers to GHRI have been described, but there has been no ethical analysis for GHRI to date.

WHAT THIS STUDY ADDS

⇒ Ethical analysis and ethical, legal and regulatory considerations for funding or conducting studies that use GHRI.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The proposed considerations aim to ensure that studies using GHRI promote a more equal global health research enterprise, while populations and investigators in LMICs receive equitable benefits from these studies.

BACKGROUND

Low- and middle-income countries (LMICs) continue to carry the largest burden of disease and injury worldwide.[1] Research is needed to reduce this burden and decrease health inequities between and within LMICs and high-income countries (HICs). However, progress towards achieving these goals has been uneven and slowed down in recent years.[1]

On a wide range of indicators of research capacity, spending, activity and outputs, LMICs fare worse than HICs.[2] For example, LMICs currently have 175 full-time investigators per million inhabitants, as compared with 353 in HICs.[3] Similarly, LMICs spend <0.02% of their gross domestic product on health research, while HICs currently spend 0.25%.[4] These sharp inequities in academic and financial resources heavily favour HICs in setting the global research agenda, as do historical patterns of social relations, including colonialism and racism.[5] Indeed, data suggest that public and private investments in health research only weakly correlate with the global burden of disease,[6] if they correlate at all. Academic and financial inequities also create persistent power imbalances in partnerships between investigators from LMICs and HICs, further compounding efforts to orient the global research enterprise towards priorities for LMICs.[7] For instance, despite long-standing calls to end 'parachute' research, investigators from HICs continue to extract data and samples from populations in LMICs without seeking collaboration with local

investigators or acknowledging their contributions.[8 9] More generally, research from LMICs tends to be marginalised or ignored. To cite two illustrative examples, studies from LMICs are published and cited less frequently and perceived to be of lower scientific quality than studies from HICs.[10]

One recent proposal to help address the above concerns is the reciprocal innovation approach to global health research or, for short, global health reciprocal innovation (GHRI). This approach has been defined as involving '(1) global health partnership rooted in the values of reciprocity, mutual learning and equity across partner institutions in HICs and LMICs; (2) a bi-directional and co-constituted approach to identifying shared health challenges across settings in long-term engagements; and (3) identification of high-quality innovations from global health partnerships for demonstration, replication, and dissemination in diverse settings'.[11 12]

In this paper, we summarise the GHRI approach and then suggest that it combines two distinct ethical commitments: (1) a commitment to promoting health innovations from LMICs, with a particular focus on encouraging research that adapts existing health innovations from LMICs for use in HICs or develops innovations in LMICs and HICs and (2) a commitment for investigators from LMICs and HICs to collaborate on such research in equitable research partnerships. We build on this analysis to develop ethical considerations for research funders, sponsors and investigators on how to fund or conduct research studies using GHRI. For example, we propose several ways in which funders can prevent such studies from displacing funding or investigator time for research with more significant benefits for populations in LMICs. We also identify issues that require special attention as sponsors and investigators build equitable research partnerships. Finally, we discuss legal and regulatory considerations for studies that use GHRI, specifically considerations related to creating memorandums of understanding (MOUs) to foster equitable research partnerships, as well as navigating potential regulatory barriers in studies that aim to adapt innovations from LMICs for use in HICs.

Throughout the paper, we use the term health innovation to refer to a wide range of interventions aimed at promoting health or health equity, including medicines, vaccines, devices, methodologies, procedures and systems. We use the terms LMICs and HICs to refer to groups of countries with varying levels of financial resources, including for health research. However, we do not wish to suggest a hierarchy of these groups of countries, and we recognise the rich historical, social and cultural diversity within them.[13] We use the term funder to refer to the organisation or person providing financial support for a research study. We use the term sponsor to refer to the organisation or person responsible for the study's conduct, noting that the same organisation or person can serve as a study's funder and sponsor. Finally, we assume that studies using GHRI will be designed and implemented consistent with recognised ethical criteria for research involving human participants.[14–17] This means, for example, that studies address socially valuable research questions, use recognised scientific methods, select participants fairly, involve reasonable risks and potential benefits for participants and generally proceed with the participants' informed consent.

Global health reciprocal innovation

GHRI is a more formalised approach to adapting innovations from LMICs for use in HICs or developing innovations in LMICs and HICs in research studies.[11 12] Proposed only recently, GHRI builds on existing approaches that emphasise the potential benefits for HICs from adapting 'frugal' innovations from LMICs[18] or 'reversing' the otherwise dominant transfer of health innovations from HICs to LMICs.[19] However, GHRI goes beyond these existing approaches by emphasising the potential benefits for HICs *as well as* LMICs when investigators from both settings build equitable partnerships to study innovations that can be used across LMICs and HICs.[11 12] As such, GHRI is also closely related to discussions about 'global learning'.[20 21]

There is no single way of implementing GHRI. For example, in the partnership that pioneered the GHRI approach, investigators from Kenya and the USA each performed an environmental scan of their local health challenges and convened a meeting to jointly identify shared challenges and possible solutions to these challenges that could be studied within the partnership. The investigators then used existing funds to launch a joint GHRI grant programme for studies that could test candidate solutions.[11 12] At present, however, GHRI is most commonly used to adapt existing innovations from LMICs for use in HICs. For example, the Enhancing Preexposure Prophylaxis in Community study adapted a text-messaging intervention that was originally developed in Kenya to support PrEP adherence in the USA.[22 23] Less commonly, GHRI is used to develop health innovations in LMICs and HICs. For instance, the Self-Management Approach and Reciprocal Learning for Type 2 Diabetes project developed a context-sensitive self-management strategy for type 2 diabetes prevention and control in Uganda, South Africa and Sweden (please see table 1 for details on both examples).[24–26] Since GHRI has been proposed recently, it has only been used in a relatively small number of research studies.[27] While more of such studies would be welcome, GHRI does not aim to transform the global health research enterprise as a whole. Instead, GHRI has been suggested as an approach for expanding the development of new solutions to shared health challenges in LMICs and HICs that emphasises collaboration and shared learning between investigators in both settings.

