Navigating the Challenges of Global Reproductive Health Research

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Abstract

Reproductive health research in low-resource settings poses unique and complex challenges that must be addressed to ensure that global research is conducted with strict adherence to ethical principles, offers direct benefit to the research subjects, and has the potential for adoption of positive findings to the target population. This article addresses challenges to conducting reproductive health research in low-resource settings in the following areas: (1) establishment and maintenance of global collaboration, (2) community partnerships, (3) ethical issues, including informed consent and the role of incentives, (4) staff training and development, (5) data collection and management, and (6) infrastructure and logistics. Particular attention to these challenges is important to ensure that research is culturally appropriate and methodologically sound and enhances the adoption of health-promoting behaviors. Rigorous evaluation of interventions in low-resource settings may be a cost-effective and time-efficient way to identify interventions for large-scale program replication to improve women's health.

Introduction

GLOBAL REPRODUCTIVE HEALTH RESEARCH explores the sensitive areas of contraception, abortion, domestic and sexual violence, pregnancy, childbirth, infertility, and sexual function. The nature of these topics, particularly in the context of cultures where women may not be empowered to make autonomous decisions, requires the researcher to carefully consider the importance of the research being done; the local social, cultural, and ethical standards; and the needs of the participants.¹

In addition to social and cultural concerns, conducting reproductive health research in low-resource settings presents researchers with a multitude of logistical challenges, including limited overseas communication, power outages, transportation difficulties, varying field conditions, political instability, shortages of trained staff, and lack of equipment. Before a project can be implemented, basic research training may be required on clinical protocols, research methodology, ethical conduct of research, and data management. Careful assessment, planning, reevaluation, training, monitoring, and supervision may be required throughout the research process.

Cultural, ethical, and logistical challenges presented to the global reproductive health research team can be complex and multifaceted. This article addresses challenges in the follow-

ing research areas: (1) establishment and maintenance of global collaboration, (2) community partnerships, (3) ethical issues, including informed consent and the role of incentives, (4) staff training and development, (5) data collection and management, and (6) infrastructure and logistics. Navigating these challenges is important to ensure that the research is ethically and methodologically sound and culturally acceptable and offers long-term benefits to participants and their communities.

Establishment and Maintenance of Global Collaboration

One of the greatest challenges to global reproductive health research can be the establishment and maintenance of a collaborative relationship between investigators from different countries and cultures. Frequently, researchers establish collaborations through existing relationships originally initiated for clinical or educational purposes or formed through personal contacts at international meetings. Other possibilities include conducting a review of the literature to identify individuals conducting research in the country or region of interest or working with national health authorities, universities, nongovernmental organizations (NGOs), or medical schools to identify appropriate experts who may be interested in collaboration.² Individuals could also ask colleagues who

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conduct research in a specific country or region to help establish contacts. Once the collaboration has been established, a joint needs assessment can identify critical areas of research.

For collaborations between global health partners to flourish, regular, frequent communication and multiple trips to the research location to develop a working relationship and understand the local context may be required. Collaborators can determine research goals, define roles and responsibilities, and build trust. Sustainability of the relationship will depend on frequent communication, including regular e-mails, calls, and site visits. Consideration should be given to the importance of building necessary infrastructure and career development and mentoring for all collaborators.

Community Partnerships

The development of international partnerships is critical to the effectiveness and sustainability of health interventions in low-resource settings, although the process of cultivating collaborative partnerships is not simple. There may be significant and historically justified mistrust from the local community regarding involvement with foreign investigators that may interfere with community-researcher partnerships. Managing the tension between the different expectations of foreign investigators and global health partners, as well as community members, about research goals, processes, and outcomes may be challenging.