Ethical considerations for global health reciprocal innovation

In the following section, we suggest that GHRI implicitly makes two distinct ethical commitments. We describe

Table 1 Illustrative examples of studies that have used a global health reciprocal innovation approach. Both examples were presented at the Global Health Reciprocal Innovation Virtual Workshop held in October 2022, sponsored by the National Institutes of Health.[61] Information about the examples was extracted from the cited publications and may not be complete.

Key characteristics of global health reciprocal innovation	Enhancing pre-exposure prophylaxis (PrEP) in community study[22 23]	Self-management approach and reciprocal learning for type 2 diabetes project[24–26]
Shared health challenge	HIV prevention and treatment, specifically supporting adherence to anti-retroviral treatment (ART) in people living with HIV or PrEP in people at risk of HIV infection	Type 2 diabetes (T2D) prevention and control, specifically promoting healthy behaviours
Shared health innovation	Bidirectional text-messaging intervention to support ART or PrEP adherence	Contextually appropriate self-management strategy for T2D prevention and control
Shared learning	Adaptation of health innovation from low- and middle-income countries (LMICs) to high-income countries (HICs)	Development of health innovation in LMICs and HICs
Flow of innovation	Text-messaging intervention was originally developed in Kenya to support ART adherence and then adapted for use in the USA to support PrEP adherence	T2D self-management strategy was developed in Uganda, South Africa and Sweden
Research methods	► Pilot study to evaluate the feasibility and acceptability of an adapted text-messaging intervention to support PrEP adherence ► Randomised controlled trial of adapted text-messaging intervention versus the standard of care	► Evidence Integration Triangle framework to clarify the problem, develop a theory of change and develop contextualised interventions in all study sites ► Cluster-randomised trial of T2D self-management strategy (facility plus community or facility only) versus usual care
Research findings	Adapted text-messaging intervention significantly increased PrEP adherence in the USA	T2D self-management strategy did not improve blood sugar levels or control in South Africa and Uganda (*results from Sweden pending at the time of writing*)
Equitable partnership	*Not discussed*	► Shared benefits of in-depth understanding of contextual differences in improving T2D self-management and the adaptability of solutions ► Joint ownership and authorship ► Access to resources and opportunities for individual and institutional capacity-building in Uganda and South Africa
Location of co-authors (in alphabetical order)	Canada, Kenya, USA*†	Belgium*, Finland, Uganda, South Africa*, Sweden†

*Location of the first author(s).
†Location of corresponding author(s).

these commitments and argue that they take a significant step towards a more equal global health research enterprise, while emphasising that investigators and populations in LMICs receive equitable benefits from studies using GHRI. However, we identify two potential ethical concerns that could arise if funders, sponsors and investigators financially support or conduct studies using GHRI without carefully considering how such studies might impact populations in LMICs. We build on GHRI's own ethical commitments, as well as general ethical commitments that undergird the field of global health,[28 29] to propose possible ways of addressing these concerns (boxes 1 and 2).

a. Two ethical commitments

In our view, GHRI combines two distinct ethical commitments. The first is a commitment to *promoting health innovations from LMICs*, with a particular focus on encouraging research that adapts existing health innovations from LMICs for use in HICs or develops innovations in LMICs and HICs. As the authors who pioneered GHRI highlight, 'many health innovations and technologies developed in LMICs are applicable in HICs' but are nonetheless disregarded.[12] GHRI aims to improve this situation by promoting research that recognises and develops innovations from LMICs.

GHRI's first ethical commitment promotes a more equal global health research enterprise. It recognises that all people are vulnerable to health challenges, many of these challenges arise across diverse global settings (eg, unhealthy lifestyles, poor access to health services[30–33]), all people have creative ways of addressing these shared challenges, and all people can learn from others, even when their circumstances differ. GHRI thus takes a staunchly egalitarian and global perspective on

Box 1 Ethical considerations for funders who financially support studies that use a global health reciprocal innovation approach.

Ethical considerations for funders in LMICs and HICs

⇒ Require that proposals for studies using GHRI contain all relevant information (eg, why GHRI was chosen and why the proposed research partnership is equitable) and facilitate their review by qualified experts (eg, by creating dedicated funding calls or tasking Centers for Excellence or research networks with reviewing proposals).

⇒ Provide appropriate logistical, ethical, legal and regulatory support for studies using GHRI (eg, by funding such support and establishing Centers for Excellence for GHRI).

⇒ Evaluate ongoing and completed studies that use GHRI (eg, do they deliver scientifically and socially valuable results without raising potential ethical concerns).

⇒ In case of negative evaluations, pause ongoing studies or funding for future studies (where appropriate) and identify and implement measures for improvement.

⇒ In case of positive evaluations, disseminate the findings (eg, to attract new study proposals or buttress public support for investing in GHRI research) and consider expanding funding for GHRI research.

⇒ Consider supporting research networks or Centers for Excellence for GHRI to assist with evaluating ongoing and completed studies and sharing lessons learned.

⇒ Fund studies on innovations in LMICs that might later be developed in studies using GHRI; investigators in LMICs should be in the lead.

Ethical considerations for funders in LMICs

⇒ Fund studies that use GHRI only when:

⇒ Studies develop health innovations in LMICs and HICs that clearly address major health needs or priorities in LMICs, *and*

⇒ Funders in HICs financially support the portion of the research conducted in HICs, as well as the incidental costs associated with building the research partnership,* *and*

⇒ Populations and investigators in LMICs receive benefits that are consistent with their needs and priorities and reasonable in relation to the burden and costs of the research partnership for them (eg, use of local research or healthcare resources), as well as the benefits of the partnership for populations and investigators in HICs.

Ethical considerations for funders in HICs

⇒ Fund studies that use GHRI through funding streams for research on health needs and priorities in HICs; do not divert funding from research that is allocated for research on health needs and priorities in LMICs.

⇒ One possible exception are studies that develop innovations in LMICs and HICs, provided they clearly address major health needs or priorities in LMICs.

⇒ Fund studies that use GHRI to address top priority research questions in both LMICs and HICs, where possible drawing on research priorities that have been set in a transparent and inclusive process using sound criteria.

⇒ When top priorities in LMICs and HICs cannot be aligned, studies should address major health needs and priorities in LMICs.

⇒ When funding studies that develop innovations in LMICs and HICs:

⇒ Fund the portion of the study conducted in HICs, as well as the incidental costs associated with building the research partnership,* *and*

⇒ Fund the portion of the study conducted in LMICs when this does not clearly address major local health needs orpriorities in LMICs, *and*

Continued

Box 1 Continued

⇒ Preferably fund the entire study, including the portion conducted in LMICs.

* Incidental costs associated with building the research partnership can include training and infrastructure investments, legal advice regarding memorandums of understanding or intellectual property rights, assistance with regulatory review or ethical consultation.

health research,[34] highlighting that all people are equal as knowers and learners and should be treated as such. This counters the long-standing dominance of innovations from HICs in global health research, as well as the associated epistemic injustices in how health-related knowledge is produced and used worldwide.[35]

The second ethical commitment of GHRI is that *investigators from LMICs and HICs collaborate in equitable partnerships on studies that adapt innovations from LMICs or develop innovations in LMICs and HICs*. According to the authors who pioneered GHRI, such studies should be conducted in sustained research partnerships that are committed to mutual benefit and learning.[11 12] For example, investigators from both LMICs and HICs might benefit from obtaining research funding and opportunities for authorship, acquiring new research skills, learning about different research and healthcare systems, expanding their professional networks, laying the groundwork for future research projects or gaining cultural skills. Of note, the commitment to equitable partnership does not imply that partners from LMICs and HICs must gain the same type or amount of benefits from the collaboration. Instead, it envisions that the benefits are consistent with each partner's needs or priorities and reasonable in relation to the burden and costs of the collaboration for them, as well as to the benefits and burdens for all partners involved. As such, this commitment is consistent with the well-known 'fair benefits' approach, which aims to avoid exploitation in health research in LMICs by providing a fair level of benefits from the research for local communities and investigators.[36] Of note, these benefits can be related to the results of research studies (eg, reasonable access to the innovation under study, if proven safe and effective) or the studies' conduct (eg, training of local investigators). The benefits can also be unrelated to the research (eg, investments in clinical infrastructure).

By envisioning that investigators in LMICs and HICs collaborate in equitable partnerships, GHRI reaffirms its egalitarian perspective on health research, based on which investigators from both settings participate equally as knowers and learners. Moreover, the commitment to equitable collaboration emphasises that populations in LMICs and local investigators receive a fair level of benefits from studies that use GHRI. This is especially relevant in studies that primarily benefit populations in HICs, such as studies that adapt successful innovations from LMICs for use in HICs.

Box 2 Ethical considerations for sponsors and investigators who conduct studies that use a global health reciprocal innovation approach.

Ethical considerations for sponsors and investigators in LMICs and HICs

⇒ Ensure that investigators jointly explore opportunities to collaborate on studies using GHRI and are not under pressure, whether real or perceived, to enter collaborations.

⇒ Evaluate the potential benefits, burdens and costs of studies using GHRI for investigators and populations in LMICs and HICs, with a particular emphasis on populations in LMICs.

⇒ Investigators in LMICs might decline collaboration on studies that do not promote their professional interests, place undue burdens on the local population (eg, by displacing research or other activities with more immediate or significant health benefits for them) or offer insufficient benefits for the local population.

⇒ Ensure the potential benefits of studies using GHRI are consistent with the needs or priorities of populations and investigators in LMICs and HICs and reasonable in relation to the studies' burden and costs for them, as well as reasonable in relation to the potential benefits for all research partners. Specifically, consider relevant existing recommendations for equitable researchpartnerships (table 2) and pay special attention to:

⇒ Ensuring that studies address top priority research questions in LMICs and HICs, where possible drawing on research priorities that have been set in a transparent and inclusive process using sound criteria; when top priorities in LMICs and HICs cannot be aligned, studies should address major health needs and priorities in LMICs, *and*

⇒ Planning studies so they do not displace research or healthcare resources (eg, investigator time, infrastructure) that otherwise would have been used to address health needs or priorities in LMICs (eg, buy out investigators' clinical time to ensure continuity of patient care while offering training opportunities for junior colleagues) *and*