One technique to facilitate these relationships is community-based participatory research (CBPR), which is increasingly used for health improvement research.³ CBPR is a collaborative process that engages community members in all aspects of the research process and employs local knowledge in understanding health problems and designing interventions.⁴ It may be important for foreign investigators to learn the culture of the research site, be sensitive to local cultural norms, and spend time in the community in order to earn the community's trust. Investigators can build rapport with key stakeholders, make formal presentations about the nature of the partnership, engage in community sensitization about the importance of the work, maintain ongoing communication, and disseminate research findings.^{4,5} A significant amount of time and commitment by the foreign investigators and community partners during the various stages of the research is central to CBPR and may vary based on the research conducted. CBPR is further discussed in detail in the article by Decker et al.⁶ in this issue.

Funding agencies increasingly recognize the importance of conducting research in the context of collaborative relationships between foreign investigators and target communities, as well as with provider agencies implementing the interventions.⁷ A community advisory board (CAB) comprising key community stakeholders, health providers, local researchers, and foreign investigators can serve to generate research ideas, ground the research in real world experiences, and aid in the interpretation of findings. Inclusion of women or members of groups that could be considered vulnerable (such as minors or female sex workers) may promote understanding of existing barriers faced in accessing care or participating in research and may lead to the development and dissemination of safe, inclusive research programs and policies. However, foreign investigators may experience resistance from local health systems to the inclusion of stake-

holders from vulnerable populations and community-based organizations.

The development of effective international partnerships requires that individuals use a team approach of joint planning and decision making, sharing of ideas, and a clear direction in terms of what the international partnership wants to achieve. Although developing international partnerships involves time, attention, reflection, and a long-term commitment, collaborative research can increase the likelihood of program sustainability, ensure cultural appropriateness, and promote colearning among all partners.^{8,9}

Example 1: Community Participation in Safe Abortion Research in Latin America

Restrictive laws limit women's access to safe abortion services in many parts of the world, and misoprostol is often self-administered to induce abortions without correct information. Research partners in an unnamed Latin America country conducted an exploratory study to identify safe, appropriate, and effective dissemination methods for misoprostol use that which would avoid increasing legal risk to individuals or jeopardizing the availability of the drug.¹⁰ In-depth interviews were conducted with physicians, pharmacy staff, women with a history of a safe abortion, and women from the community. Participants were asked about women's sources of reproductive health knowledge, abortion laws, channels for referral, communication methods, and information about misoprostol use. Focus group discussions with safe abortion advocates and community providers were conducted. The study included both rural and urban participants and sought practical, nonthreatening methods for dissemination of information to increase the safety of misoprostol use. Establishing partnerships with women's health advocates, medical professionals, and community members was instrumental to the research effort and provided valuable insight from sources not generally included in the medical decision-making framework. Similarly, when research findings are disseminated and scaled up, it has been shown that women's health advocates, progressive policymakers, medical professionals, and grass roots organizations can work together to significantly improve access to family planning, emergency contraception, and safe abortion services (where legal).¹¹⁻¹³

Ethical issues

Questions surrounding the ethics of conducting research in low-resource settings have been discussed in detail elsewhere^{1,14-16} and include the use of placebos, working with low and nonliterate populations, sustainability of programs once research is completed, and whether a randomized clinical trial (RCT) is appropriate given the context, the epidemiology of the disease or condition, and the efficacy of the already available control or standard of care. In this article, we focus on two ethical issues that have particular salience in reproductive health research: informed consent and incentives.

Informed consent

The ethical cornerstone of research is the process of voluntary informed consent. Although numerous guidelines exist,¹⁷⁻²⁰ the actual process of appropriately informing par-

ticipants about research can be difficult and time consuming and involves consideration of perspectives across cultures that may be radically different.²¹

The principles of informed consent emphasize the autonomy of the individual and the right to make knowledgeable decisions about risks and benefits associated with participation. However, the modern western premises of autonomy and individual agency may not necessarily be accepted or relevant in nonwestern cultures. Communal consciousness and living are the norm in many societies, where community leaders and families play key roles in decision making.²¹ A community consent process whereby the research team obtains permission from community leaders for the trial to take place may be necessary before individuals feel it is possible to give individual consent.¹