⇒ Collaborating in all research stages (eg, study design, data analysis and interpretation, publication) and avoiding merely instrumental or tokenistic partnerships; relevant investigators in LMICs should be invited, and supported as needed, to take leading roles, *and*

⇒ Paying special attention to IP rights, notably by:

⇒ Following relevant patent or trademark rules for existing innovations,

⇒ Including investigators behind the original innovation in any novel patents or trademarks and exempting populations which helped to develop the innovation from these patents or trademarks; consider exempting populations in LMICs more generally, and

⇒ Considering recording IP rights in an MOU (see **Section 4. Legal considerations**), *and*

⇒ Recognizing past contributions of investigators in LMICs beyond IP rights, notably by:

⇒ Recognizing investigators behind the original innovation (eg, in publications or presentations),

⇒ Inviting investigators behind the original innovation to collaborate on studies using GHRI,

⇒ Considering how original investigators who do not wish to collaborate might be supported in recognition of their innovation and general structural injustices in the global research enterprise (eg, if desired, offer support with identifying opportunities for funding, networking, or legal or regulatory assistance).

⇒ Build long-term research partnerships that facilitate mutual respect and open discussion of how to equitably distribute the potential benefits, burdens and costs of studies using GHRI (where appropriate).

Thus, by combining these two ethical commitments, GHRI has the potential to promote a more equal global health research enterprise in studies that offer an equitable distribution of benefits for populations and investigators in both LMICs and HICs.

b. Two potential ethical concerns

Two potential ethical concerns could arise if GHRI's ethical commitments are not implemented carefully.

The first potential concern is that research using GHRI could reduce the availability of research funding and/or investigator time to conduct studies that have more significant potential benefits for populations in LMICs. Because GHRI has been proposed only recently, there are currently few funding opportunities for studies using the approach. Most research funders will, therefore, need to create new funding opportunities, for example, by launching dedicated GHRI funding calls or including a specific interest in GHRI in existing calls. Yet because research budgets are finite, funding opportunities for studies using GHRI could displace funding for studies whose results could yield more significant benefits for populations in LMICs. For example, given their promise for populations in HICs, funders in HICs might start to support studies that adapt innovations from LMICs. Yet this could reduce the funders' available resources to support studies that primarily benefit populations in LMICs.

Similarly, investigators in LMICs—who are often in short supply[3] —might collaborate on studies using GHRI and, therefore, have less time to spend on studies with more significant potential benefits for local populations. Investigators in LMICs could also have less time to benefit local populations in other ways, for example, by providing clinical care, training clinicians or contributing to local health policy or governance. The resulting loss of benefits for populations in LMICs could be notable because international research collaborations, which are integral to the GHRI approach, can be time-consuming. Moreover, investigators in LMICs are uniquely positioned to help address local health challenges, meaning their expertise and experience cannot be easily replaced.

Thus, studies using GHRI could reduce the available funding and investigator time for studies with more significant potential benefits for populations in LMICs and, hence, delay health improvements in LMICs. Furthermore, to the extent that studies using GHRI benefit populations in HICs, it is even conceivable that

global health inequities might deepen. If studies using GHRI displace funding and investigator time for studies focused on addressing health challenges in LMICs, there could also be fewer innovations from LMICs to adapt or develop. This could compromise the GHRI approach in the longer term.

Even if studies using GHRI do not displace funding or investigator time to conduct studies for the benefit of populations in LMICs, a second potential ethical concern is that populations in LMICs may not receive equitable benefits from these studies. At the moment, GHRI is most commonly used in studies that adapt existing innovations from LMICs for use in HICs. However, these studies are primarily designed to yield results for the benefit of populations in HICs. For example, many innovations from LMICs are low cost and, therefore, have the potential to free up resources for other health interventions, allowing HICs to achieve greater health gains within limited healthcare budgets. Similarly, innovations from LMICs often address health challenges that affect underserved or otherwise vulnerable populations. If successfully adapted, these innovations can help to improve the health of similarly vulnerable groups in HICs and promote health equity there.[10] Of course, the results of studies that adapt existing innovations from LMICs can also benefit populations in LMICs. For example, in the 'Belong to Baltimore' initiative, a programme to address social isolation from Brazil was adapted for community members in the USA. The initiative in Baltimore prompted the originator organisation, Saude Crianca, to more rigorously evaluate when and why their own programme works and thereby identify opportunities for improvement.[37] However, especially if the existing innovations that are being adapted for use in HICs are already of high quality, the benefits of refining them may not be significant for populations in LMICs.

When the results of studies using GHRI may not have significant benefits for populations in LMICs, there is a risk that other benefits from the research may not be equitable. For example, research capacity building in LMICs is a common benefit in research collaborations between LMICs and HICs, including in studies using GHRI. However, although capacity building stands to benefit investigators in LMICs, the downstream benefits for populations in LMICs can be uncertain. For instance, investigators from LMICs who pursue professional opportunities in HICs can face challenges reintegrating into their home research institutions after a stay abroad,[38] meaning their enhanced skills and expertise may not benefit populations in LMICs. Of note, the potential concern that populations in LMICs reap insufficient benefits from studies using GHRI is real even in well-intentioned research partnerships. For instance, the partnership that pioneered the RI approach has been criticised for perceived inequities.[39]