Women in many parts of the world lack power and self-determination within society and are sometimes subjected to physical harm and psychological abuse when seeking to improve their own health or safety.¹⁴ Researchers may need to explore how taboos, cultural norms about sexuality, and gender roles impact expressions of individual autonomy, voluntary participation, and informed consent.²² In some societies, the low social status of women and lack of control over their sexual and reproductive lives may complicate education about health services or research topics and compromise voluntary informed consent.²³ Furthermore, issues of reproductive health tend to affect populations that might be considered vulnerable to the research process, such as adolescents, minors, and victims of rape or abuse.²² In many low-resource settings, vulnerability is compounded by poverty, lack of access to healthcare, poor education, and repressive policies toward women.²⁴

Solutions to these complex issues are not simple. Key informant community members or use of a CAB may be able to provide insight into how research activities could inadvertently increase risk for women, as well as offer suggestions for how best to mitigate potential danger. A CAB could provide advice that might also lead to ideas that decrease the likelihood that a woman will face discrimination for participation in the research.²⁵

The education and health literacy level of participants also pose barriers to the consent process because education level is predictive of a women's ability to comprehend research concepts and purpose. Research staff can ensure that each participant understands the consent process by constructing and uniformly asking a set of simple questions about the study and whether or not the women understand both the benefits and risks of participation.²⁶ International guidelines on ethics in clinical trials recommend that researchers not only ensure that participants receive sufficient information about research but also determine if consent is free from coercion, including pressure from family members.²⁷ A therapeutic misconception may exist when participants do not realize that the primary purpose of clinical research is to produce knowledge rather than provide a beneficial intervention. For example, women participating in a contraceptive trial may enroll in order to receive free contraceptives and may not understand that the product's efficacy and safety are not established or equivalent to the available gold standard. Although this possibility exists globally, it may be more likely to occur when a population is poor, vulnerable, or naïve to the research process or purpose of a study.²⁸

Although translation and back-translation between languages have become common practices to ensure consistency in informed consent documents, there has been too little attention on how the conceptualization of ideas may be different between groups.²⁹ A multistep process involving translation, back-translation, and assessing for cultural equivalence, with validation for comprehension carried out through the piloting of documents, may be required.^{30,31}

Example 2: Informed Consent for a Randomized Clinical Trial in Tibet

In 2000, the Tibetan Autonomous Region (TAR) Health Bureau requested assistance with a maternal-child health project with the long-term goal of increasing Tibetans' research capacity.^{26,31} The collaboration culminated in a triple-blind RCT of a traditional Tibetan medication, *Zhi Byed 11* (ZB11), with a western medicine (misoprostol) for postpartum hemorrhage prevention.³² The development of a culturally appropriate, ethically sound informed consent resulted in a 2-year, 4-staged process of qualitative investigation,³¹ involving three languages, Chinese, Tibetan, and English, and a multidisciplinary team (anthropologists, obstetricians, midwives, and nurses).

The initial phase entailed in-depth interviews with healthcare providers and antenatal or postpartum women to assess understanding of research. This was followed by 20 iterations of a consent document before the team reached consensus about a suitable version that would simultaneously be acceptable to and understood by participants and meet institutional review board (IRB) requirements. Document piloting resulted in major revisions, including addition of illustrations, length reduction, and language simplification.

Several areas of concern were identified revealing major cultural differences in key concepts.²⁶ Views of risks varied substantially from western perceptions. A prevalent Tibetan concept *rten 'brel*, or omen, leads many Tibetans to believe that if one talks about possible negative outcomes or risks, this discussion can actually bring the negative outcomes into reality. In this setting, care was taken to explain potential outcomes neutrally, for example, by stating "every woman bleeds during delivery. There are always risks during any delivery and ways to minimize risks."

Indication of consent proved challenging, particularly with nonliterate participants. Thumb printing, considered by the western IRBs to be an acceptable way of documenting consent, was associated with negative historical connotations, including indentured servitude and confirmation of guilt during the Cultural Revolution. Finally, the gender composition of the interview teams affected responses, with all-female teams the most successful.