These potential ethical concerns are genuine and important to address, although readers should recognise that they are not specific to GHRI. All studies use funding and investigator time that are then not available for other research. Moreover, because funding and investigator time are currently limited in LMICs,[3 4] potential concerns about displacing more beneficial studies or activities apply to all research in LMICs—not just to studies using GHRI. And more generally, any research approach can be implemented without careful attention to otherwise sound ethical commitments. However, the identified potential ethical concerns are heightened in studies using GHRI because most of these studies currently adopt innovations from LMICs for use in HICs. Thus, if GHRI is not implemented carefully, *populations in LMICs might lose benefits from displaced funding or investigator time while populations in HICs benefit*—even though populations in LMICs are already worse off. This differs from standard concerns about displaced funding or investigator time, given that funders in HICs and LMICs primarily invest in research that aims to benefit their own populations, and so populations either within HICs or within LMICs stand to lose or benefit from pursuing some studies over others.

c. Ways of addressing potential ethical concerns

The following ethical considerations for funders (box 1) and sponsors and investigators (box 2 and table 2) aim to address the potential concerns identified above, notably by offering detailed recommendations on when studies using GHRI might be appropriate to fund and how they might be implemented equitably. We hope that the proposed considerations will facilitate the ethical conduct of studies using GHRI while also providing a basis for holding funders, sponsors and investigators to account in case of perceived inequities.

To minimise the possibility that research using GHRI might delay health improvements in LMICs, funders should ensure that such research addresses major health needs or priorities in LMICs and does not displace funding for research with more significant potential benefits for populations in LMICs. Funders in LMICs generally spend their limited research budgets on pressing local health needs or priorities.[40–42] Consequently, it seems advisable for them to fund studies using GHRI only when these studies develop innovations of major local importance, and when funders in HICs cover both the study portion conducted in HICs and the incidental costs associated with building the research partnership (eg, training and infrastructure investments). Moreover, given that research funding is more abundant in HICs than in LMICs,[4] funders in HICs should ideally cover the full costs of studies that develop innovations in LMICs and HICs—including the study portion conducted in LMICs.

Funders in HICs should generally support studies using GHRI through funding streams for research on health needs or priorities in HICs to avoid displacing resources for research that more directly addresses health needs or priorities in LMICs. One possible exception is studies that develop health innovations in LMICs and HICs, provided the studies clearly address major health needs

Table 2 Selected recommendations for building equitable partnerships between investigators in LMICs and HICs. Note these recommendations combine ethical obligations and ethical ideals.

Embrace mutual learning and equitable research contribution[45 46 49 50 52 53]	▶ Embrace mutual learning and knowledge exchange ▶ Promote equitable contribution to and shared responsibility for the research ▶ Promote fluent communication between all researcher partners
Strengthen local ideas and resources[29 50 52]	▶ Respect, preserve and strengthen local research personnel and infrastructure ▶ Widen local research participation (eg, develop local research networks) ▶ Tap into local ideas and innovations ▶ Respect, preserve and strengthen local clinical personnel and healthcare infrastructure
Recognise and address power imbalances[15 45 47 48 50–54]	▶ Foster mutual respect and trust ▶ Promote diversity and inclusivity ▶ Recognise and address potential biases or prejudices ▶ Acknowledge each research partner's strengths and weaknesses and provide support as needed ▶ Develop equitable research budgets and plans (eg, roles, responsibilities and opportunities, project milestones) ▶ Manage research budgets and monitor research progress, in a fair and transparent way ▶ Promote equitable ownership and access to research data and samples ▶ Ensure fairness in disseminating research findings (eg, fair opportunities for authorship, academic presentations and media engagements, fair acknowledgements) ▶ Fairly share any financial benefits from the research (eg, patents or trademarks)
Develop fair and respectful research agreements[15 45–54]	▶ Engage all research partners early ▶ Develop research contracts in a fair and transparent way ▶ Ensure accountability to funders and local authorities ▶ Comply with local policies, regulations and oversights ▶ Where applicable, use memorandums of understanding to set out clear and mutually agreed terms of collaboration (see **Section 4. Legal considerations**)
Benefit local communities[15 45–54]	▶ Address local health needs and priorities, as defined by local communities themselves or with their participation ▶ Translate research findings into context-specific applications ▶ Provide research and/or healthcare infrastructure as needed ▶ Transfer knowledge and research and/or clinical skills ▶ Minimise any negative impact of the research on the local community and environment (eg, compensate for harm)
Promote long-term collaboration[15 47 49 50 52 54]	▶ Secure funding to support sustainable research programmes ▶ Commit to long-term collaborative research partnerships and the development of healthcare systems ▶ Build reliable and trustworthy relationships for the long term

and priorities in LMICs. In general, funders in HICs should strive to financially support such studies only when they address top-priority research questions in both LMICs and HICs, drawing on research priorities that have been set in a transparent and inclusive process using sound criteria.[43] However, when top research priorities in LMICs and HICs cannot be aligned, studies that develop innovations in LMICs and HICs should address major health needs or priorities in LMICs, as these are ethically more urgent to address.[44] Finally, we recommend that funders in both LMICs and HICs exercise good stewardship of funding for studies using GHRI, for example, by facilitating high-quality review of grant proposals and regularly evaluating funded studies (box 1).

To address the potential ethical concern that the benefits of studies using GHRI are not equitable for populations in LMICs, investigators interested in conducting such studies should carefully explore their foreseeable potential benefits, burdens and costs in both settings. Because improving the health of populations in LMICs generally has ethical priority,[44] sponsors and investigators should give special attention to the studies' implications for populations in LMICs, including the possibility that they displace research or other activities with more significant health potential benefits for these populations. Investigators, especially those in LMICs, should not be under perceived or real pressure to enter collaborations on studies using GHRI. If investigators do not wish to collaborate, for example, because they are working on higher-priority research or other projects, this should be respected.