This experience highlights the benefits of bilateral communication and education and the importance of allowing adequate time for the process of informed consent. Flexibility in the creation of the informed consent process can be based on mutual understanding of the ethical and cultural concerns. This is likely to be regionally and ethnically specific and may be considered whenever new research efforts are being initiated.

Incentives

Compensation for participation in research through the use of incentives continues to be an ethical research issue. Studies

have demonstrated that incentives have a positive effect on response rates^{33,34}; however, use of financial compensation or provision of free healthcare services may distort the judgment of research participants or unduly influence an individual's decision-making autonomy, thereby compromising the informed consent process.³⁵ An example of this occurred in a clinical trial in a government hospital in Africa, where the local hospital asked the research team to pay for blood transfusions for study participants. The research team maintained that unless there was also guaranteed provision of blood to those who elected not to participate, this would have compromised the voluntary nature of participation. After considerable negotiation, it was agreed that the hospital would continue to accept the responsibility of ensuring blood transfusions for every patient in need.

Such benefits as food, supplies, and other tangible items may serve as an alternative to monetary incentives and may even be perceived to be more valuable than cash.³⁶ For example, researchers conducting a study on breastfeeding in India decided to use multiple nonmonetary incentives to increase participation.³⁷ A peer support group was created to encourage women to breastfeed, and women were given badges to wear identifying their participation in the program. The use of nonmonetary incentives increased the status of women, established community recognition for the program, and increased education surrounding reproductive health issues.

It may be worthwhile to consider choosing an item or service that participants would not be likely to purchase and that has potential secondary benefits, such as education, nutrition, or empowerment. Local IRBs can help determine whether monetary or nonmonetary incentives are an inappropriate motivating factor for research participation and minimize the possibilities of coercion and undue influence.³⁸

Staff training and development

Research concepts and methods may not be familiar to healthcare workers or community members who are recruited as study staff. Anecdotal evidence of the importance of staff training comes from an HIV treatment research program in 2003 in South Africa. One of the site supervisors was asked what was in a box on the top shelf in his back office; he pulled it down and said, "Files." When asked which files, he stated, "Oh, they [the subjects] are dead, what happens to them doesn't matter anymore." When asked if the data had been entered, he asked, "What for?"

Data collection and management training manuals have been developed by international research organizations and can serve as a model for more specific courses tailored to particular types of research and settings.³⁹ Providing regular information on the progress and problems of the research program may keep staff motivated to seek improvement and strive for excellence. Possibly the most important component of maintaining the integrity of a program is ensuring that staff are appreciated and realize the important contributions they make to the study and to improving patient outcomes. Continuous supportive supervision promotes and maintains high standards in research.

Strict adherence to research methods ensures the validity of research, yet barriers are common and multifaceted, including cultural and structural constraints and traditional, long-used

ways of thinking. For example, adherence to research protocols often requires clinical staff to undergo a shift in paradigm from individualized patient care to a protocol-driven, evidence-based approach. This shift may be particularly difficult in settings where the concept of healing involves consideration of individual characteristics to guide patient-specific therapy, such as in traditional Tibetan Medicine. The implementation of evidence-based practice is challenging,⁴⁰ and incorporating a research protocol into quality patient care is a skill that may need to be explained before study initiation. Providing training on evidence-based medicine and implementing research protocols, as well as using local opinion leaders to disseminate this practice, may improve adherence to the research methods.⁴¹

Staff may also face challenges if they are not fully engaged in the research process. For example, in the hospital setting, a large number of healthcare workers may be involved in patient care but not necessarily part of the research team. Educating a large and varied number of staff in the preimplementation phase of a study can minimize the number of barriers the research staff have to face later and may also increase referrals from providers outside of the study. An example of this comes from a large cluster-randomized trial on the nonpneumatic antishock garment in Zambia and Zimbabwe, where initial reluctance to allow use of the device in the operating theater was reversed once the anesthesiologists witnessed how the device worked in patients with hemorrhagic shock. Initial training may need to be reinforced by frequent retraining, both to refresh staff on the protocol and to train new staff. Encouraging dialogue and proactive communication among field workers, supervisors, and project coordinators may help identify problems and training needs, which can then be addressed. Ongoing problem-solving sessions with input from experienced clinicians and researchers can be helpful.