Sponsors and investigators who wish to collaborate should take special care in implementing GHRI's ethical commitment to equitable research partnerships. This involves considering relevant existing recommendations,[15 45–54] which combine ethical obligations and ethical ideals. Existing recommendations have traditionally stressed that research in LMICs should address local health needs or priorities, and local populations should receive a fair level of benefits from the research. However, more recent recommendations have moved towards more egalitarian research partnerships that, in line with GHRI, place greater emphasis on engaging all research partners in all stages of the research, investing in mutually beneficial innovations, and committing to long-term collaborative research partnerships (table 2). In the context of GHRI, it is especially important that studies address high-priority research questions in both LMICs and HICs and, when this is not feasible, major health issues in LMICs. In addition, sponsors and investigators should plan studies such that they do not displace resources (eg, investigator time, infrastructure) that otherwise would have been used to address local health needs or priorities. Finally, sponsors and investigators should pay special attention to intellectual property (IP) rights, as well as recognising past contributions of investigators in LMICs beyond these rights (box 2 and table 2).

Legal considerations for global health reciprocal innovation

Attention to legal and regulatory elements of studies using GHRI is essential to promote equity between all parties who are part of a collaboration, establish transparent agreements and understandings and preempt partnership conflict. Legal elements of GHRI should be considered early in research partnerships, especially given potential power imbalances in access to legal advice between LMIC and HIC partners. Further, real and perceived legal and regulatory barriers have been cited as primary inhibitors against the use of GHRI.[55] This is particularly true in the case of innovations that support public health goals and do not have the benefit of a large corporate sponsor to facilitate introduction to the market.[55] As such, prompt consideration and analysis of these elements can address potential hurdles early and facilitate the use of GHRI in global health research. However, as a caution, attention to ethical considerations regarding GHRI discussed above is not resolved simply by signing an MOU. Instead, the MOU can act as a starting point in a relationship that must be nurtured and reexamined to ensure that the partnership remains mutually beneficial and respectful over time.

a. Using an MOU to promote equity

Legal considerations relating to a GHRI research partnership include IP issues, ownership of shared assets, legal elements in the conduct of research (eg, informed consent, research ethics review) and operational issues. Some of these issues will be present at the start of the partnership and easier to fully consider at that time, while other legal issues may not be relevant or apparent at the early stages of a partnership. We, therefore, recommend that current and potential legal issues be addressed in an MOU early in the partnership to define roles, responsibilities and expectations in the collaboration; establish guidelines for IP and benefit sharing; and incorporate agreements around the management of data and samples (eg, data sharing and material transfer agreements). Because MOUs are not legally binding and therefore more flexible documents than legal contracts, they are also appropriate vehicles to document partnership values and goals that are not legal in nature.

It would be impossible to provide a 'one-size-fits-all' legal framework for studies using GHRI, given the multiplicity of legal contexts and types of studies. Working across national boundaries implicates multiple bodies of law and multiple jurisdictions, which demarcate the geographical limits of a court's authority, and therefore which court would hear a dispute and what law is used.[56] As such, drafting complex contracts with sophisticated and binding 'choice of law' and 'choice of forum' clauses, stating which law a court case would use and where is usually reserved for business contexts with the participation of lawyers with expertise in private international law.[57] However, studies using GHRI tend to start less as a business arrangement and more as a global health partnership with collaboration and research as the primary foci. As such, an MOU is recommended—and commonly used—by organisations engaged in global health and is appropriate for GHRI partnerships. Nonetheless, on occasion, research-related MOUs and agreements contain a choice of law and forum clauses that almost invariably favour investigators in HICs. A recent case in Malawi demonstrated this,[58] as the court, in this case, upheld the forum selection clause, potentially exposing the Malawian investigators to expensive litigation in a foreign jurisdiction and effectively without a remedy, given the unequal bargaining power of investigators in Malawi. GHRI partners should review MOUs closely and openly to verify that all clauses are understood and mutually agreeable.

We recommend the use of an MOU for studies using GHRI and below set forth priority legal and regulatory concepts to consider and important elements to consider during MOU development.

Although there are alternative definitions, generally, an MOU is a written agreement between parties that expresses their aligned will and the intent of a common line of action. An MOU can be bilateral (between two parties) or multilateral (between more than two parties). Although an MOU is not legally binding, it serves as a serious declaration that can be persuasive if a disagreement arises, if new parties enter the partnership or if litigation takes place. An MOU is typically broad and requires the parties' best faith efforts to collaborate on the goals outlined in the MOU. A well-drafted MOU should be easy to modify and renew by agreement of both parties. An MOU typically does not commit any party financially

but can serve as a prelude to a binding contract. Given these benefits, MOUs are highly regarded by healthcare organisations across the globe forfoster collaboration.

b. Key substantive elements of a MOU

An MOU can be an important tool in a global health partnership and can address elements that are legal and regulatory in nature and also record non-legal elements of a partnership to promote equity between partners, such as language regarding authorship of publications and communications around a partnership.

Before drafting the MOU, all partner values and goals for the collaboration should be discussed transparently and well documented. A structural tool to help ensure these elements are included into the MOU is to include the following sections in the document: Overall Purpose, Goals, Responsibilities and Terms. It is important to be aware of power dynamics and cultural norms that may make it difficult for a party to state the values and goals in person, quickly or transparently. Sufficient time, understanding and a trained intermediary with experience in both LMICs and HICs are important supports to ensure a mutually satisfactory MOU. Even with the best intentions, however, organisations in LMICs may not have the capacity and resources to adequately assess and negotiate agreements, highlighting the need to strengthen grant management and administrative capacity to engage in GHRI.