Building local research capacity should be a major goal of global research efforts. Care needs to be taken not to create too much of a drain from clinical or programmatic work to research. Mechanisms of integration, collaboration, and communication between research and health service programs may be sought in an effort to balance these demands when possible.¹⁶ Training programs may not only provide education on basic requirements of clinical protocols and data management but also incorporate theoretical aspects of research development, including standardization, voluntary informed consent, bias reduction, blinding, randomization, and monitoring. Similarly, grant and manuscript writing, research design, and data analysis are essential components of research; however, these skills may be lacking in low-resource settings. Mentorship in these areas may help ensure integrity of the current project and build sustainability for future research.

Data collection and management

Global reproductive health research frequently is conducted in settings without previous research infrastructure; therefore, clinical trials in these settings face many challenges to ensure quality data collection and management.⁴² The quality of available national and local health statistics may not be adequate for the data to serve as baseline information. A study conducted in Taiwan in the 1990s demonstrated that

maternal mortality was underreported by 58%, with misclassification in 53% of cases. Similar studies conducted elsewhere confirm underreporting of maternal death in 44% of cases in Ghana and in 57% of cases in Indonesia.^{43,44} Systematic underreporting may be related to stigma associated with certain diseases, such as reproductive tract infections, or to the prevalence of asymptomatic illness.⁴⁵ Additionally, data collection may be considered low priority by overworked health providers. Training staff to use data collection forms, data collection procedures, and the process of validating data will increase research proficiency and ensure high-quality data but may face resistance (as has been noted in the authors' experiences).

Misreporting during data collection can occur because of cultural differences between the interviewer and participants or community members.^{46,47} A challenge to the researcher is to ensure that quantitative and qualitative measures are equivalent across groups, that questions capture the same constructs, and that the underlying explanations for phenomena are included.⁴⁸ Attaining cultural humility in tool development requires translations and adaptations into languages other than English, as well as confirming that the complexity of language matches the literacy levels of the population of interest.⁴⁹ The involvement of a community advisory board may be helpful in developing culturally appropriate measures, addressing cultural issues, establishing community acceptability of data collection methods, and disseminating findings.⁴²

Foreign investigators may have expertise in data management, which can be integrated into the local institutional context. Local and supervisory validity checks can allow for correction of systemic issues and identify errors in data entry or management at an early stage. Using external supervisory data checks and monitoring to identify staff who are having difficulty may allow for early intervention, as indicated in the following example.

Example 3: Quality Assurance for a Randomized Clinical Trial in India

As part of an RCT conducted in India, a rigorous data monitoring system was established. This system consisted of staff trainings, supervision, and multiple validations of data to assess consistency and quality.^{1,37} Field research managers reviewed data collection forms, and double data entry was performed to detect incorrect and inconsistent data. A sample of participants was reinterviewed to verify the validity of information; all data were sent to a data-monitoring center in the United States. Continuous feedback about data quality was solicited from staff and supervisors. Because of this carefully constructed system, a problem was identified during the first 3 months of the study, when field research managers reinterviewed participants and discovered that three midwives in one primary health facility had fabricated data. The entire research team was notified of the problem, and investigators discussed the misconduct of data falsification and fabrication. The study replaced the midwives in question and discarded approximately 30 cases. Additional staff was hired, and retraining was conducted on the study objectives, data collection procedures, and the importance of valid data.

Fabrication and falsification of data are among the most serious challenges to the integrity of research.⁴² Fictitious data can be obtained in a study if an efficient data quality assurance

system is not used. Some studies may be unable to replace staff who falsify data. In these instances, researchers can meet with staff to investigate the reasons for fabrication, conduct trainings on study objectives and the ethical conduct of research, monitor data collection methods, and provide staff supervision. It is critical for studies to assure and improve data quality by implementing such techniques as validity checks, double data entry, and reinterviewing participants.⁴²

Infrastructure and logistics

Low-resource settings present researchers with a multitude of logistical challenges. A lack of information technology, data management infrastructure, and technical support on location can cause an inability to rapidly correct systemic problems, compounding errors over time.⁴² Storage and security of medical supplies and patient data may be threatened because of heat, erratic power supply, humidity, or insecure facilities.¹⁵ Further, as space may be limited and the project offices may close after the study is over, data storage becomes an issue and an expense that lasts beyond the life of the project. Careful assessment of existing infrastructure and institutional capacity at project startup can target resources to bring research methodology and service provision up to the standard of care being applied in the research setting. This will be site specific and could be included as information given to funders, who need to understand funding both the necessary preparatory phase and poststudy storage issues. A detailed understanding of the situation on the ground before study initiation will also help establish evaluation criteria with which to compare outcomes and to determine the project's impact.

Overseas communication, although critically important to the success of the project, is hindered by poor connections and large time differences. Establishing regularly scheduled communications for staff from different locations via conference call or Internet may help facilitate this process. Some of the unforeseen risks in clinical trials, such as power outages, transportation breakdowns, poor roads, erratic weather, and shortage of equipment, may be so common in low-resource settings that they should be considered foreseeable.⁵⁰ Managing these logistical challenges often requires flexibility, creativity, and local knowledge to find site-specific solutions. For example, in a clinical trial of surgical technique to repair fistula, breakdown of vital equipment threatened to delay the work for weeks. A local anesthesiologist heard about the problem and brought the research team to a previously unknown equipment graveyard, where the investigators located a replacement part and continued work. Foresight to anticipate potentially difficult events, such as monsoon flooding forcing road closure, can result in plans to ensure access to backup supplies, such as development of alternative supply routes or overstocking at certain times of the year. Consideration may be given to alternative power sources, such as solar or battery-operated equipment, that can be used during power outages when interruption in services would compromise research or patient care. Careful planning coupled with innovative thinking in the face of challenges may help ensure that research efforts continue uninterrupted.

Budgeting for international research programs requires consideration of these important logistical challenges. Initial infrastructure investments are likely to be higher than in

domestic-based research, and the shelf life of equipment may be shorter.^{42,50} Research in low-resource settings should never be considered a low-cost endeavor.¹⁵ Planning for multiple and, perhaps, unknown risks is never easy; however, budgeting that allocates funding toward these potential challenges may help minimize adverse impacts on research.

Conclusions

Although challenges to conducting global reproductive health research exist, identification of appropriate interventions and findings leading to lifesaving health advances make these challenges worth the effort. International partnerships among researchers, practitioners, advocates, and activists are critical, as they bring the best opportunities to develop a coherent, effective, and interdisciplinary approach to tackle global reproductive health problems. The ideals of reproductive rights, safe motherhood, and women's empowerment, harnessed with evidence from rigorous scientific trials that are culturally and contextually relevant, present opportunities to positively impact women's health and lives.^{51,52} There are challenges that may not have simple solutions, but foreign and local investigators can creatively adapt to the ever-changing circumstances in low-resource settings. Global reproductive health research requires cultural humility, education, and collaboration among diverse stakeholders as well as thoughtful attention to ethical and logistical issues.

In the past two decades, there have been important advances in reproductive health in both the biomedical and behavioral sciences, from preventive screenings to psychosocial interventions, that have reduced morbidity and mortality globally.⁵³ However, there is a vast amount of work that remains to improve women's reproductive health and rights.^{51,54} Well-designed research programs can answer questions surrounding reproductive health issues in low-resource settings while at the same time increasing local capacity, building sustainable systems where they are most needed, and contributing to policy changes, program development, and advocacy. Despite the challenges, this article is meant to encourage and advocate for increased dedication to high-quality global reproductive health research.

Disclosure Statement

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