Box 3 sets forth key legal considerations for GHRI partners to discuss transparently and enshrine in an MOU as early as possible.

c. Key process elements for developing and entering into an MOU

MOUs promote equity in global health partnerships through their content but also through the process of developing the MOU because coming to the 'table' as partners to flesh out and enshrine shared goals can be an act of equity itself. Very little guidance is available regarding the process for developing and entering into MOUs in global health, much less in GHRI in particular. As such, the following best practices (box 4) were developed by two of the authors based on years of experience in this area, one as Assistant Vice President for Global Engagement at a large research university (VR) and the other as an Executive Director of a global health initiative at a major healthcare system (JZ). On completion of an MOU, it is common—and a good practice—to honour the occasion. An MOU signing ceremony, even if virtual, is an important way to share the terms of the MOU with a broader group and nurture a relationship based on a shared vision and goals.

Regulatory considerations for reciprocal innovation in global health research

In the context of studies that adapt innovations from LMICs for use in HICs, innovation(s) developed in and for LMICs must traverse the regulatory approval pathways established in HICs and demonstrate applicability,

Box 3 Legal considerations for creating MOUs for studies using a global health reciprocal innovation approach.

Ownership of separate and shared assets

The MOU should document assets of the partnership.

⇒ An ownership clause can document assets of the partnership that are owned individually or institutionally and assets that are shared (eg, lab equipment jointly used for a study may belong to one party with the expectation that it will devolve back to that party at the end of the partnership)

⇒ An ownership clause should also clarify ownership of assets secured during the partnership or with partnership funds (eg, an app or written training materials purchased with joint grant funds), as well as distribution of assets when the partnership is over.

⇒ An ownership clause can be in the body of the MOU or an Appendix that can be updated as needed.

Intellectual property (IP)

The MOU can establish agreed upon models for sharing ownership and benefits of IP.

⇒ The MOU should establish agreements around authorship of publications, division of funds in case grants or contracts are received, and branding (ie, naming the partnership or innovation and publicizing it).

⇒ When the future fruits of the partnership are unknown, it is advisable to state in the MOU that a separate agreement will detail the IP rights of the parties.

⇒ If it is known at the creation of the MOU that some IP will clearly belong to a specific party, it is advisable to include a clause such as "All documents, trainings, promotional materials, and other IP created by (name ororganization) will be owned by (name or organization), who will have exclusive rights to distribute or monetize it, or to create derivative works."

⇒ If the partnership creates an intervention or product that could be commercialized, licensed, or marketed, such as an app, the MOU should state that neither party will enter into a licensing agreement unilaterally and that consultation and a formal contract is required to market or license elements developed by the GHRI research partnership.

Research ethics review

International joint research projects have additional approval steps to consider when conducting research involving human participants, first and foremost that approval must be sought from multiple research ethics committees (RECs).

⇒ Each institution and partner will have different requirements and procedures for REC review. It is important to consider ethical review issues in the MOU and determine responsibilities in this area.

⇒ Document in the MOU a commitment to adhering to all local, national and international laws and guidelines and what support the LMIC partner may need (eg, training, staff support to complete requirements regarding REC review). Consider whether there is flexibility in the process that could promote equity (eg, acceptance of a single REC to prevent overlap of effort and duplicative REC reviews).

⇒ The REC review process considers the elements of study plans, procedures, recruitment, selection of study instrument (if any), and how to protect human participants. In GHRI, the parties involved may have varying cultural, social, and religious norms that should be thoroughly communicated and considered in the REC review process and later in the research. The MOU can address the importance of these considerations in a broad way

Continued

Box 3 Continued

and elaborate on any specific areas that could create misunderstandings or delays in the future.
⇒ A particular area of focus between LMIC and HIC partners should be the staffing capacity of the LMIC organization to undertake REC compliance activities and monitoring. Addressing these issues in advance and providing adequate support will promote equity and successful outcomes.

Operational aspects of partnership

Engaging financially with a partner in another country implicates legal and compliance rules on both sides of the partnership.
⇒ The MOU should acknowledge current and future issues in finance and set forth agreements regarding how specialized assistance will be secured and paid for to ensure compliance with applicable laws.
  ⇒ Some issues may arise regarding needing the flexibility to send or receive funds in multiple currencies and using the time and services of a local partner's personnel.
  ⇒ If funds are transferred internationally to perform obligations under a grant, there may be tax and fiscal implications in the sending country, as well as corporate and business law implications in the receiving country.
  ⇒ Often specialized advice and infrastructure are required to carry out research and other programs.

For larger governmental grants, the LMIC partner will also be expected to abide by the grant's terms and regulations, which may put the LMIC partner in a very uncomfortable place as they may not have the operational infrastructure or be ready to comply.

validity, safety, performance, effectiveness and quality to populations in HICs. These pathways and accompanying requirements are set forth by the healthcare regulatory agencies of individual countries and regions (eg, US Food and Drug Administration (FDA), European Medicines Agency) that allow the devices to be placed on the local market. Meeting the requirements of regulatory agencies in HICs can be challenging, especially for less-resourced research funders. Challenges include finding appropriate local partner(s) who can help with conducting safety and efficacy studies in the local context; obtaining research ethics committee approval for these studies; and preparing data from these studies for regulatory review. Therefore, before importing and implementing innovations in HICs, the GHRI partners need to consider these challenges and how to address them (box 5).

Box 4 Best Practices for developing and entering into MOUs for studies using a global health reciprocal innovation approach.

Best Practices

⇒ Determine early on the internal process at each organization for writing and executing an MOU, including who has signatory authority to sign on behalf of each organization.
⇒ Be transparent about the length of time it may take your organization to draft, review and execute the MOU.
⇒ Determine early on if any of the collaborating partners has a pre-existing MOU template that can be used, and which institutional template will be used.
⇒ Ensure both parties understand that the MOU is not legally binding and that subsequent agreements may be needed for individual projects or activities, especially where funding or IP is transferred between institutions.
⇒ Have matching MOUs in the preferred language of each partner organization. For higher resource organizations entering MOUs with lower resource institutions, this may mean the higher resource institution pays for translation.
⇒ Keep the MOU as concise and digestible as possible. A typical MOU does not need to be more than 3-4 pages and highly stylized legal terminology is not necessary, except to the extent it is needed for clarity or to meet the context.

Box 5 Regulatory considerations for studies that adapt innovations from LMICs for use in HICs.

Relevant considerations

⇒ Appropriateness of the innovations for the given HIC populations, particularly to what extent the populations in which the innovations have been validated in LMICs are comparable to those in HICs *and*
⇒ End user impression and acceptability of the innovations *and*
⇒ The broader health setting and other health priorities, including other local disease priorities in the HIC, where appropriate, *and*
⇒ Obtaining validation data about the innovation from the relevant population (this can be accomplished with a pre-submission consultation with a regulatory agency for advance guidance) *and*
⇒ Cultural, environmental, race, ethnic, societal and demographic issues, including, but not limited to, distance to care, aging in place, urban versus rural contexts, costs associated with medical shipping and storage in the HICs *and*
⇒ Local healthcare delivery models in the given HIC, availability of other companion modalities needed as part of the proposed intervention, and issues around patient contact and follow-up *and*
⇒ The possible mistrust of the pre-market and post-market validation data collected in the LMICs.

a. Regulatory considerations for adapting tools from LMICs in the US context

The following sections provide an example from the US perspective, but regulatory agencies in other HICs have similar regulatory considerations with some modifications. GHRI partners should consult and follow applicable HIC guidelines. In the USA, the FDA regulates companies that manufacture, repackage, relabel and/or import drugs and medical devices sold in the USA. Drugs and devices that are imported from LMICs into the USA need to conform to the same FDA regulations as domestically produced products.

b. Premarket considerations in the USA

Developers should consider approaching FDA early in drug or device development to request feedback from the FDA regarding planned or potential drug or device submissions and requirements for approval.[59] They should prepare to provide a description of the drug or device and its intended use in the USA, intended population and age groups, nonclinical and clinical studies, case report forms, manufacturing methods and labelling to obtain the FDA approval. Proper planning and preparation for obtaining the FDA's

exemption status or approval can lead to market share advantages, improvements to operational and quality process efficiencies and a positive impact on patient care.

c. Post-market considerations in the USA

GHRI partners must follow certain requirements and regulations once the drugs or devices are on the market, including registering the establishment where they are produced or distributed; tracking quality management systems; and reporting malfunctions, serious injuries or deaths associated with the drugs or devices.[60] Post-market requirements also include conducting and reporting results from post-approval studies to the FDA, since obtaining the premarket approval is contingent on demonstrating continued performance of the drugs or devices in real-world settings; reporting post-market surveillance studies required under section 522 of the act, which show continued safety and effectiveness (or continued probable benefit, in the case of a humanitarian device exemption) of the approved drug or device; requesting humanitarian drug or device exemption, when a drug or device is intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8000 individuals/year; and/or submitting product development protocol application.

CONCLUSION

GHRI has the potential to promote a more equal global health research enterprise through studies that offer an equitable distribution of benefits for populations and investigators in both LMICs and HICs. However, studies using GHRI also raise potential ethical concerns and face legal and regulatory barriers. In this paper, we have proposed ethical, legal and regulatory considerations for funders, sponsors and investigators to address these concerns and barriers. We hope that our proposed considerations will help realise the potential of GHRI and move the global health research enterprise forward into a new era where all people are treated equally as knowers and learners, and populations in LMICs benefit equitably from these studies.

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Acknowledgements This paper was sparked by discussions at the Global Health Reciprocal Innovation Virtual Workshop held in October 2022, sponsored by the National Institutes of Health. Thanks to Nalini Anand, Blythe Beecroft, Linda Kupfer, Joseph Millum, Arthur Rose, Carla Saenz, Seema Shah, Robert Steel, participants in the 2023 Indo-US Research Ethics Workshop hosted by the Indian Council for Medical Research and two anonymous reviewers for helpful comments.

Contributors AR, BA, RD and VR conceived the idea for the paper and wrote the first draft. CB, MH, AK, MO and JZ revised the paper critically for important intellectual content. All authors approved the final version and agreed to be accountable for all aspects of the work.

Funding AR is supported in part by the Clinical Center Department of Bioethics, which is in the Intramural Program of the National Institutes of Health (Grant/Award #: N/A). MH is supported in part by the National Institute for Health and Care Research Applied Research Collaboration Northwest London (Grant/Award #: N/A).

Disclaimer The views expressed here are those of the authors and do not necessarily reflect the policies of the National Institutes of Health or the US Department of Health and Human Services. The views expressed in this publication are not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement There are no data in this work.

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